

Anticancer Drugs—I

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I. OVERVIEW

In a small fraction (approximately 10%) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Figure 35.1 provides a list of the anticancer agents discussed in this chapter.

II. PRINCIPLES OF CANCER CHEMOTHERAPY

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cells that can arrest the progression of tumor growth. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines, which are the building blocks for DNA or RNA synthesis (Figure 35.2).

أولاً. النظرة العامة : تؤدي المعالجة الكيميائية عند حوالي ١٠% من مرضى السرطان الممثلين للأورام الانتقائية ، الشفاء أو هدأة طويلة . لكن في معظم الحالات تسبب المعالجة الدوائية تراجع المرض فقط ، وقد تؤدي المضاعفات أو النكوس إلى الموت .

ثانياً. مبادئ المعالجة الكيميائية للسرطان : تسعى هذه المعالجة إلى إنجاز تأثير سامّ للخلية مميت أو موت الخلية المبرمج في خلايا السرطان لإيقاف تطور نمو الورم . إذ يجري توجيه الهجوم إلى الدنا أو ضد مقرّات استقلابية ضرورية لتضاعف الخلية ، مثلاً ، توافر البورينات والبيريميدينات (وحدات البناء لتصنيع الدنا والرنا) (الشكل ٣٥ . ٢) .

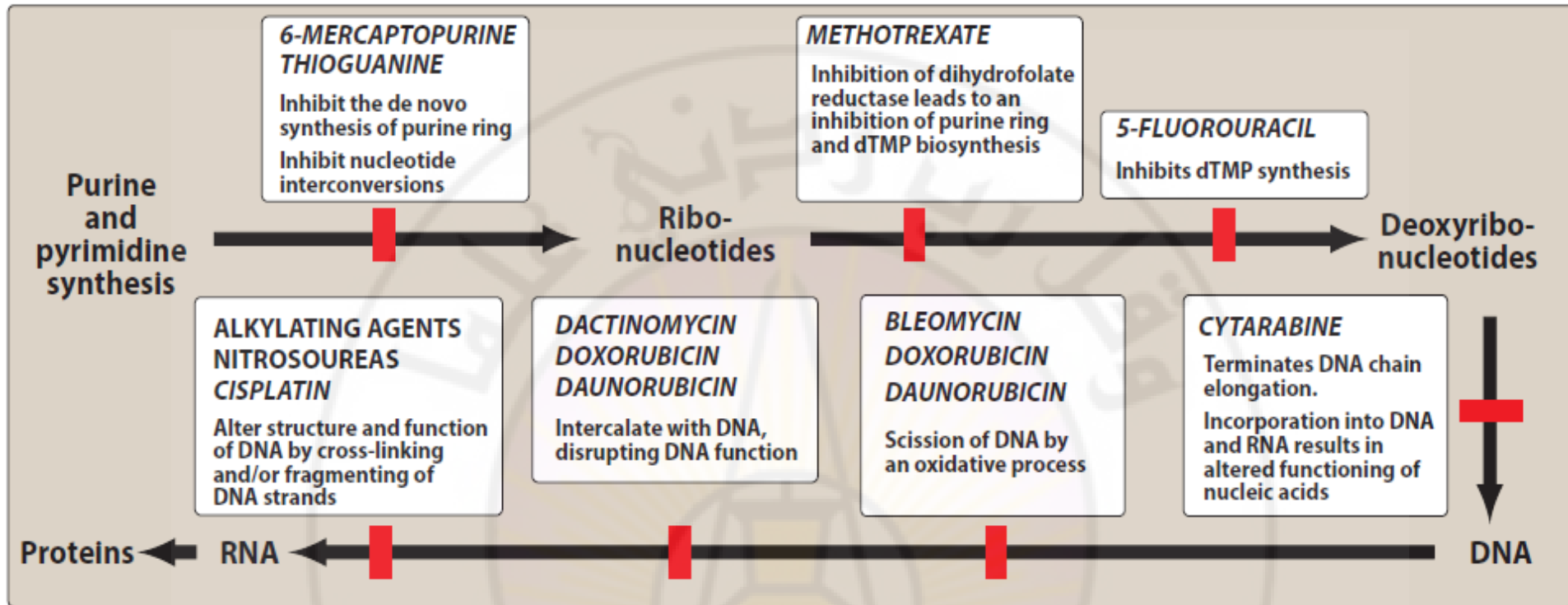


Figure 35.2

Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

مثالياً ، ينبغي للأدوية المضادة للسرطان أن تعترض عمليات خلوية فريدة للخلايا الخبيثة .

لسوء الحظ ، معظم هذه الأدوية لا تتميز نوعياً الخلايا الورمية ، لكن تؤثر على كل الخلايا المتكاثرة ، الطبيعية والشاذة .

لكل الأدوية المضادة للورم منحنى جرعة—استجابة حادّ (شديد الانحدار) لكلاً من التأثيرات العلاجية والسامة .

A. Treatment strategies

1. **Goals of treatment:** is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (prevent the cancer from enlarging and spreading) to extend survival and maintain quality of life. Thus, the individual maintains a “near-normal” existence, with the cancer treated as a chronic disease. In all cases, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, therapy using biological modifiers, or a combination of these treatment modalities (Figure 35.3) .

أ. استراتيجيات المعالجة :

١. **غايات المعالجة :** شفاء (أي ، بقيا مديدة خالية من المرض) . يتطلب الشفاء الحقيقي إزالة كلّ خلية ورميّة .

إذا لم يكن الشفاء ممكناً ، تكون الغاية السيطرة على المرض (منع السرطان من التضخم والانتشار) لمدّ البُقيا والمحافظة على جودة الحياة . هكذا ، يحافظ الفرد على وجوده طبيعياً تقريباً ، مع السرطان المُعالج كمرض مزمن .

في كلّ الحالات ، يُنقّص حِمْل/عِبء الخلايا الورمية بدئياً (تُزال كتلته) ، إمّا بالجراحة و/أو التشعيع ، متبوعاً بمعالجة كيميائيّة ، ومناعية ، ومعالجة تستعمل مُعدّلات بيولوجيّة ، أو بتوليف هذه الوسائل العلاجية .

In advanced stages of cancer, the likelihood of controlling the cancer is unlikely, and the goal is palliation (alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not extend survival. The goal of treatment should always be kept in mind, as it often influences treatment decisions. Figure 35.4 illustrates how treatment goals can be dynamic. **2. Indications for treatment:** Chemotherapy is sometimes used when neoplasms are disseminated and are not amenable to surgery.

Chemotherapy may also be used as a **supplemental treatment** to attack micrometastasis following surgery and radiation treatment, in which case it is called **adjuvant chemotherapy**. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as **neoadjuvant chemotherapy**, and chemotherapy given in lower doses to assist in prolonging remission is known as **maintenance chemotherapy**.

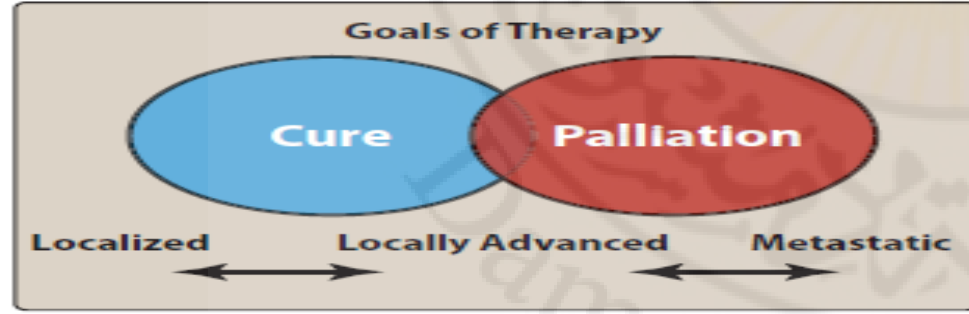


Figure 35.4

Goals of treatment with chemotherapeutic agents. Reprinted and amended with permission from Dr. Thomas George, MD.

تتمثل الغاية في المراحل المتقدمة من السرطان في التلطيف (تفريغ الأعراض وتفادي السمية المهددة للحياة). أي يمكن استعمال المعالجة الكيميائية لتفريغ أعراض السرطان وتحسين جودة الحياة ، رغم أن الأدوية لا تطيل البُقيا . ينبغي وضع غاية المعالجة دوماً في الذهن .. يوضح الشكل ٣٥ . ٤ كيف تكون غايات المعالجة ديناميكية .

٢. توصيات من أجل المعالجة : تستعمل المعالجة الكيميائية أحياناً عندما تكون الأورام مُنتشرة وغير مطواعة للجراحة . قد تستعمل أيضاً كمعالجة تكميلية (إضافية) لتهاجم النقائل المجهريّة بعد الجراحة والمعالجة بالتشعيع (معالجة كيميائية مساعدة) . تعطى قبيل الجراحة كمحاولة هدفها انكماش السرطان (معالجة كيميائية مساعدة مُحَدَّثَة) ، وتعطى بجرعات أصغر لتساعد في إطالة الهدأة (معالجة كيميائية مداومة/صيانة) .

A

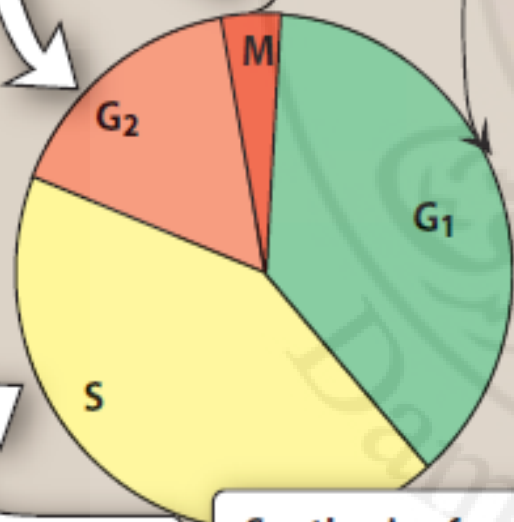
The cell cycle

Synthesis of cellular components required for mitosis

Resting state (cell is not dividing)

Mitotic phase (cell divides)

G₀



DNA is replicated

Synthesis of enzymes needed for DNA synthesis

3. Tumor susceptibility and the growth cycle: The fraction of tumor cells that are in the replicative cycle (“growth fraction”) influences susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to chemotherapy, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nondividing cells (those in the G₀ phase; Figure 35.5) usually survive the toxic effects of many chemotherapeutic agents.

a. Cell cycle specificity of drugs: Both normal cells and tumor cells go through growth cycles (Figure 35.5).

٣. حَسَاسِيَّة (اِسْتَعْدَاد) الورم ودورة النمو :

تؤثر نسبة خلايا الورم التي تكون في دورة التضاعف (نسبة النمو) في الحساسية تجاه معظم أدوية المعالجة الكيميائية للسرطان .

الخلايا السريعة الانقسام أكثر حساسية للمعالجة الكيميائية . تنجو الخلايا غير

المنقسمة (تلك التي في الطور —ج ٠؛ الشكل ٣٥. ٥—أ) عادةً من التأثيرات السامة للكثير من أدوية المعالجة الكيميائية .

أ. نوعية الأدوية للدورة الخلوية : تذهب

الخلايا الطبيعية والورمية عبر دورات نمو (الشكل ٣٥. ٥—أ) .

B

Cell cycle-specific drugs

Antimetabolites
 Bleomycin
 Etoposide
 Vinca alkaloids



Effective for high-growth-fraction malignancies such as hematologic cancers

C

Cell cycle non-specific drugs

Alkylating agents
 Antibiotics
 Cisplatin
 Nitrosoureas



Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are dividing) are said to be cell cycle-specific (Figure 35.5), whereas other agents are cell cycle-nonspecific. Although the nonspecific drugs generally have greater toxicity in cycling cells, they are also useful against tumors that have a low percentage of replicating cells.

قد يختلف عدد الخلايا في المراحل المتنوعة من الدورة في النسيج الطبيعية والتنشؤية (الورمية). تُدعى الأدوية الفعالة فقط ضد الخلايا المتكررة (الخلايا المنقسمة) نوعية—الدورة الخلوية (الشكل ٣٥. ٥-ب)، لكن بقية الأدوية غير نوعية—الدورة الخلوية (ج) (تظل سميتها الأكثر في الخلايا الدائرة وتفيد ضد الأورام ذات نسبة التكرار/التضاعف القليلة).

b. Tumor growth rate: The growth rate of most solid tumors is initially rapid, but growth rate usually decreases as the tumor size increases (Figure 35.3). This is due to a deficiency of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Tumor burden can be reduced through surgery, radiation, or use of cell cycle–nonspecific drugs that promote the remaining cells into active proliferation, thus increasing susceptibility to cell cycle–specific chemotherapeutic agents.

B. Treatment regimens and scheduling. Drug dosages are usually calculated on the basis of the body surface area, in an effort to tailor the dosage to each patient.

ب. معدل نمو الورم : سريع بدئياً لمعظم الأورام الصلبة ، لكنه ينقص عادةً مع زيادة حجم الورم .. سبب ذلك عوز التغذية والتغذويات والأكسجين جرّاء التوعية الدموية غير الكافية وقلة دوران الدم . يمكن إنقاص عبء (حِمل) الورم بالجراحة والتشعيع ، أو باستعمال الأدوية غير النوعية—للدورة/الدورة الخلوية ممّا يعزز الخلايا الباقية في تكاثر نشط ، وبالتالي زيادة الحساسية لأدوية المعالجة الكيميائية النوعية—للدورة الخلوية .

ب. **تدابير وجدولة المعالجة :** تُحسَب جرعات الدواء عادةً على أساس مساحة سطح الجسم ، كجهد لتفصيل تَقْدِيرُ الجُرْعَات لكل مريض .

2. Log kill phenomenon:

{{ The log kill is an important concept to understand. The anticancer drugs kill a constant fraction of cells instead of absolute number.}}

The anticancer drugs act by first-order kinetics.. This means that a constant fraction of the cells (say, 50%) are killed by one dose.. The number of tumor cells is usually expressed in exponential.. The drug that reduces the tumor cell load from 10^8 cells to 10^5 cells is said to have achieved a 3 log kill .

٢. ظاهرة القتل اللوغاريتمي :

{{القتل اللوغاريتمي مفهوم مهم إدراكه . إذ أنّ الأدوية المضادة للسرطان تقتل نسبة ثابتة من الخلايا بدلاً من عدد مُطلق}}} .

تعمل الأدوية المضادة للسرطان بحرائك الرتبة-الأولى .. هذا يعني أنّ نسبة ثابتة من الخلايا (ولنقل ، ٥٠%) تُقتل بجرعة واحدة .. يُعبّر عن عدد خلايا الورم عادةً أُسيّاً .. الدواء الذي ينقص حمل خلايا الورم من 10^8 خلية إلى 10^5 خلية يقال أنّه أنجز قتل لوغاريتمي—٣ (3—log kill) .

c. Treatment protocols: Many cancer treatment protocols have been developed, and each is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called R-CHOP, used for the treatment of non-Hodgkin lymphoma, consists of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone. Therapy is scheduled intermittently to allow recovery or rescue of the immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection.

بروتوكولات المعالجة : كل منها لحالة تنشؤية/ورمية خصوصية . تعرف عادةً بترخيمَة (لفظة مشتقة من الحروف الأوائل لعبارة ما) . مثال ، التدبير الشائع المسمّى **R-CHOP** ، يستعمل لمعالجة اللَمْفُومَةُ اللاهودجكينية ، يتكوّن من :

rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone.

تجري جدولة **المعالجة على نحو متقطع** للسماح بتحسّن جهاز المناعة أو إنقاذه ، الجهاز الذي يتأثر أيضاً بأدوية المعالجة الكيميائية ، بهذا نقص اختطار العدوى الخطرة .

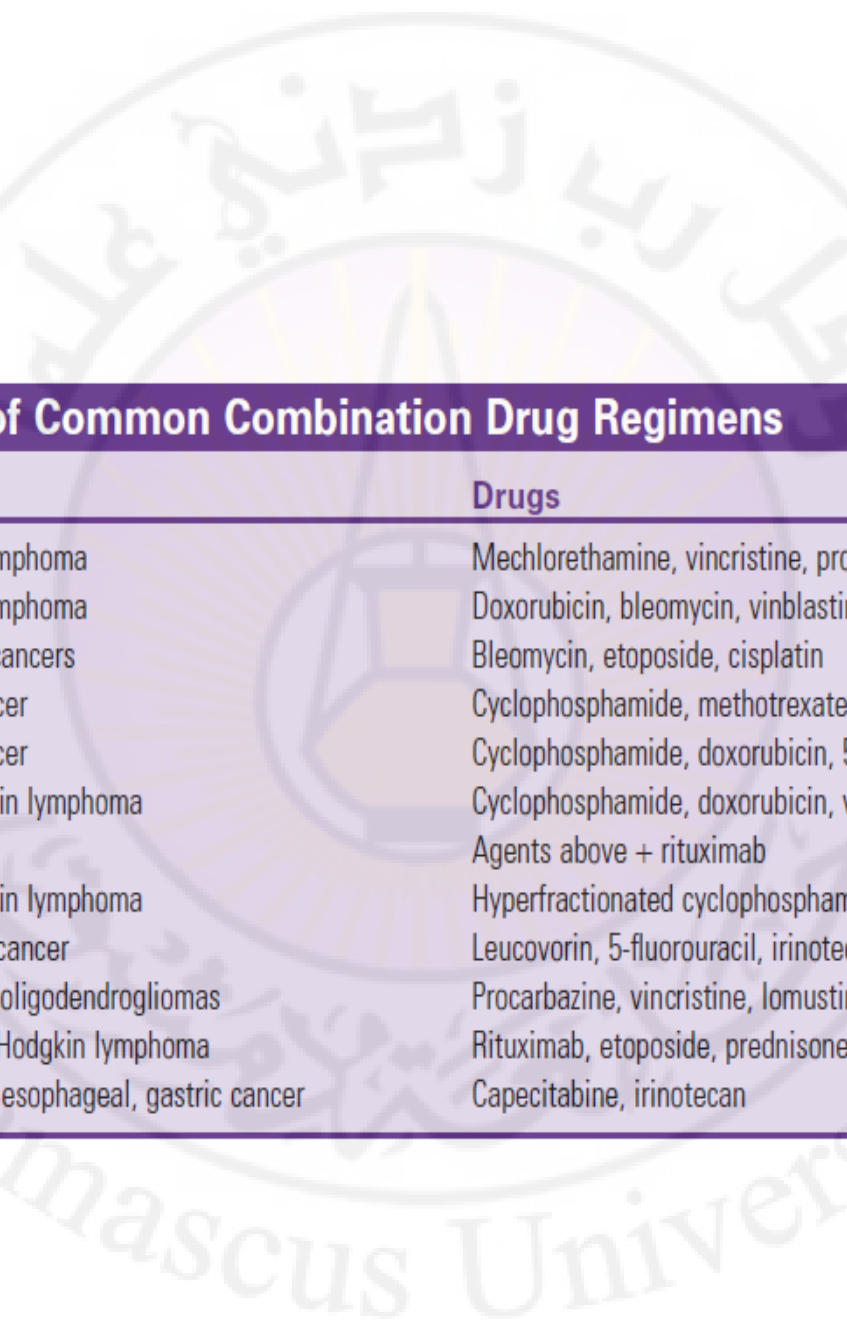


TABLE 67.1 Examples of Common Combination Drug Regimens

Terminology	Cancer	Drugs
MOPP	Hodgkin lymphoma	Mechlorethamine, vincristine, procarbazine, prednisone
ABVD	Hodgkin lymphoma	Doxorubicin, bleomycin, vinblastine, dacarbazine
BEP	Germ cell cancers	Bleomycin, etoposide, cisplatin
CMF	Breast cancer	Cyclophosphamide, methotrexate, 5-fluorouracil
CAF	Breast cancer	Cyclophosphamide, doxorubicin, 5-fluorouracil
CHOP	Non-Hodgkin lymphoma	Cyclophosphamide, doxorubicin, vincristine, prednisone
CHOP-R		Agents above + rituximab
Hyper-CVAD	Non-Hodgkin lymphoma	Hyperfractionated cyclophosphamide, vincristine, adriamycin, dexamethasone
FOLFIRI-Cetuximab	Colorectal cancer	Leucovorin, 5-fluorouracil, irinotecan, cetuximab
PVC	Anaplastic oligodendrogliomas	Procarbazine, vincristine, lomustine
R-EPOCH	B-cell non-Hodgkin lymphoma	Rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin
XELIRI	Colorectal, esophageal, gastric cancer	Capecitabine, irinotecan

C. Resistance and toxicity with chemotherapy. Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1. Resistance: Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a drug by mutating, particularly after prolonged administration of suboptimal doses. The development of drug resistance is minimized by short term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population.

المقاومة والسُميّة مع المعالجة الكيميائية : أدوية السرطان ذيفانات تمثّل تهديد مميت للخلايا . لهذا طوّرت الخلايا اليّات دفاعية لحماية ذاتها من الذيفانات الكيميائية ، متضمنةً أدوية المعالجة الكيميائية .

١. المقاومة : بعض خلايا الورم (مثل الورم الميلانيني / الميلانوم) مقاومة بالوراثة لمعظم أدوية السرطان .

قد تكتسب أنماط ورم مقاومة للتأثيرات السامة للخلية بطفرة ، خصوصاً بعد إعطاء جرعات دون الأمثل فترة كبيرة .

يمكن تصغير تطور مقاومة الدواء بالمعالجة **المكثفة المتقطعة القصيرة الأجل** بتوليف من الأدوية . التوليفات الدوائية فعّالة أيضاً ضد مجال أوسع من الخلايا المقاومة في مجموع الورم .

{{المقاومة الدوائية للأدوية المضادة للسرطان مشابهة لمقاومة مضادات المكروبات}} .

2. Multidrug resistance: Stepwise selection of an amplified gene that codes for a transmembrane protein (**P-glycoprotein** for “permeability” glycoprotein; Figure 35.6) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate– dependent pumping of drugs out of the cell in the presence of **P-glycoprotein**. Cross-resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the **Vinca alkaloids** are also resistant to *dactinomycin* and to the *anthracycline* antibiotics, as well as to *colchicine*, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH.

٢. مقاومة تعديد الأدوية : يُعدّ الانتقاء التدريجي لمورثة مضخمة تُشَفِّر لبروتين عبر الغشاء (البروتين السَّكْرِي—**P**) من أجل “النفاذية” ؛ (الشكل ٣٥. ٦) مسؤولاً عن مقاومة تعديد الأدوية . سبب هذه المقاومة هو ضخ الأدوية المُعْتَمِد على—ثلاثي فُسْفَات الأدينوزين إلى خارج الخلية في وجود الـ **P-glycoprotein** .

ثمّة مقاومة—مُتَصَالِبَة أيضاً بعد استعمال أدوية غير متعلقة ببنية الدواء . مثال ، الخلايا المقاومة للتأثيرات السامة للخلية **لقلوانيات العناقية** تكون مقاومة أيضاً **لداكتينوميسين** والآنتراسيكلينات و**الكولشيسين** ، والعكس صحيح . كلّ هذه الأدوية موجودة طبيعياً ، ولكلّ منها حلقة أروماتية كارهة للماء وشحنة موجبة في الباهاء المعتدلة .

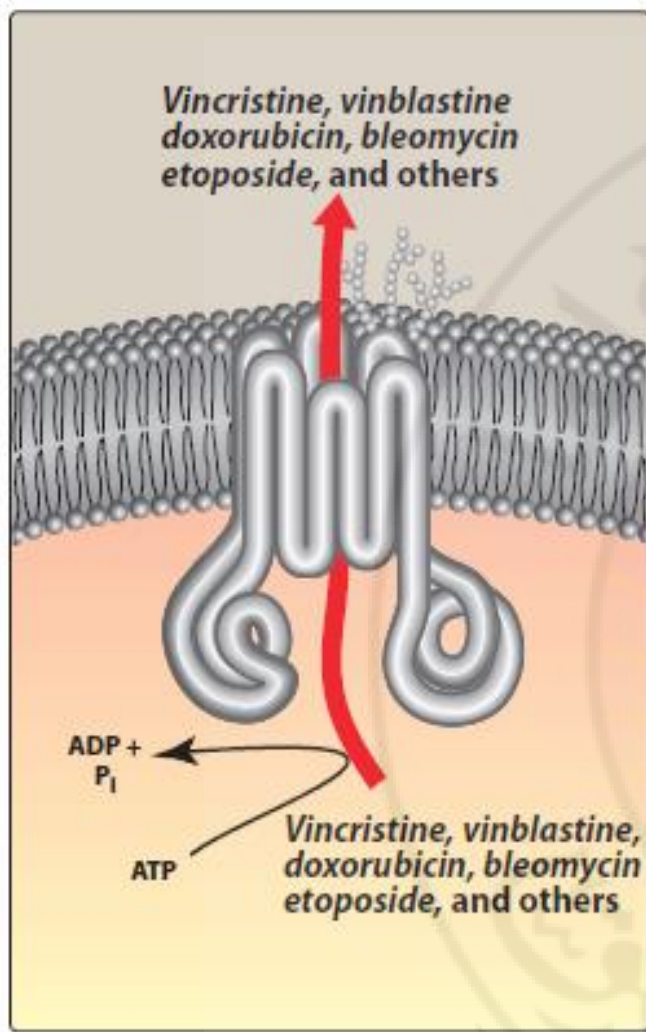


Figure 35.6

The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell. Modified from N. Kartner, and V. Ling, Sci. Am. (1989).

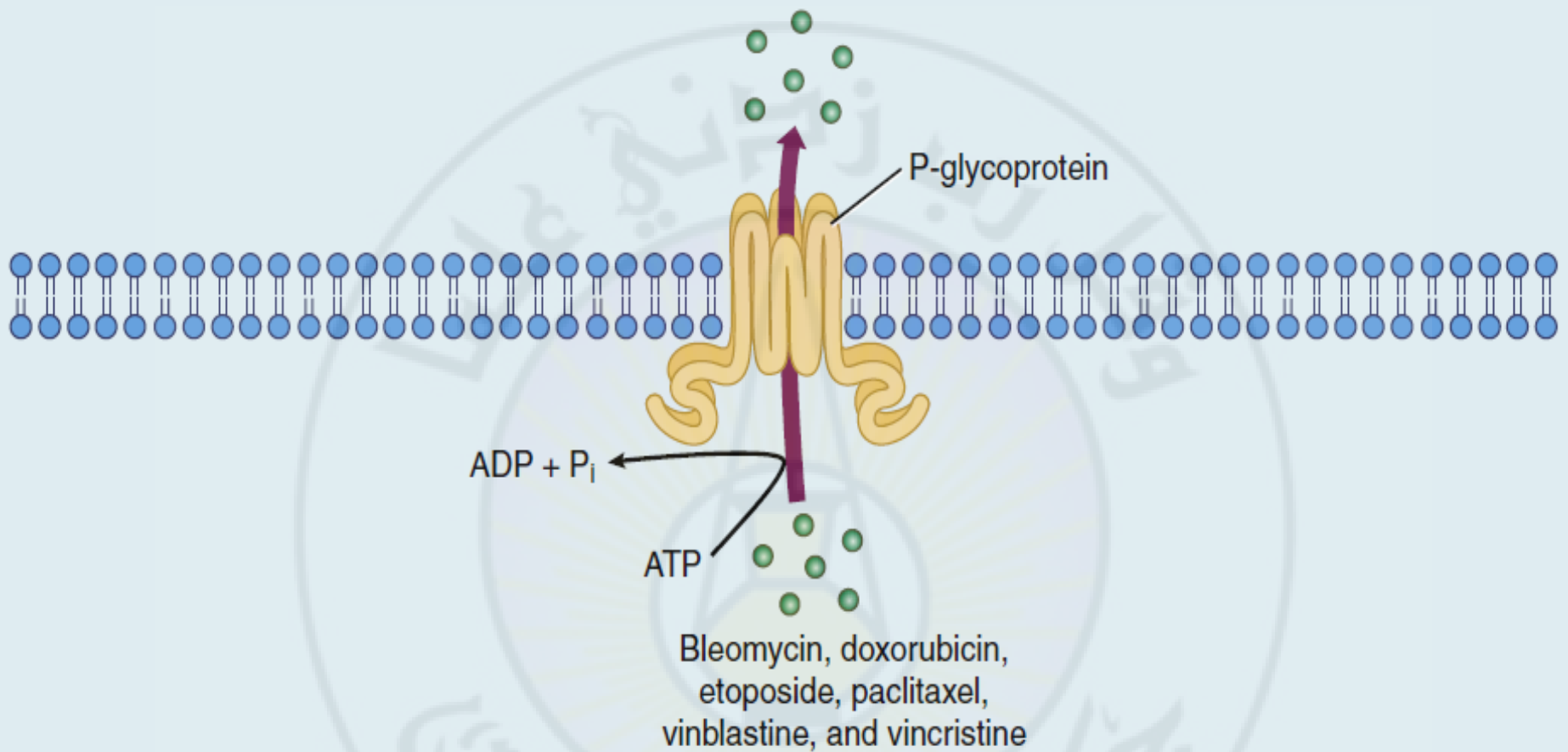


Fig. 45.2 The P-glycoprotein (Pgp) mechanism of drug efflux. Pgp uses adenosine triphosphate to actively export bleomycin and many other naturally occurring antineoplastic drugs from the cell. Because some agents (e.g., verapamil) inhibit the Pgp pump and thereby allow antineoplastic drugs to stay in the cell, these agents are being studied as potential adjuncts to cancer chemotherapy. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate.

[Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, *verapamil*) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. The third-generation P-gp inhibitor, elacridar, has been found to be an efficient inhibitor of [human breast cancer resistance protein \(BCRP\)](#); however, clinical translation of the promise is yet to be demonstrated not just for elacridar but also for other P-gp inhibitors in this class.

(ملاحظة : يجري التعبير عن الـ **P-glycoprotein** طبيعياً بمستويات قليلة في معظم أنماط الخلايا ، لكن المستويات الأكبر توجد في الكلية والكبد والبنكرياس والمعي الدقيق والقولون وغدة الكظر . يقترح أنّ وجود هذا البروتين مسؤول عن المقاومة الداخلية المنشأ للمعالجة الكيميائية الملاحظة مع السرطانات الغُدِّيّة) .

بعض الأدوية (مثل **فيراباميل**) تثبط بالتراكيز الكبيرة هذه المضخة وبالتالي تعترض إخراج الدواء المضاد للسرطان . لكن هذه الأدوية غير مرغوبة بسبب تأثيراتها الضائرة .

مثبط الـ **P-gp** من الجيل—الثالث ، الـ **elacridar** ، مثبط كُفء لبروتين مقاومة سرطان الثدي البشري (**BCRP**) ؛ على كل حال ، يجب إثبات الترجمة السريرية لهذا الأمل ليس فقط من أجل الـ **elacridar** ، لكن أيضاً لباقي مثبطات الـ P-gp في هذا الصنف .

3. Toxicity: Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy. Common adverse effects: Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 35.7), whereas other adverse reactions are confined to specific agents, such as bladder toxicity with cyclophosphamide, cardiotoxicity with doxorubicin, and pulmonary fibrosis with *bleomycin*. *The duration of the adverse effects* varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities can be irreversible.

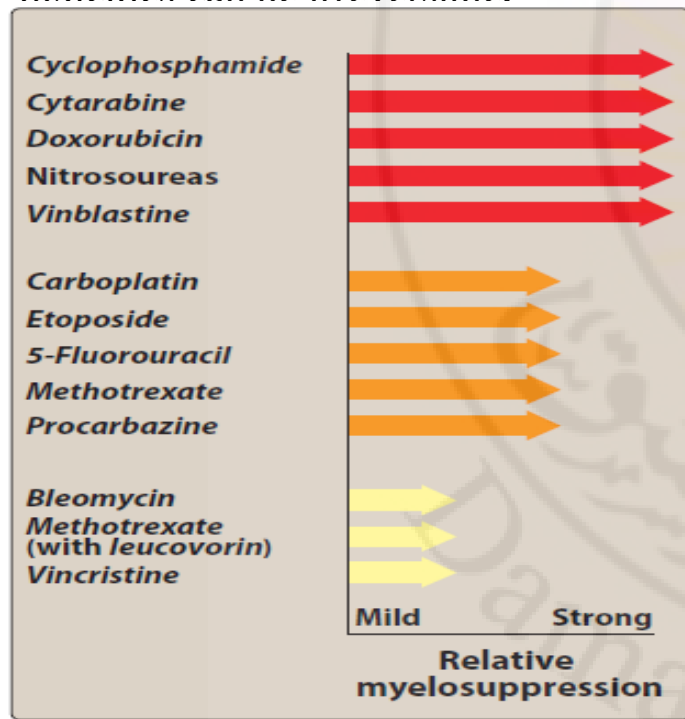


Figure 35.7

Comparison of myelosuppressive potential of chemotherapeutic drugs.

٣. السُمِّيَّة : المعالجة التي تبغى قتل خلايا السرطان السريعة الانقسام تؤثر أيضاً على الخلايا الطبيعية المتكاثرة بسرعة (مثل مخاطية الشدق و نقي العظم والمخاطية الهضمية وجريبات الشعر) ، مساهمة بالمظاهر السامة للمعالجة الكيميائية .

أ. التأثيرات الضائرة الشائعة : المنسب العلاجي لمعظمها ضيق . يحدث قيء شديد والتهاب فم وكبت نقي العظم (شكل ٣٥. ٧) وثعلبة .. يُضَبِّط القيء عادةً بمضاداته .

بعض الأضرار نوعية مثل سُمِّيَّة المثانة مع سيكلوفسفاميد و سُمِّيَّة القلب مع دوكسوروبيسين ، و تليف الرئة مع بليوميسين .. قد تكون السُمِّيَّات الثلاثة الأخيرة لا عكوسة . للبوسلفان Busulfan سُمِّيَّة رئوية أيضاً .

{{معظم الأدوية المضادة للسرطان تضر بحويصلات الشعر وتسبب فقد الشعر}}} .

هذا صحيح خصوصاً مع الـ cyclophosphamide والـ doxorubicin والـ vincristine والـ methotrexate والـ dactinomycin .

{{يعد تضرر النبيب الكلوي التأثير الجانبي الرئيس للـ cisplatin والجرعة الكبيرة من الـ methotrexate . يستطيع الـ Cyclophosphamide أن يسبب التهاب المثانة النزفي}}} .

الضرر الكلوي غير شائع بعد استعمال الأدوية المضادة للسرطان ؛ لكنّه تأثير جانبي مهم لبعض الأدوية الواجب تعلمها . يوصى بالتمية الكافي مع كثير من هذه الأدوية .

{{يتربط تسمم القلب مع استعمال الـ doxorubicin والـ daunorubicin (الأنتراسيكلينات)}}} . "D-rubicins" .

{{يسبب الـ Bleomycin تليف رئوي ، قد يكون مميتاً}}} .

{{الـ Vincristine معروف بسميته للجهاز العصبي}}} .

ثمة تقارير عن سمية عصبية للجرعة الكبيرة من آيفوسفاميد ، ربما بسبب المستقلب chloroacetaldehyde .

b. Minimizing adverse effects: Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, local perfusion of the tumor (for example, a sarcoma of the arm), removal of some marrow of the patient prior to intensive treatment and then reimplantation afterwards, or intensive hydration and diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with methotrexate can be effectively counteracted by administering folinic acid (leucovorin). With the availability of human granulocyte colony– stimulating factor (filgrastim), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.

4. Treatment-induced tumors: Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.] Most tumors that develop from cancer chemotherapeutic agents respond well to treatment strategies.

ب. تصغير التأثيرات الضائرة : باستخدام أدوية حاصنة للخلية ، وإرواء موضعي للورم (مثل ساركوما الذراع) ، وإزالة بعض النقي من المريض قبيل المعالجة المركزة ثم إعادة الزرع بعد ذلك ، أو إمهاء مركزة و إدرار البول لمنع سميات المثانة .

يمكن اعتراض فقر الدم الضخم الأرومات الحادث بالميثوتريكسات بإعطاء حامض الفولينيك (لوكوفورين) .

يمكن اعتكاس قلة العدلات المترابطة مع أدوية سرطان كثيرة جزئياً بتوفير العامل المنبه للمستعمرات المحببة البشري (filgrastim) .

المركابتوايثانسلفونات **Mercaptoethanesulfonate(mesna)** “يحتبس” الأكرولين المنطلق من السيكلوفوسفاميد فينقص حدوث التهاب المثانة النزفي .

يثبط **الديكسرازوكسان dexrazoxane** تكوين الجذور الحرة ويمنح حماية ضد تسمم القلب بالأنثراسيكلينات (مثل الدوكسوروبيسين) .

٤. **الأورام المحرّضة—بالمعالجة (خصوصاً مع العوامل المؤلّكة) :** قد تحدث أورام (مثل ابيضاض غير لمفاوي حاد) بعد ١٠ سنوات أو أكثر من شفاء السرطان الأصلي لأن معظم مضادات الورم مُطَفِّرات . معظم الأورام المحرّضة بأدوية السرطان تستجيب جيداً لاستراتيجيات المعالجة .

III. ANTIBIOTICS .

The antitumor antibiotics (Figure 35.14) owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to **intercalation**, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cell cycle–nonspecific, with *bleomycin* as an exception.

ثالثاً. الصادّات : تمارس الصادّات المضادة

للورم فعلها السام للخلية بتأثيراتها مع الدنا ،
فتعرقل وظيفته . إضافةً لإقحامها في الدنا
تثبط المصاوغين التمزّعين الـ

topoisomerases (I , II) وتنتج جذور
حرّة تساهم في تأثيراتها السامة للخلايا .

غير نوعيّة—لدورة الخلية ، باستثناء الـ

bleomycin .

ANTIBIOTICS
Bleomycin
Daunorubicin
Doxorubicin
Epirubicin
Idarubicin
Mitoxantrone
Actinomycin D (dactinomycin)
Mitomycin C
Bleomycin

أ. الأنتراسيكلينات : الـ **Doxorubicin** (المُشابه المهدركس للداونوروبيسين) والـ

daunorubicin والـ **Idarubicin** والـ **epirubicin** ، والـ **mitoxantrone**.

يستعمل الدوكسوروبيسين بالتوليف لمعالجة ضرب من الساركومة ، متضمنة الثدي

والرئة ، ومعالجة الالبيضاخ للمفاوي الحاد واللمفومات . يستعمل الـ Daunorubicin

والـ idarubicin لمعالجة الالبيضاخ الحاد والـ mitoxantrone لسرطان البروستاتة .

١. آلية الفعل : الأنتراسيكلينات تُقَحَم بين الأسُس في الدنا

المزدوج—الطاق ، تثيط/تسمم توبوايزوميراز—II الدنا ،

تولد جذور حرة أكسجينية وجذور حرة شبه/نصف كينونية .

ربما أيضاً تعرقل سيولة الغشاء الخلوي (تخل بنقل الأيون) .

للتوبوايزوميراز—٢ دور في تضاعف الدنا وضروري

لتفريق الكروموزوم .. (الشكل ٣٥ . ١٥) .

٢. التأثيرات الضائرة : السمية القلبية الالاعكوسة المعتمدة—

الجرعة هي التفاعل الضائر الأخطر وخصوصاً مع

الداونوروبوسين والدوكسوروبوسين . سبب هذه السمية توليد

جذور حرة وببيروكسيد شحمي . إضافة التراستوزوماب إلى

بروتوكولات الدوكسوروبيسين أو الإبيروبيسين يزيد فشل

القلب الاحتقاني .

ثمّة بعض النجاح مع خالب الحديد الـ **dexrazoxane** في

التحصين ضد السمية القلبية للدوكسوروبيسين .

الدوكسوروبيسين المُمَحَفَظ—بالليبوزوم أقل سميّة للقلب من

المستحضر المعياري .

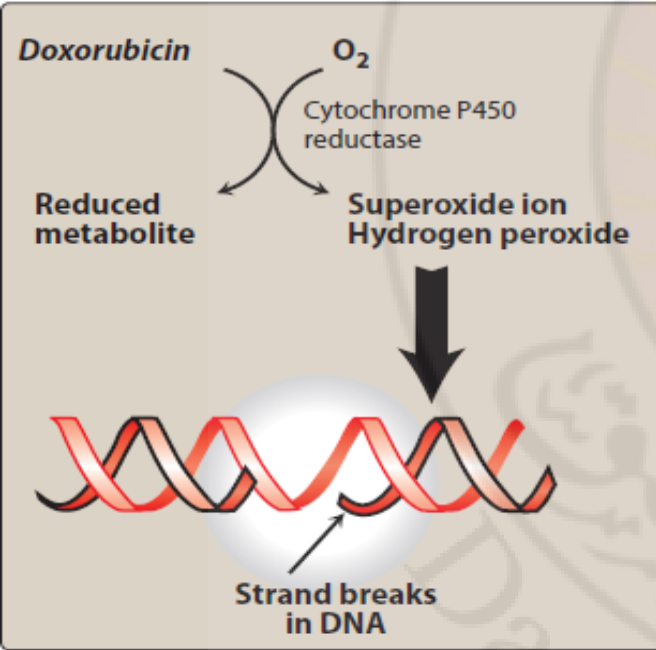
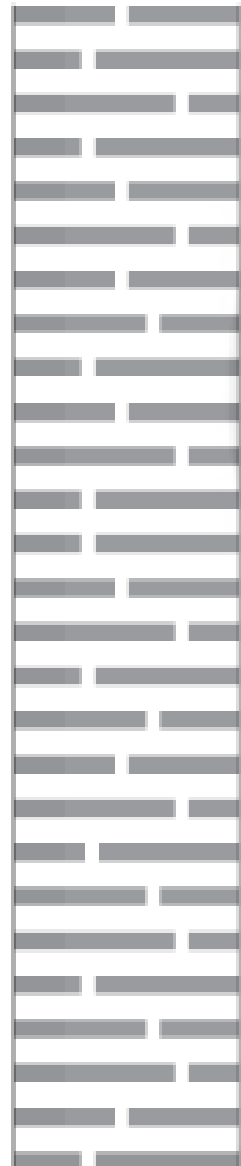


Figure 35.15

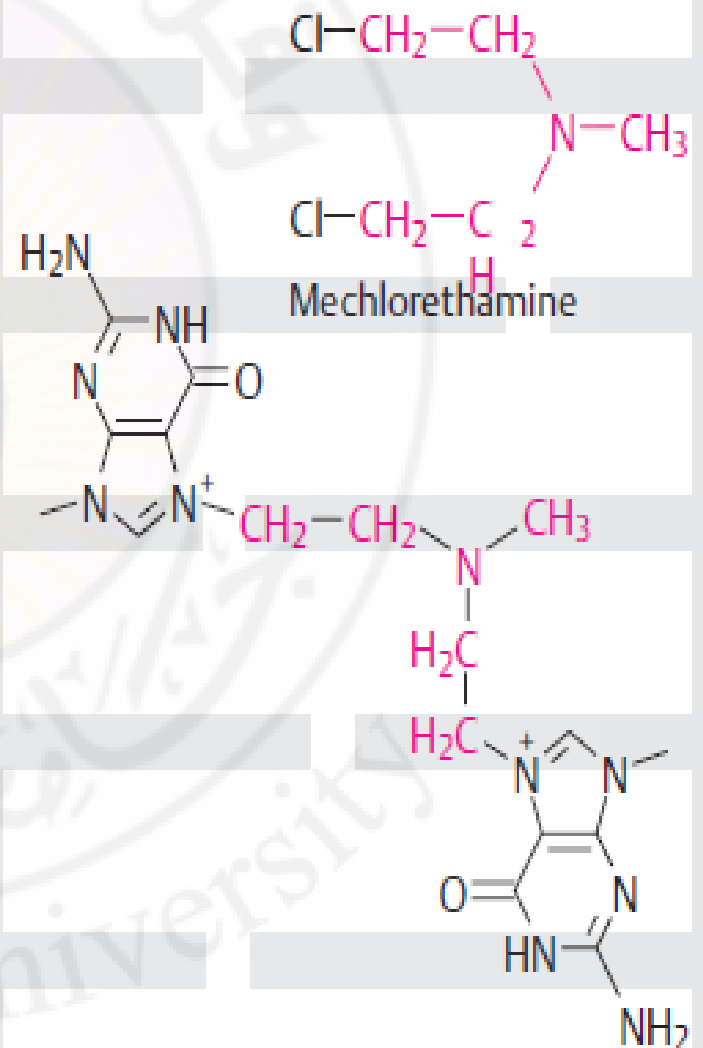
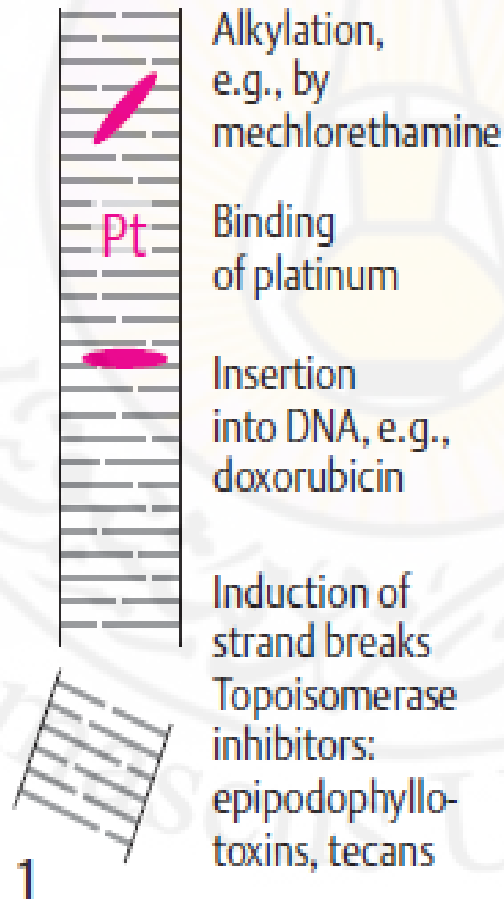
Doxorubicin interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

A. Cytostatics: alkylating agents and cytostatic antibiotics (1),
inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)

DNA



Damage
to template



B. **Bleomycin** is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. Bleomycin is cell cycle-specific and causes cells to accumulate in the G2 phase. It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma. **Mechanism of action:** A DNA-bleomycin- Fe^{2+} complex appears to undergo oxidation to bleomycin- Fe^{3+} . The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 35.16).

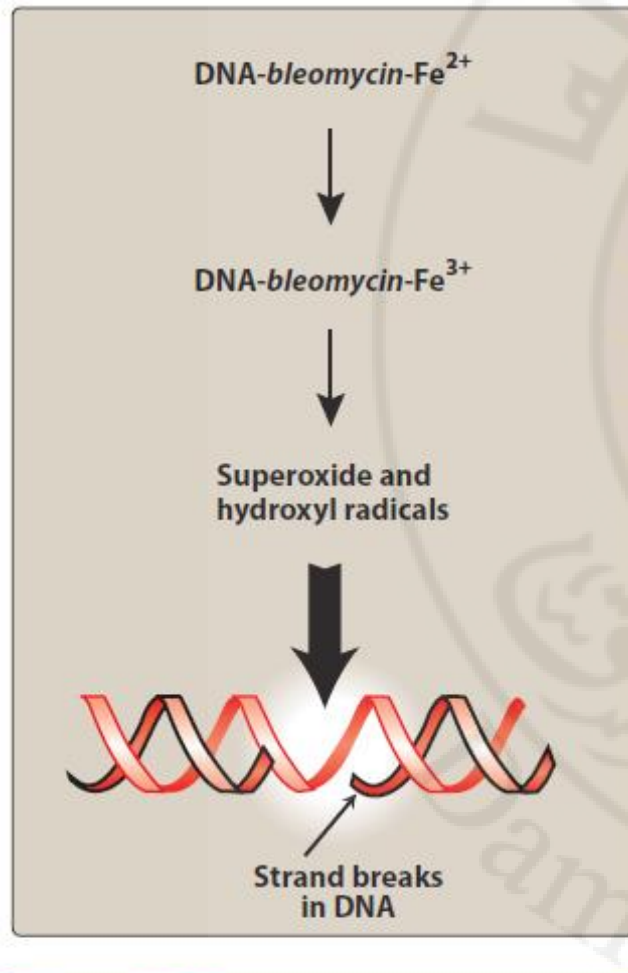


Figure 35.16

Bleomycin causes breaks in DNA by an oxidative process.

ب. **Bleomycin** : مزيج من ببتيدات سُكَّرِيَّة خَالِبَة لِلنحاس ، مثل الأنتراسيكلينات الصادّة ، تسبب شق/انقسام الدنا بعملية مؤكسدة . نوعي—لدورة الخلية ويسبب تراكم الخلايا في الطور—ج ٢ . يستعمل لمعالجة سرطانات الخصية و لمفوما هودجكن .

١، آلية الفعل : يَخضع المَرَكَّب $\text{DNA-bleomycin-Fe}^{2+}$ للأكسدة إلى bleomycin-Fe^{3+} . إذ تتفاعل الإلكترونات المحررة مع الأكسجين لتكوّن فوق أكسيد أو جذور هيدروكسيل ، التي تهاجم روابط الـ phosphodiester للدنا ، مؤديةً إلى انكسار الطاق (الشكل ٣٥ . ١٦) .

٢. التأثيرات الضائرة : السمية الرئوية هي التأثير الضائر الأخطر ، متروكة إلى تليف مميت أحياناً “رئة البليوميسين bleomycin lung” . تنتشر تبدلات الجلد الضخامية وفرط تصبغ اليدين . كبت النقي نادر مع البليوميسين .

C. Dactinomycin (actinomycin D) . *Dactinomycin (clear, gold-colored liquid) is a chromopeptide antibiotic first discovered for cancer. Most of the chromopeptides contain planar phenoxazone actinosin which is responsible for the color. Dactinomycin is used for the treatment of solid tumors in children and choriocarcinomas in adults. Dactinomycin is used alone or in combination with other agents in chemotherapy regimens. It is mostly used for the treatment of rhabdomyosarcoma and Wilm's tumor in children.*

1. Mechanism of action: *Dactinomycin binds to double-helical DNA and makes a complex. This complexation blocks the transcription of DNA by RNA polymerase. Dactinomycin, a potent anticancer agent, exhibits cytotoxicity by inhibiting all rapidly proliferating cancer cells*

ج. الـ (Dactinomycin (actinomycin D) :

١. آلية الفعل : يرتبط (يقحم) بالدنا الحلزوني—المزدوج ويكوّن معقد يمنع انتساخ الدنا ببوليميراز الرنا. يحرض أيضاً كسور الدنا الوحيدة الطاق ، ربما بإنتاج الجذور الحرة .

يستعمل لمعالجة الأورام الصلبة عند الأطفال والسرطانات المشيمائية

٢. التأثيرات الضائرة : يسبب كبت تكوين الدم مع قلة الكريات الشاملة (في الدم) .. يسبب التهابُ المُستقيم وإسهال و التهابُ اللسان و التهابُ الشفة وتقرحات و ثعلبة و غثيان وقهم وقياء (خلال ساعات من تناوله) . التسرّب أثناء الإعطاء الوريدي يسبب إصابة موضعية .

ACTIVE THROUGH HORMONAL PATHWAY

Estrogen and receptor modulators

Ethinyl estradiol

Diethylstilbestrol diphosphate
(fosfestrol)

Selective estrogen receptor modulators (SERMS)

Tamoxifen

Toremifene

Estrogen receptor down-regulators

Fluvestrant

Aromatase inhibitors

Letrozole

Anastrozole

Exemestane

Antiandrogen

Flutamide

Bicalutamide

Nilutamide

GnRH analogs

Leuprolide

Nafarelin

Goserelin

IV. STEROID HORMONES AND THEIR ANTAGONISTS

Tumors that are sensitive to steroid hormones may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; or 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or 3) both. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy—surgical removal of one or both testes—for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, treatment with the antiestrogen *tamoxifen* prevents estrogen stimulation of breast cancer cells; Figure 35.24). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 35.25A).

رابعاً . الهرمونات الستيرويدية ومناهضاتها : الأورام الحساسة لهذه الهرمونات إما (١) مستجيبة للهرمون ، يتراجع فيها الورم بعد معالجته بهرمون نوعي ؛ أو (٢) معتمدة على الهرمون ، إزالة الهرمون المنبه فيها يجعل الورم يتراجع ؛ أو (٣) كلاهما .

إزالة المنبهات الهرمونية من الأورام المعتمدة—الهرمون تتم بالجراحة (مثل استئصال الخصية—نزع جراحي لخصية أو اثنتين—للمرضى بسرطان البروستاتة المتقدم) أو بالأدوية (مثلاً، معالجة سرطان الثدي بالتاموكسيفين تمنع تنبيه الإستروجين لخلايا سرطان الثدي ؛ الشكل ٣٥ . ٢٤) . لكي يؤثر الهرمون بخلية يجب أن تمتلك مستقبلات داخل خلوية (عُصارية خلوية) نوعية لهذا الهرمون (الشكل ٣٥ . ٢٥ أ) .

A. Tamoxifen (estrogen receptors modulators). *Tamoxifen is a selective estrogen modulator (SERM)*. It is an estrogen antagonist in breast tissue and an agonist in other tissues, such as bone and the endometrium. *Tamoxifen is used for first-line therapy in the treatment of estrogen receptor-positive breast cancer. It is also used for prevention of breast cancer in high-risk women.* 1. Mechanism of action: *Tamoxifen competes with estrogen for binding to estrogen receptors in the breast tissue and inhibits estrogen-induced growth of breast cancer* (Figure 35.25B). The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed.

أ. **Tamoxifen** (من محورات مستقبلات الإستروجين

"SERM") : محور انتقائي لمستقبلات الإستروجين .
مناهض في نسيج الثدي و **ناهض في باقي النسيج** ، مثل
 العظم وبطانة الرحم . يستعمل خط -أول في معالجة
 سرطان الثدي الإيجابي—مستقبلات الإستروجين ولمنع
 سرطان الثدي عند النساء كثيرات—الاختطار .

١. **آلية الفعل** : يتنافس مع الإستروجين في الارتباط
 بمستقبلاته في نسيج الثدي فيثبط النمو المَحَرَّض—
 بالإستروجين (الشكل ٣٥ . ٢٥ ب) . النتيجة تثبيط
 تأثيرات الهرمون الطبيعي وغيره من عوامل النمو .

٢. **التأثيرات الضائرة** : هبات حرارية و غثيان وقياء وطفح
 جلد ونزف مهبلي ومفرزات مهبلية (بسبب الفعالية
 الإستروجينية للتاموكسيفين وبعض مستقبلاته في النسيج
 البطاني الرحمي) . قد يسبب **سرطان بطانة الرحم** و
 انصمام خثري ..

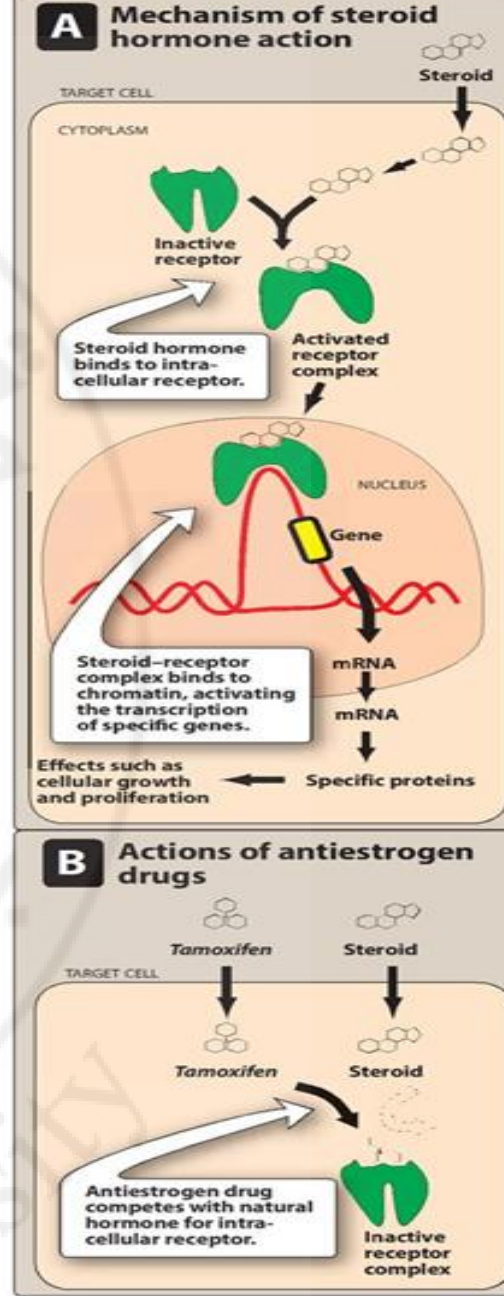


Figure 35.25

Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA.

B. Fulvestrant (IM) and raloxifen . Fulvestrant is an estrogen receptor antagonist , for patients with hormone receptor– positive metastatic breast cancer. *This agent binds to and causes estrogen receptor down-regulation on tumors and other targets.* Raloxifene is an oral SERM that blocks estrogen effects in the uterine and breast tissues, while promoting effects in the bone to inhibit resorption. This agent reduces the risk of estrogen receptor–positive invasive breast cancer in postmenopausal women. Both drugs are known to cause hot flashes, arthralgias, and myalgias.

C. Estrogens. A high dose of *estrogen is known to reduce testosterone levels through the negative feedback mechanism in the hypothalamo-hypophyseal axis.* The side effects associated with *estrogens are stroke, myocardial infarction, pulmonary embolism, impotence, and loss of libido in man while treating for prostate cancer.,* Considering the side effects associated with estrogens and availability of other safer alternatives, *estrogen therapy is not used. Diethylstilbestrol, a synthetic estrogen, and its phosphate derivative, fosfestrol, are used for treating prostate carcinoma .*

ب. (IM) Fulvestrant و raloxifen : الـ Fulvestrant مناهض لمستقبلات الإستروجين لسرطان الثدي النقيلي الإيجابي—مستقبلات الهرمون ... الـ raloxifen فموي يحصّر تأثيرات الإستروجين في نسيج الرحم والثدي ، بينما يعزز تأثيراته في العظم ليثبط الارتشاف. ينقص اختطار سرطان الثدي غير الغزوي الإيجابي—مستقبلات الإستروجين عند النساء بعد الإياس . الدواء ان يسببان هبّات حرارة وآلام مفاصل وعضلات .
ج. الإستروجينات : الجرعة الكبيرة تنقص مستويات التستوستيرون بآلية الارتجاع السلبي في المحور الوطائي—النخامي .

السكتة واحتشاء عضلة القلب والانسداد الرئوي والعنانة ونقص الشبق عند الرجال تأثيرات جانبية أثناء معالجة سرطان البروستاتة . لهذا لا تستعمل في وجود البدائل الأكثر مأمونية . يستعمل **Diethylstilbestrol** ، الإستروجين الصناعي ومشتقه الفسفاتي الـ **fosfestrol** لمعالجة سرطانة البروستاتة .

D. Aromatase inhibitors. The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

1. **Anastrozole** and **letrozole** are nonsteroidal aromatase inhibitors. These agents are considered first-line drugs for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. Anastrozole and letrozole do not predispose patients to endometrial cancer. Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

2. **Exemestane**: A steroidal, irreversible inhibitor of aromatase, exemestane, is well absorbed after oral administration and widely distributed. Hepatic metabolism occurs via the CYP3A4 isoenzyme. Because the metabolites are excreted in urine, the doses of the drug must be adjusted in patients with renal failure. Major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

د. مثبطات الأروماتاز : تفاعل الأروماتاز في الكبد والدهن والعضل والجلد ونسج الثدي ، متضمناً الخباثات مسؤول عن صنع الإستروجين خارج الكظر من الـ **androstenedione** ، فالأرتمة المحيطية مصدر مهم للإستروجين للنساء بعد الإياس . مثبطات الأروماتاز تنقص إنتاج الإستروجين عند هؤلاء النساء .

١. **Anastrozole** و **letrozole** مثبطان للأروماتاز لا ستيرويديان . خطـأول لعلاج سرطان الثدي بعد الإياس . فمويان .. لا يؤهبان المرضى لسرطان بطانة الرحم . يستقلبان في الكبد ويطرحان مع مستقلبتهما في البول .

٢. **Exemestane** : مثبط أروماتازستيرويدي غير عكوس ، يمتص من الهضم ويتوزع . يستقلب بالـ CYP3A4 . ينبغي ضبط الجرعة في فشل الكلية . يسبب غثيان وتعب وهبات حرارة . لوحظ حدوث ثعلبة/حاصة (فقد الشعر الموضّع) والتهاب الجلد .

E. Leuprolide, goserelin, and triptorelin (GnRH analogs) . GnRH is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones: 1) luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and 2) follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen. Leuprolide, goserelin ,and triptorelin , are synthetic analogs of GnRH. As GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen synthesis are reduced (Figure 35.26). Response to *leuprolide in prostatic cancer* is equivalent to that of orchiectomy with regression of tumor and relief of bone pain. These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer.

٥. Leuprolide و goserelin و triptorelin (مشابهة لـ GnRH) (مشابهات صناعية لـ GnRH) : يفرز الـ GnRH من الوطاء وينبه النخامة الأمامية لإفراز الهرموني الموجهتين للمناسل : (١) **LH** المنبه الأولي لإفراز التستوستيرون من الخصيتين ، و (٢) **FSH** ، المنبه لإفراز الإستروجين .

تحتل هذه الأدوية الثلاث مستقبلات GnRH في النخامة ، مما ينزع حساسيتها وبالتالي تثبيط إطلاق الموجهتين . هكذا ، ينقص تصنيع الأندروجين والإستروجين (الشكل ٣٥ . ٢٦) . الاستجابة للوبروليد في سرطان البروستات تعادل استئصال الخصية مع تراجع الورم وتفريج ألم العظم . تنفع للنساء قبل الإياس المصابات بسرطان ثدي متقدم وقد حلت محل الإستروجين في معالجة سرطان البروستات .

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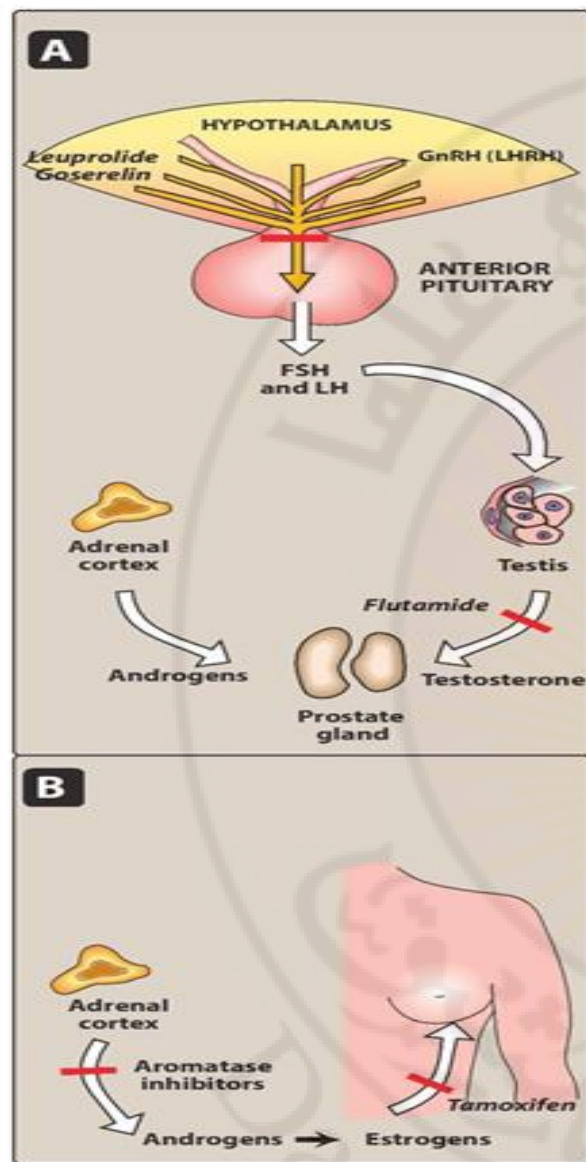


Figure 35.26

Effects of some anticancer drugs on the endocrine system. **A.** In therapy for prostatic cancer. **B.** In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; LHRH = luteinizing hormone-releasing hormone.

Leuprolide is available as

- 1) a **subcutaneous** daily injection,
- 2) a **subcutaneous depot** مَذْخَر injection, or
- 3) an **intramuscular depot** injection to treat metastatic carcinoma of the prostate.

Goserelin acetate is a **subcutaneous implant**, and **triptorelin pamoate** is **injected intramuscularly**. Levels of androgen in prostate cancer patients may initially rise, but then fall to castration levels.

The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

F. Antiandrogens. *Flutamide* [FLOO-ta-mide], *nilutamide* [nye-LOO-ta-mide], *bicalutamide* [bye-ka-LOO-ta-mide], and *enzalutamide* [enz-a-LOO-ta-mide] are oral antiandrogens used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its action in the prostate (Figure 35.24). Adverse effects include gynecomastia, constipation, nausea, and abdominal pain. Rarely, liver failure has occurred with *flutamide*. *Nilutamide* can cause visual problems. f

و. مضادات الأندروجين : Flutamide و nilutamide و bicalutamide و enzalutamide . فموية لمعالجة سرطان البروستاتة .

تتنافس مع الهرمون الطبيعي على الارتباط بمستقبل الأندروجين فتمنع فعله في البروستاتة.

تنادي الذكر والإمساك والغثيان وألم البطن تأثيراتها الضائرة . نادراً فشل الكبد مع الفلوتاميد . قد يسبب النيلوتاميد مشاكل بصرية .

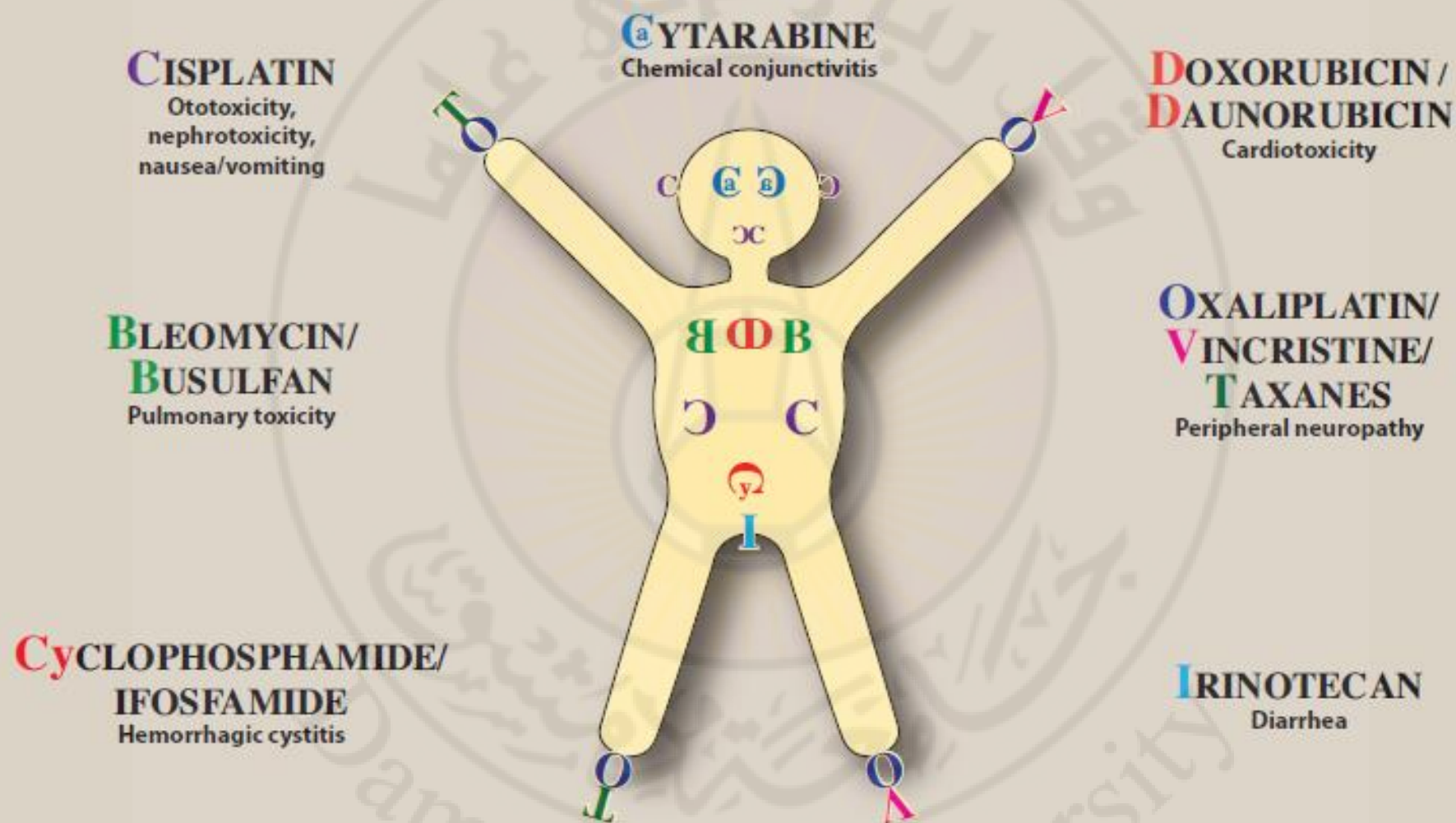


Figure 35.33
Chemo Man—a summary of toxicity of chemotherapeutic agents.

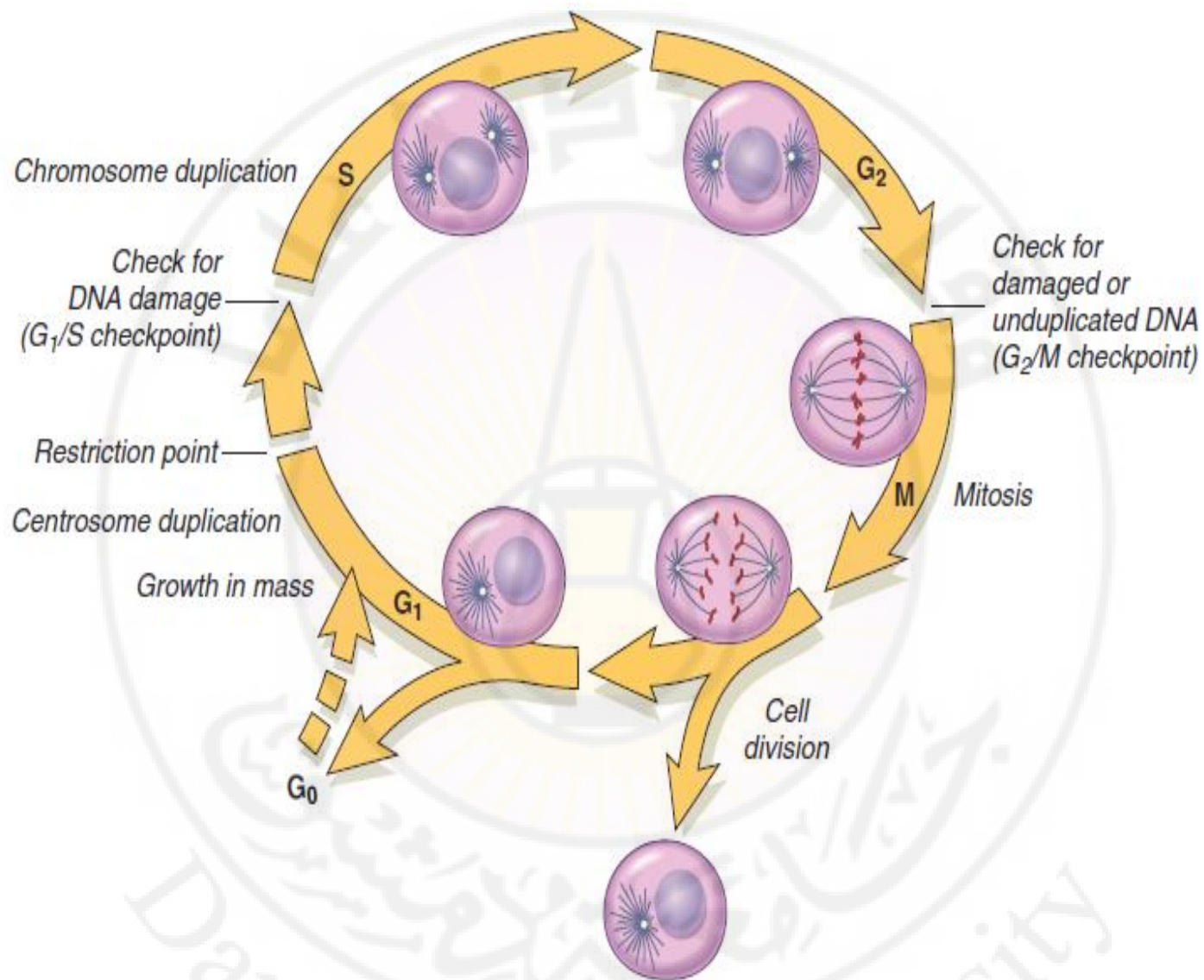


Fig. 1.17 Cell-cycle landmarks. The figure shows the cell-cycle phases (G₀, G₁, G₂, S, and M), the location of the G₁ restriction point, and the G₁/S and G₂/M cell-cycle checkpoints. G₁ restriction point refers to the phase in G₁ at which the cell gets committed to the cell cycle without further need of the growth factor that initiated cell division. Cells from labile tissues such as the epidermis and the gastrointestinal tract may cycle continuously; stable cells such as hepatocytes are quiescent but can enter the cell cycle; permanent cells such as neurons and cardiac myocytes have lost the capacity to proliferate. (Modified from Pollard TD, Earnshaw WC: Cell biology, Philadelphia, 2002, Saunders.)

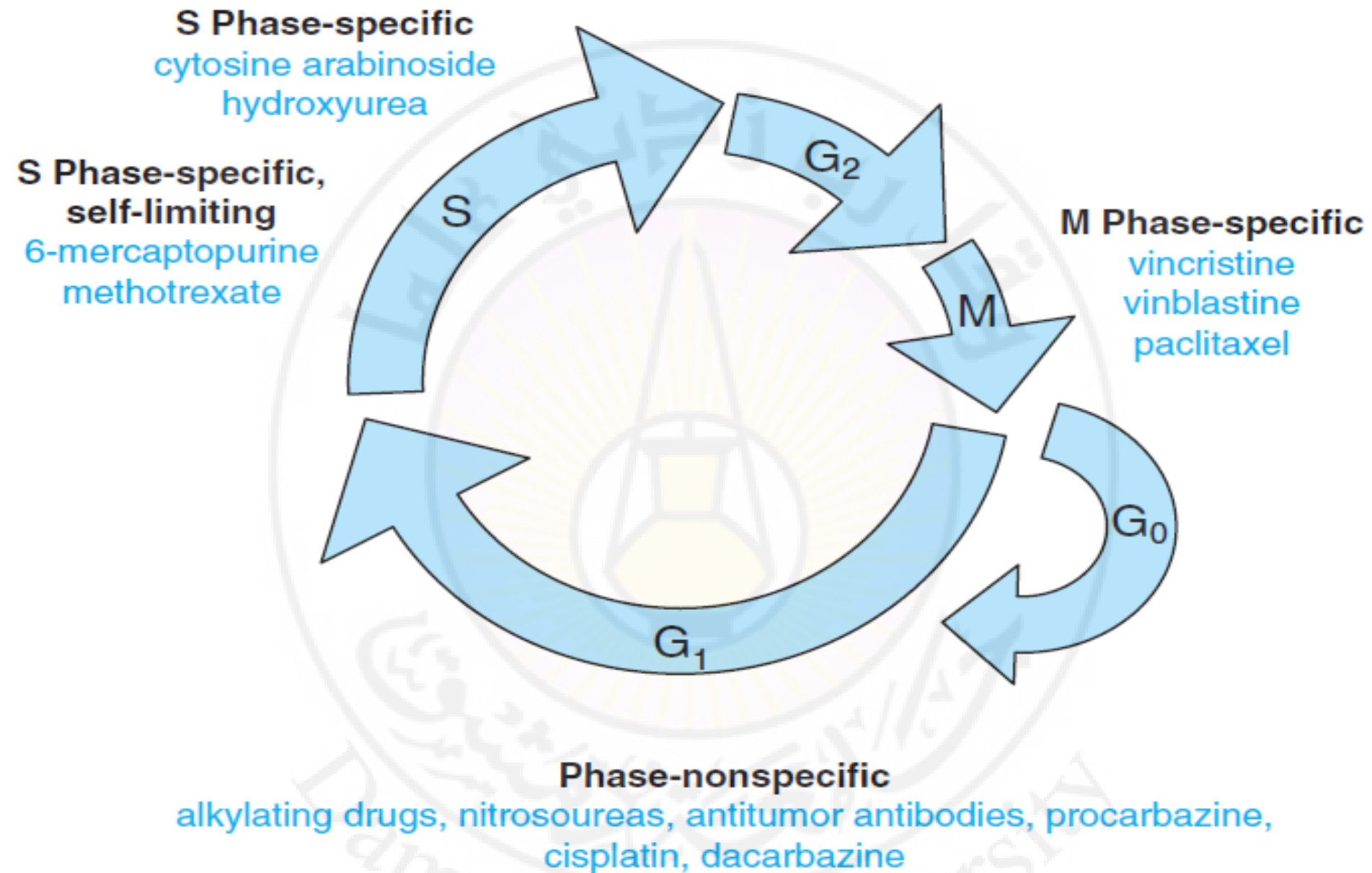


FIGURE 51-2 *The cell cycle and the relationship of antitumor drug action to the cycle.* G₁ is the gap period between mitosis and the beginning of DNA synthesis. Resting cells (cells that are not preparing for cell division) are said to be in a subphase of G₁, G₀. S is the period of DNA synthesis, G₂ the premitotic interval, and M the period of mitosis. Examples of cell cycle-dependent anticancer drugs are listed in *blue* below the phase in which they act. Drugs that are cytotoxic for cells at any point in the cycle are called phase-nonspecific drugs.

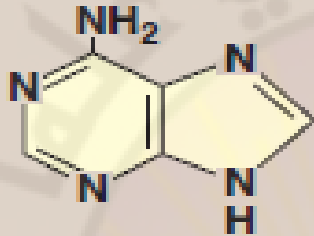
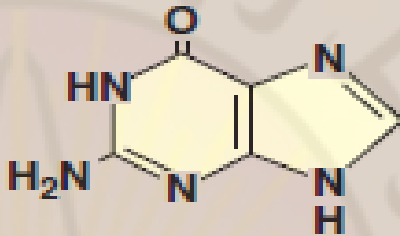
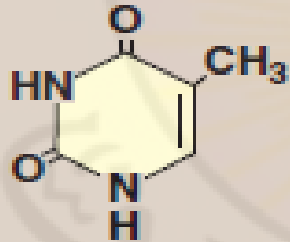
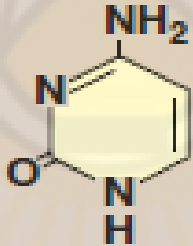
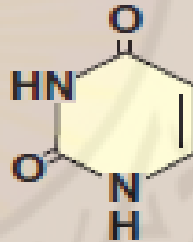
DNA and RNA Purines		
		
Adenine (A)	Guanine (G)	
RNA Pyrimidines		
		
Thymine (T)	Cytosine (C)	Uracil (U)
DNA Pyrimidines		

Figure 22.1
Purines and pyrimidines commonly found in DNA and RNA.

Angiogenesis inhibitors

: **Bevacitumab** ,
Sunitinib .

Protease inhibitors :

Bortezomib

EGF-receptor

inhibitors : **Cefitinib** ,
cefuximab

Anarmed mono clonal

antibodies :

Rituximab ,
trastuzomab .

Drug	Mechanism of Action ¹
Bortezomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway
Carfilzomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway; maintains activity in bortezomib-resistant tumors
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery
Ziv-aflibercept	Inhibits binding of VEGF-A, VEGF-B, and PlGF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis
Sunitinib, pazopanib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR- α and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis

Notice that two of the listed antibodies for CD20 (a B-cell antigen) have a radioactive label. The antibody brings the radiation to the tumor cells to increase specificity of the radiation. **Ibritumomab tiuxetan** is a combination molecule. The antibody is the ibritumomab piece that is bonded to the chelator tiuxetan. The chelator provides the binding site for the radioactive ligand .

الأضداد **ANTIBODIES**: يجري تطوير أضداد تستهدف تعبير البروتين في خلايا الورم لتحسين النوعية في معالجة السرطان . القائمة في الأعلى التالية عينة موجودة—مع الهدف البروتيني للضد :

alemtuzumab—CD^{٥٢};

bevacizumab—vascular endothelial growth factor (VEGF) ;

cetuximab—epidermal growth factor receptor (EGFR);

gemtuzumab ozogamicin—CD33;

ibritumomab tiuxetan labeled with yttrium 90—CD20 ;

tositumomab labeled with I-131—CD20;

trastuzumab—HER2 (human epidermal growth factor receptor 2)

لاحظ أنّ اثنين من الأضداد للـ CD20 (a B-cell antigen) تمتلك وسم نشط إشعاعياً . الـ **ibritumomab tiuxetan** توليفي ، القطعة **ibritumomab** ترتبط بالخالب **tiuxetan** . يوفر الخالب مقر الارتباط للربطة النشطة إشعاعياً .

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Afatinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus	P-gp inhibitors and inducers	CBC, CMP	Administer on an empty stomach Reduce dose for significant diarrhea Use effective contraception for female patients
<i>Dabrafenib</i>	Inhibits mutated BRAF kinases	Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity	CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6	Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if warfarin)	Use effective contraception for female patients Administer on empty stomach May cause new primary malignancies
<i>Dasatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, diarrhea	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation
<i>Erlotinib</i>	Inhibits EGFR tyrosine kinase	Rash, ILD, hepatotoxicity	CYP3A4 substrates, acid-reducing agents, warfarin	CMP	Rash equated with increased response
<i>Ibrutinib</i>	Inhibits Bruton's tyrosine kinase	Neutropenia, thrombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia	CYP3A inhibitors and inducers	CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome	Avoid grapefruit juice and Seville oranges Can cause hepatitis B reactivation Use effective contraceptive
<i>Idelalisib</i>	Inhibits phosphatidylinositol 3-kinase	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection	CYP3A inducers and substrates	CBC, LFTs, pulmonary symptoms, infection	Use effective contraception for female patients
<i>Imatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, CHF	CYP3A4 substrates, warfarin	CBC, BCR-ABL	Monitor for development of heart failure
<i>Nilotinib</i>	Inhibits BCR-ABL kinase	Myelosuppression, QT prolongation, hepatotoxicity	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation Administer on empty stomach
<i>Osimertinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, dry skin, nail toxicity, fatigue	Strong CYP3A inducers	CBC, ECG, electrolytes	Use effective contraceptive for female patients
<i>Pazopanib</i>	Multi-tyrosine kinase inhibitor	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting	CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; <i>simvastatin</i> ; drugs that reduce gastric pH	ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP	Use effective contraceptive for female patients
<i>Sorafenib</i>	Inhibits multiple intracellular and cell surface kinases	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue	CYP3A4 inducers, warfarin	BP, CMP	Wound healing complications, cardiac events
<i>Sunitinib</i>	Multi-tyrosine kinase inhibitor	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism	CYP3A4 substrates	BP, CMP, TSH	Monitor for development of heart failure
<i>Trametinib</i>	Reversible inhibitor of mitogen-activated extracellular kinases	Pyrexia, rash, diarrhea, vomiting, lymphedema	CYP2C8 substrates, P-gp	Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP	Used in combination with <i>dabrafenib</i> Administer on empty stomach
<i>Vemurafenib</i>	Inhibits mutated BRAF serine-threonine kinase	Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma	CYP3A4 inhibitors and inducers, CYP1A2 substrates	ECG, electrolytes, CMP, uveitis	May cause new primary cutaneous malignancies Use effective contraception in female patients

BMP = basic metabolic panel; BP = blood pressure; CBC = complete blood count; CHF = congestive heart failure; CMP = complete metabolic panel; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ILD = interstitial lung disease; INR = international normalized ratio; LFT = liver function test; LVEF = left ventricular ejection fraction; P-gp = P-glycoprotein; TSH = thyroid-stimulating hormone; UA = urinalysis.

Figure 35.32

Summary of tyrosine kinase inhibitors.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	MONITORING PARAMETERS	NOTES
<i>Bevacizumab</i>	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Cetuximab</i>	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea	Electrolytes, vital signs during infusion	Premedication with antihistamine required before infusion; rash equated with increased response
<i>Daratumumab</i>	Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis	Infusion reactions, diarrhea, fatigue, pyrexia	CBC with differential, vital signs during infusion	Can bind CD38 on red blood cells Type and screen patients before starting therapy Premedication with antihistamines, antipyretics, and corticosteroids required
<i>Ramucirumab</i>	Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands	Proteinuria, hypertension, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Rituximab</i>	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal infusion reaction, TLS, mucocutaneous reactions, PML	Vital signs during infusion, TLS labs	Fatal reactivation of hepatitis B Premedication required before infusion Increased risk of nephrotoxicity when given with <i>cisplatin</i>
<i>Trastuzumab</i>	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting	LVEF, CBC, pulmonary toxicity due to infusion reaction	Embryo-fetal toxicity Neutropenia in combination with chemotherapy Premedication with antihistamine and <i>acetaminophen</i> required

BP = blood pressure; CBC = complete blood count; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor protein 2; GI = gastrointestinal; LVEF = left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; TLS = tumor lysis syndrome; VEGF = vascular endothelial growth factor.

Figure 35.31

Summary of monoclonal antibodies. (For drug dosages, refer to Appendix at the end of the book.)

Alkylating Agent	Mechanism of Action
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function
Chlorambucil	Same as above
Cyclophosphamide	Same as above
Bendamustine	Same as above
Melphalan	Same as above
Thiotepa	Same as above
Busulfan	Same as above
Carmustine	Same as above
Lomustine	Same as above
Altretamine	Same as above
Temozolomide	Methylates DNA and inhibits DNA synthesis and function
Procarbazine	Methylates DNA and inhibits DNA synthesis and function
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function

Antimetabolites:

Drug	Mechanism of Action
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA
6-Thioguanine	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase.

TABLE 54-3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, nausea and vomiting, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase.

TABLE 54-4 Natural product cancer chemotherapy drugs: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Bleomycin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, head and neck cancer	Allergic reactions, fever, hypotension	Skin toxicity, pulmonary fibrosis, mucositis, alopecia
Daunorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL	Nausea and vomiting, fever, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression
Docetaxel	Inhibits mitosis	Breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer, ovarian cancer, bladder cancer	Hypersensitivity	Neurotoxicity, fluid retention, myelosuppression with neutropenia
Doxorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma	Nausea, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression, stomatitis
Etoposide	Inhibits topoisomerase II	Non-small cell and small cell lung cancer; non-Hodgkin's lymphoma, gastric cancer	Nausea, vomiting, hypotension	Alopecia, myelosuppression
Idarubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting	Myelosuppression, mucositis, cardiotoxicity
Irinotecan	Inhibits topoisomerase I	Colorectal cancer, gastroesophageal cancer, non-small cell and small cell lung cancer	Diarrhea, nausea, vomiting	Diarrhea, myelosuppression, nausea and vomiting
Mitomycin	Acts as an alkylating agent and forms cross-links with DNA; formation of oxygen free radicals, which target DNA	Superficial bladder cancer, gastric cancer, breast cancer, non-small cell lung cancer, head and neck cancer (in combination with radiotherapy)	Nausea and vomiting	Myelosuppression, mucositis, anorexia and fatigue, hemolytic-uremic syndrome
Paclitaxel	Inhibits mitosis	Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer	Nausea, vomiting, hypotension, arrhythmias, hypersensitivity	Myelosuppression, peripheral sensory neuropathy
Topotecan	Inhibits topoisomerase I	Small cell lung cancer, ovarian cancer	Nausea and vomiting	Myelosuppression
Vinblastine	Inhibits mitosis	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma	Nausea and vomiting	Myelosuppression, mucositis, alopecia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), vascular events
Vincristine	Inhibits mitosis	ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	None	Neurotoxicity with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia, SIADH
Vinorelbine	Inhibits mitosis	Non-small cell lung cancer, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression, constipation, SIADH

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia.

Alkylating Agent :

(Nitrogen Mustards : Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, Bendamustine, Altretamine

Alkyl sulfonates : Busulfan

Nitrosoureas : Carmustine, Lomustine....

Each one Forms DNA crosslinks, resulting in inhibition of DNA synthesis and function)

(Triazine : Dacarbazine , Temozolomide

Methylhydrazine : Procarbazine

Each one Methylates DNA and inhibits DNA synthesis and function)

Cisplatin Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins

TABLE 54-5 Miscellaneous anti-cancer drugs: Clinical activity and toxicities.

Drug	Mechanism of Action ¹	Clinical Applications ¹	Acute Toxicity	Delayed Toxicity
Bortezomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway	Multiple myeloma, mantle cell lymphoma	Nausea and vomiting, fever	Peripheral sensory neuropathy, diarrhea, orthostatic hypotension, fever, pulmonary toxicity, reversible posterior leukoencephalopathy (RPLS), congestive heart failure (CHF), rare cases of QT prolongation
Carfilzomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway; maintains activity in bortezomib-resistant tumors	Multiple myeloma	Fever	Fatigue, cardiac toxicity with CHF and myocardial infarction, myelosuppression, pulmonary toxicity, hepatotoxicity, orthostatic hypotension
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling	Non-small cell lung cancer, pancreatic cancer	Diarrhea	Skin rash, diarrhea, anorexia, interstitial lung disease
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit	CML, gastrointestinal stromal tumor (GIST), Philadelphia chromosome-positive ALL	Nausea and vomiting	Fluid retention with ankle and periorbital edema, diarrhea, myalgias, congestive heart failure
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.	CML	Nausea and vomiting	Diarrhea, fluid retention, myelosuppression, skin rash hepatotoxicity
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer, head and neck cancer (used in combination with radiotherapy), non-small cell lung cancer	Infusion reaction	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer	Infusion reaction (rarely)	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, glioblastoma multiformae	Hypertension, infusion reaction	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, proteinuria
Ziv-aflibercept	Inhibits binding of VEGF-A, VEGF-B, and PlGF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer	Hypertension	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, diarrhea, mucositis, proteinuria
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, hepatocellular cancer	Nausea, hypertension	Skin rash, fatigue and asthenia, bleeding complications, hypophosphatemia
Sunitinib, pazopanib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR- α and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, GIST	Hypertension	Skin rash, fatigue and asthenia, bleeding complications, cardiac toxicity leading to congestive heart failure in rare cases

¹See text for acronyms.

Anticancer Drugs

Kourtney LaPlant and Paige May

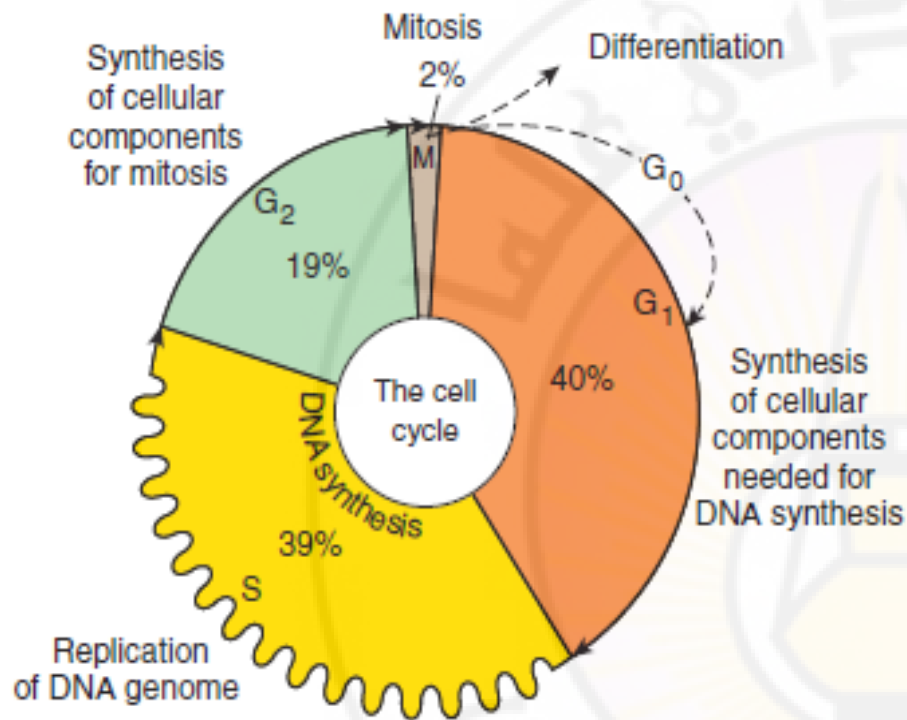
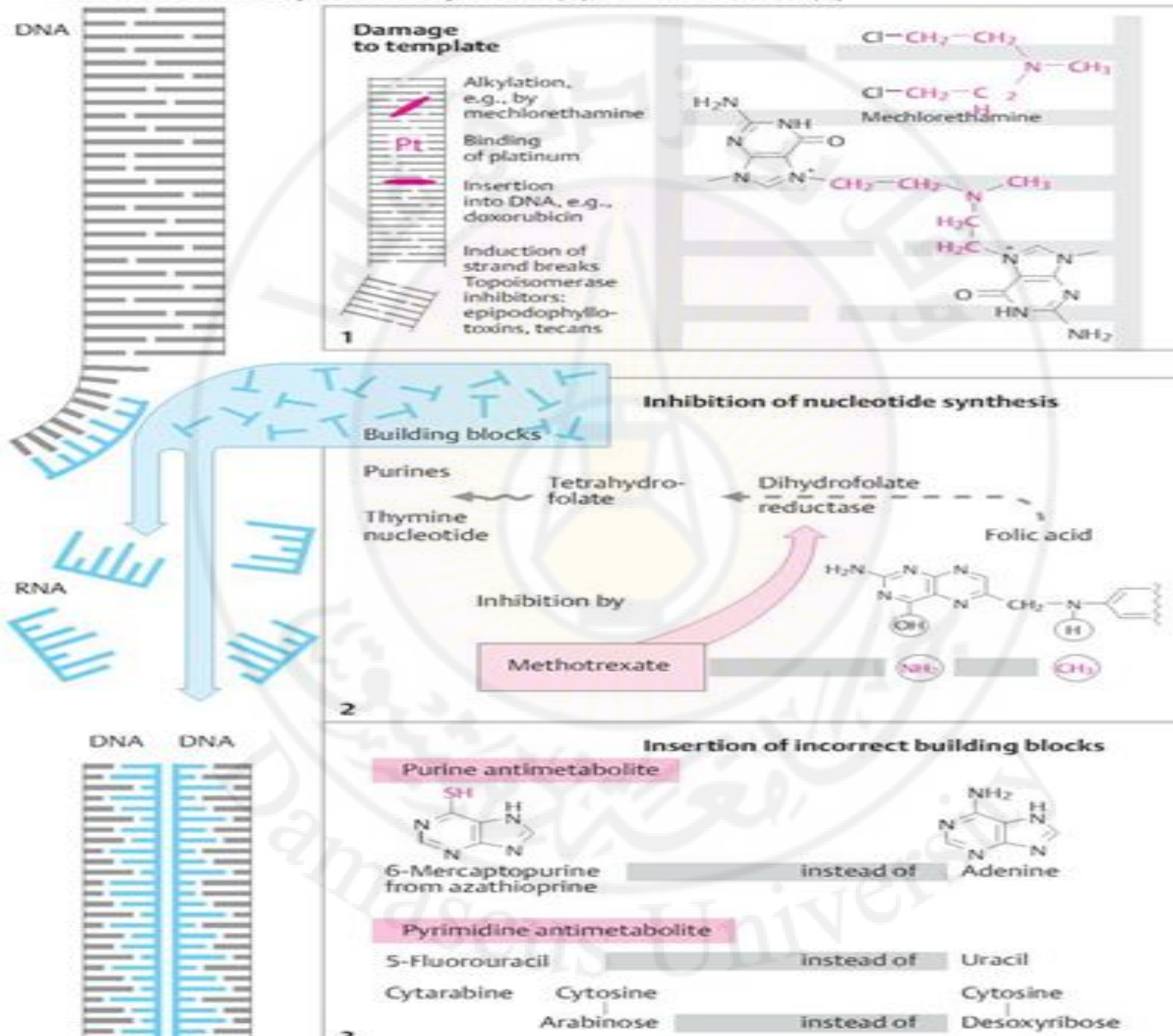


FIGURE 54-2 The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G₁, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle-specific (CCS) drugs (see Table 54-1). A second group of agents called cell cycle-nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G₀ compartment. CCNS drugs can kill both G₀ and cycling cells (although cycling cells are more sensitive).

Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase)	Alkylating agents
Capecitabine	Altretamine
Cladribine	Bendamustine
Clofarabine	Busulfan
Cytarabine (ara-C)	Carmustine
Fludarabine	Chlorambucil
5-Fluorouracil (5-FU)	Cyclophosphamide
Gemcitabine	Dacarbazine
6-Mercaptopurine (6-MP)	Lomustine
Methotrexate (MTX)	Mechlorethamine
Nelarabine	Melphalan
Pralatrexate	Temozolomide
6-Thioguanine (6-TG)	Thiotepa
Topoisomerase II Inhibitor (G₁-S phase)	Antitumor antibiotics
Etoposide	Dactinomycin
Topoisomerase I Inhibitors (Camptothecins, G₂-M)	Mitomycin
Irinotecan	Platinum analogs
Topotecan	Carboplatin
Taxanes (M phase)	Cisplatin
Albumin-bound paclitaxel	Oxaliplatin
Cabazitaxel	Anthracyclines
Docetaxel	Daunorubicin
Paclitaxel	Doxorubicin
Vinca alkaloids (M phase)	Epirubicin
Vinblastine	Idarubicin
Vincristine	Mitoxantrone
Vinorelbine	
Antimicrotubule inhibitor (M phase)	
Ixabepilone	
Eribulin	
Antitumor antibiotics (G₂-M phase)	
Bleomycin	

A. Cytostatics: alkylating agents and cytostatic antitumorics (1), inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)



HISTORY Alkylating Anticancer Drugs

The discovery and initial development of alkylating anticancer drugs are based on observations of the effects of chemical warfare in World War I (Chabner and Roberts, 2005). The pervasively **toxic sulfur mustard gas** that caused topical burns to skin, eyes, lungs, and mucosa also caused aplasia of the bone marrow and lymphoid tissue and ulceration of the GI tract (Krumbhaar, 1919). In 1942, **Louis Goodman and Alfred Gilman**, the originators of this text, demonstrated the activity of **nitrogen mustards against mouse lymphoma**. Their clinical studies of intravenous nitrogen mustards in patients with lymphoma launched the modern era of cancer chemotherapy (Gilman and Philips, 1946).

R. Lymphoma

Hodgkin lymphoma encompasses a distinctive group of neoplasms that are characterized by the presence of a *tumor giant عَمَلَق cell, the RS cell. Unlike most NHLs, Hodgkin lymphomas arise in a single lymph node or chain of lymph nodes* and typically spread in a stepwise fashion to anatomically contiguous مُجاوِر nodes. Although the Hodgkin lymphomas are now understood to be unusual tumors of B cell origin, they are distinguished from the NHLs by their unusual pathologic and clinical features.

يمكن تقسيم الأدوية إلى مجموعتين : الأدوية السامة للخلايا و الهرمونات . كل العوامل المؤلكة والصادات ومضادات الاستقلاب والأدوية المتنوعة هي سامة للخلايا .

Bleomycin :the cytotoxicity of bleomycin is due to **oxidative damage to DNA**. Bleomycin causes DNA fragmentation with predominantly single strand breakage, but also some double-strand breakage. Bleomycin causes scission of DNA by interacting with oxygen and ferrous ion . G2 and mitotic phases

Daunorubicin : Daunorubicin, an anthracycline antibiotic inhibits DNA topoisomerase II. Anthracyclines also intercalate into DNA and generate free radicals.

Doxorubicin : is an anthracycline antitumor antibiotic that **enhances formation of free oxygen radicals that alter cell membranes and induce Topoisomerase II (deoxyribonucleic acid) DNA damage**.

Epirubicin

Idarubicin : Idarubicin binds to DNA by intercalation and inhibits synthesis of nucleic acids, particularly DNA, and inhibits the activity of topoisomerase II, resulting in strand breaks. In addition, the quinone group of anthracyclines is reduced by cytochrome P450 reductase to generate semiquinone free radicals and oxygen radicals that attack DNA

Mitoxantrone : It interferes with DNA synthesis by intercalation with DNA or by inhibiting topoisomerase II.

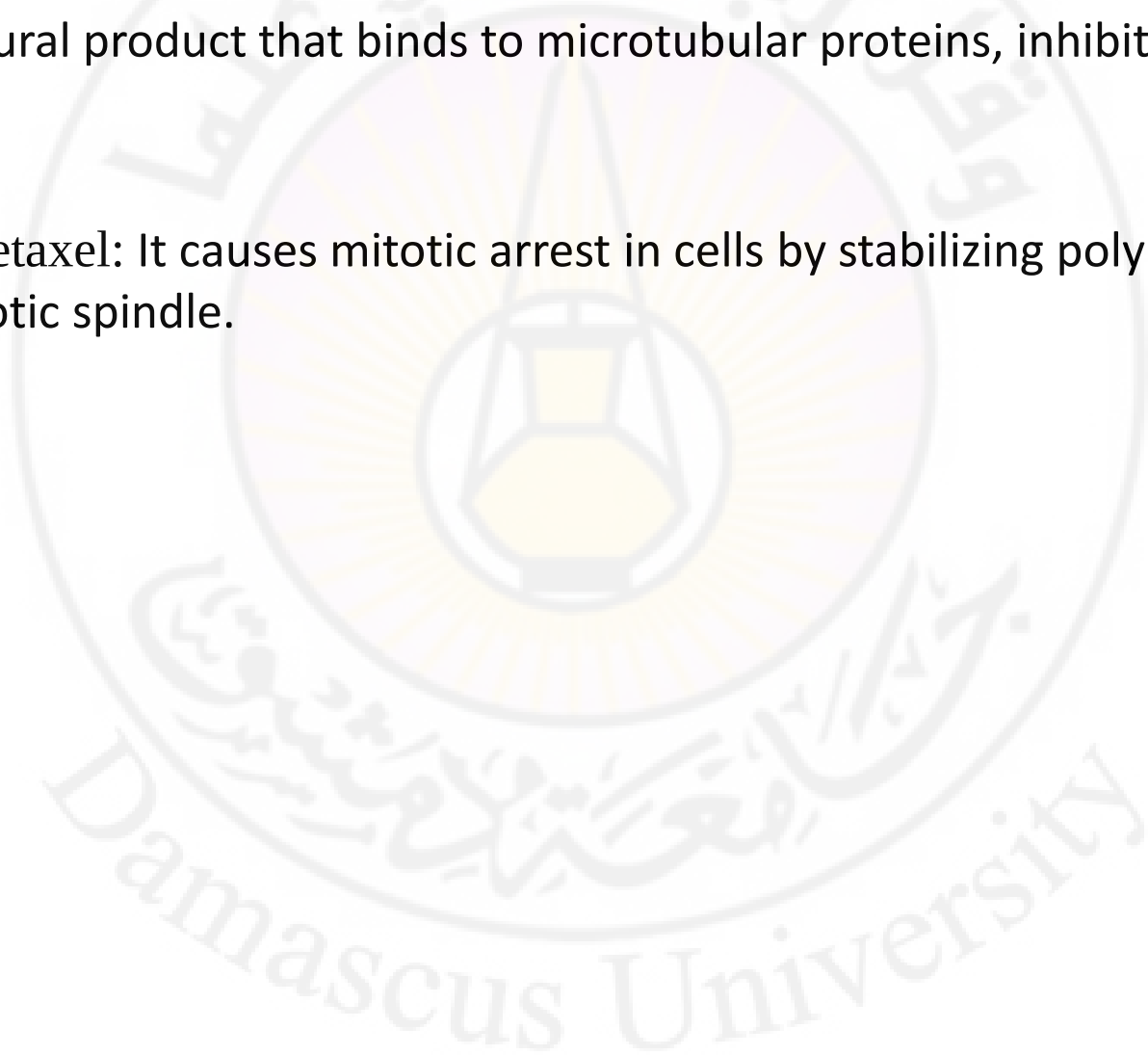
Actinomycin : Dactinomycin inhibits DNA-dependent RNA polymerase (choriocarcinoma)

Mitomycin

Vincristin : A vinca alkaloid, vincristine, acts by inhibiting mitosis . depolymerizes microtubules and causes mitotic arrest . A cytotoxic effect by binding to tubulin and preventing its polymerization. This action interferes with the formation of the mitotic spindle and mitosis.

Vinblastin : natural product that binds to microtubular proteins, inhibiting microtubule assembly.

Paclitaxel ; docetaxel: It causes mitotic arrest in cells by stabilizing polymerized tubulin and the mitotic spindle.



Topotecan : Topotecan cytotoxicity is due to inhibition of **topoisomerase I, an enzyme that relieves torsional strain إجهاد التَوَائِي during DNA replication**. Topotecan, like other camptothecin derivatives, inhibits topoisomerase I activity. The cleavable complex normally formed between DNA and topoisomerase I is stabilized by topotecan causing breaks in single-stranded DNA that cannot be religated. Because DNA synthesis is necessary for cytotoxicity, the action of topotecan may be S-phase-specific . A is a topoisomerase II inhibitor . An inhibitor of topoisomerase I which is involved in DNA replication. inhibitor of topoisomerase I.

Irinotecan : By inhibiting topoisomerase I, irinotecan relieves torsional strain in DNA, thereby causing reversible, single-strand breaks. **Irinotecan interferes with processes linked to DNA unwinding .. الفك /إرخاء /استرخاء**

Etoposide : causes DNA strand breaks in cells by **binding to topoisomerase II and preventing re-joining of DNA strands**. It binds to tubulin and causes mitotic arrest. **Etoposide prevents cells from entering mitosis or destroys them in the premitotic phase. Cells in the S G2 phases of the cell cycle are more sensitive to etoposide. Etoposide induces double-strand breaks in DNA by forming a ternary complex with topoisomerase II and DN A. Resistance to etoposide develops because of enhanced expression of Pglycoprotein.**

teniposide, forms ternary complexes with topoisomerase II and DNA, resulting in double-stranded DNA breaks and inhibition of repair . **Teniposide prevents cells from entering mitosis or destroys them in the premitotic phase. Cells in the late S and early G2 phases of the cell cycle are more sensitive to teniposide. Teniposide, which forms a ternary complex with topoisomerase II and DNA, induces double-strand breaks in DNA. Although teniposide binds to tubulin at a site different from vinca alkaloids, it does not interfere with microtubular structure or function.**

Mechlorethamine : immediately cyclizes, forming an ethylene immonium ion in a nonenzymatic reaction. The cyclic ring is highly reactive and reacts with the N-7 of guanine. While alkylation of any of the nucleophiles in the cell may occur, **the N-7 of guanine produces the only anti-cancer effect.** The second chloroethyl group then cyclizes and alkylates the DNA again. The internal cyclization of the bis-chloroethyl group is necessary for the pharmacological activity of nitrogen mustard and determines the ability to alkylate at the N-7 position of guanine. The two alkylations may occur on the same strand, or on two separate strands, leading to double or single strand breaks by the DNA repair enzymes Chabner et al (2001).

Chlorambucil : a derivative of nitrogen mustard, is an alkylating agent. Since it interacts with cellular DNA to produce chromosomal cross-linkages, it is cell cycle-phase nonspecific agent Chabner et al (2001).

Cyclophosphamide : Cyclophosphamide is activated in the liver by cytochrome P-450 enzymes to 4-hydroxy cyclophosphamide, which in turn isomerizes into aldophosphamide. Aldophosphamide is converted to phosphoramidate mustard, the alkylating agent, and acrolein, a cytotoxic moiety affecting the bladder Chabner et al (2001).

Bendamustine : ..

Melphalan : The mechanism of action of melphalan is similar to nitrogen mustard. Because of the amino acid in the molecule it is subject to carrier-mediated transport. Melphalan cyclizes in the cell, forming an ethylene immonium ion. The nitrogen becomes highly reactive and the ring opens and attaches to the N-7 of guanine. While alkylation of any of the nucleophiles in the cell may occur, alkylation of the N-7 of guanine is responsible for the anti-cancer effect. The second chloroethyl group then cyclizes and alkylates the DNA again. Because the internal cyclization of the bis-chloroethyl group determines the ability of the drug to alkylate at the N-7 position of guanine it is necessary for the biological activity of nitrogen mustards. The two alkylations may occur on the same strand or on separate strands, leading to double or single strand breaks by the DNA repair enzymes Chabner et al (2001)

Thiotepa : Thiotepa is activated in the liver and rapidly converted by mixed-function oxygenases to its major metabolite, triethylene phosphoramidate (TEPA). TEPA alkylates the N-7 position of guanine and induces DNA cross-links, leading to double or single stranded breaks, and, ultimately, inhibition of DNA replication Chabner et al (2001).

Busulfan : alkylates DNA at the N7 position of guanine causing interstrand cross-linkage Chabner et al (2001).

Carmustine : Carmustine alkylates the N-7 position of guanine to cause crosslinking of DN A. This results in intra دَاخِل - and inter بَيْن -strand breaks that inhibit DNA replication. Unlike the nitrogen mustards, nitrosoureas undergo spontaneous, nonenzymatic degradation resulting in the formation of highly electrophilic carbonium ions that alkylate DN A. The spontaneous degradation of carmustine may also inactivate certain DNA repair enzymes by generation of carbamoylating proteins Chabner et al (2001).

Lomustine : undergoes spontaneous nonenzymatic degradation that results in the formation of 2-chloroethyl carbonium ions that alkylate DN A. Like other alkylating agents, lomustine alkylates the N-7 of guanine to cause DNA cross-linking. This results in intraand inter-strand breaks that ultimately inhibit DNA replication. The spontaneous degradation of lomustine may also inactivate some DNA repair enzymes because of the formation of carbamoylating proteins Chabner et al (2001).
It crosses CNS

Altretamine : An alkylating agent, altretamine is a cancer chemotherapeutic agent. Its mechanism of action is alkylation of DNA leading to strand breaks Chabner et al (2001).

Dacarbazine : alkylates the N-7 of guanine to cause cross-linking of DNA, causing breaks in the DNA strands and, ultimately, inhibition of DNA replication Chabner et al (2001). Unlike the nitrogen mustards, dacarbazine methylates the N-7 of guanine by way of its methyl group Chabner et al (2001).

Procarbazine : Procarbazine appears to act by inhibiting DNA, RNA, and protein synthesis, possibly by blocking transmethylation of the methyl group of methionine into t-RN A. Procarbazine metabolism yields cytotoxic hydrogen peroxide. Azoxy metabolites of procarbazine liberate diazomethane, a potential methylating agent. These reactions can cause chromosomal damage, chromatid breaks, and translocations Chabner et al (2001). Repair of methylation of guanine via guanine-O6-alkyl transferase can lead to resistance.

Temozolomide : is an imidazotetrazine derivative of decarbazine and used via oral route.

Streptozotocin : like the other nitrosoureas, is an alkylating agent that acts by alkylating the N-7 of guanine to cause cross-linking of DN A. This results in intra- and inter-strand breaks that ultimately inhibit DNA replication. specifically for the treatment of pancreatic tumors . derived from *Streptomyces achromogenes* variety. It also displays antibacterial properties.

Antimetabolites :

5-Fluorouracil : A potent inhibitor of thymidylate synthase it interferes with DNA synthesis and with RNA function.

5-Fluorouracil is activated intracellularly to a 5'-monophosphate nucleotide (FUMP) either directly by 5-phosphoribosyl-1-pyrophosphate (PRPP) or in two steps by way of conversion to fluorouridine by uridine phosphorylase and then to FUMP by uridine kinase. FUMP is activated to FUDP and then reduced by the enzyme ribonucleotide reductase to F-dUDP, which leads to the formation of F-dUMP. 5-FU may also be directly converted into FdR by thymidine phosphorylase and then to FdUMP by thymidine kinase. FdUMP forms a ternary complex with thymidylate synthetase and the folate cofactor, N⁵, N¹⁰-methylenetetrahydrofolate. Thus, 5-FU inhibits the conversion of dUMP to thymidylate (TMP). Addition of 5-formyl-tetrahydrofolate (leucovorin) increases the formation of the ternary complex and enhances responses to 5-FU.

Capacitabine : ..

Methotrexate : Methotrexate (MTX) induces an effect similar to 5-fluorouracil (5-FU) by interrupting the formation of thymine within the cell, which leads to the inability to replicate DNA. Unlike 5-FU, which inhibits the action of thymidylate synthetase, MTX binds tightly to dihydrofolate reductase (DHFR) and blocks the formation of tetrahydrofolate, leading to the depletion of associated folate co-factors. However, the same effect-arrestment of DNA, RNA, and protein synthesis as is induced by 5-FU results.

Pemetrexed : Pemetrexed, thymidylate synthase and transferase inhibitor, is used in a treatment for several solid tumors. This compound is not only a thymidylate synthase inhibitor but also a potent inhibitor of human dihydrofolate reductase. Pemetrexed probably acts upon multiple intracellular targets and the antitumor effect may be derived from its simultaneous inhibition of multiple folate-requiring enzymes. Thus, this compound has been designated as a multitargeted antifolate. The drug also causes concentration- and time-dependent apoptosis Norman (2001).

Cytarabine : A pyrimidine antimetabolite, cytarabine, inhibits DNA polymerase and causes chain termination.

Cytarabine diffuses into cells and is activated by deoxycytidine kinase to the monophosphate. It is converted to the di- and tri-phosphates by non-specific cellular enzymes. Cytosine triphosphate inhibits DNA polymerase by competition of Ara-CTP for dCTP. It is also a weak inhibitor of ribonucleotide reductase. Cytarabine is a cell cycle S-phase specific drug Chabner et al (2001).

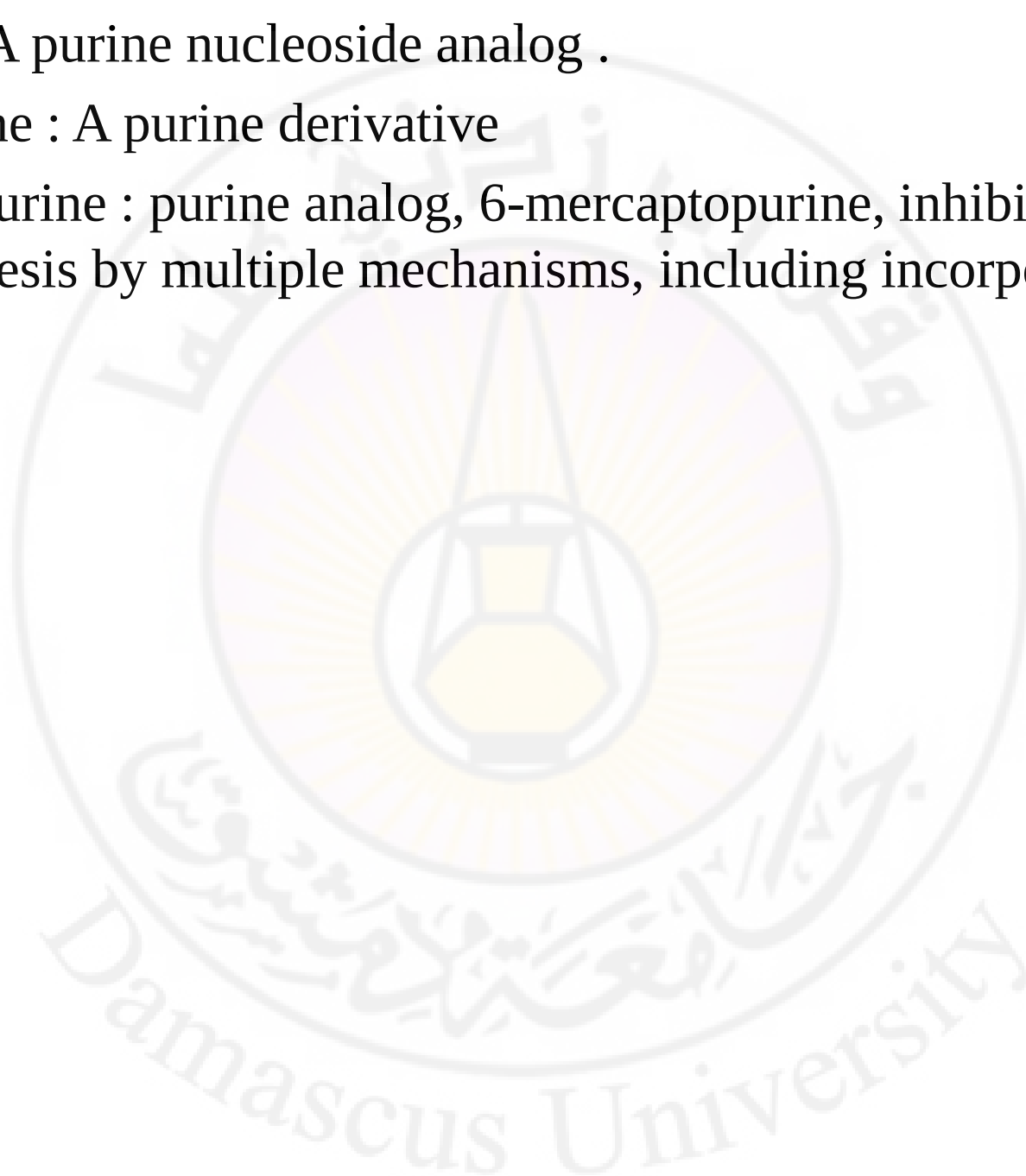
Gemcitabine : After diffusing into cells, gemcitabine is activated by nucleoside kinases to di- and triphosphate forms. Gemcitabine diphosphate inhibits ribonucleotide reductase, leading to a reduction in the concentration of deoxynucleotides and inhibition of DNA synthesis. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. Because dCTP concentrations are already reduced by the diphosphate, the incorporation of the triphosphate is increased causing further inhibition of DNA synthesis. Unlike cytarabine, a closely related antimetabolite, gemcitabine is not cell cycle S-phase specific Chabner et al (2001).

Fludarabine : After diffusing into the cell it is activated by deoxycytidine kinase to the monophosphate, which is then converted to the di- and tri-phosphates by non-specific cellular enzymes. Fludarabine triphosphate is incorporated into DNA and inhibits the enzymes responsible for DNA synthesis. Since apoptosis is a major effect of fludarabine, it does not require cell division to be cytotoxic Chabner et al (2001).

Cladribine : A purine nucleoside analog .

6-Thioguanine : A purine derivative

6-Mercaptopurine : purine analog, 6-mercaptopurine, inhibits nucleic acid synthesis by multiple mechanisms, including incorporation into DNA.



The DNA topoisomerases are nuclear enzymes that **reduce torsional stress** الإجهاد الإلتوائي in supercoiled مُفْرِطُ الِئْتِاف DNA, allowing selected regions of DNA to become sufficiently untangled to permit replication, repair, and transcription. Two classes of topoisomerase (I and II) mediate DNA strand breakage and resealing.

Camptothecin analogues inhibit the function of topoisomerase I; other drugs, such as anthracyclines, epipodophyllotoxins, and acridines, inhibit topoisomerase II.

The camptothecins bind to and stabilize the normally transient DNA–topoisomerase I cleavable complex. Although the initial cleavage action of topoisomerase I is not affected, the religation step is inhibited, leading to the accumulation of single-stranded breaks in DNA. These lesions are reversible and not by themselves toxic to the cell. However, the collision تَصَادُم of a DNA replication fork with this cleaved strand of DNA causes an irreversible double-strand DNA break, ultimately leading to cell death.

Tangle = حَبِيكَة [ج: حَبَائِك] (تشابك أو عقدة عصبية) .

Pharma. The **alkylating agents** are a diverse group of anticancer drugs that covalently bind an alkyl group or a substituted alkyl group to cellular constituents. Their common property is the capacity to become strong **electrophiles** through the formation of carbonium ion intermediates or to form transition complexes with the target molecules. These reactions yield covalent linkages by alkylation with various nucleophilic groups such as **sulfhydryl** or **carboxyl**.

Clinically, the most important actions of the alkylating agents are those that **effect DNA synthesis and cell division**. Although they interact with cells in all phases of the cell cycle, their therapeutic effects and toxicity are due primarily to interference with rapidly proliferating cells.

Pharma. The **antimetabolites** represent a relatively large group of anticancer agents that **structurally resemble natural substrates, but differ enough to interfere with their metabolism.**

___Included are

folic acid antagonists, such as methotrexate;

purine antimetabolites, such as 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, and cladribine; and the

pyrimidine antimetabolites such as 5-fluorouracil, 5-fluorodeoxyuridine, cytarabine, and gemcitabine.

Antimetabolites disrupt nucleic acid synthesis by interfering with production of a major nucleotide metabolite or by substituting for the natural metabolite.

Like most cytotoxic anticancer agents, antimetabolites are toxic to normal cells, especially those in the bone marrow and gastrointestinal tract.

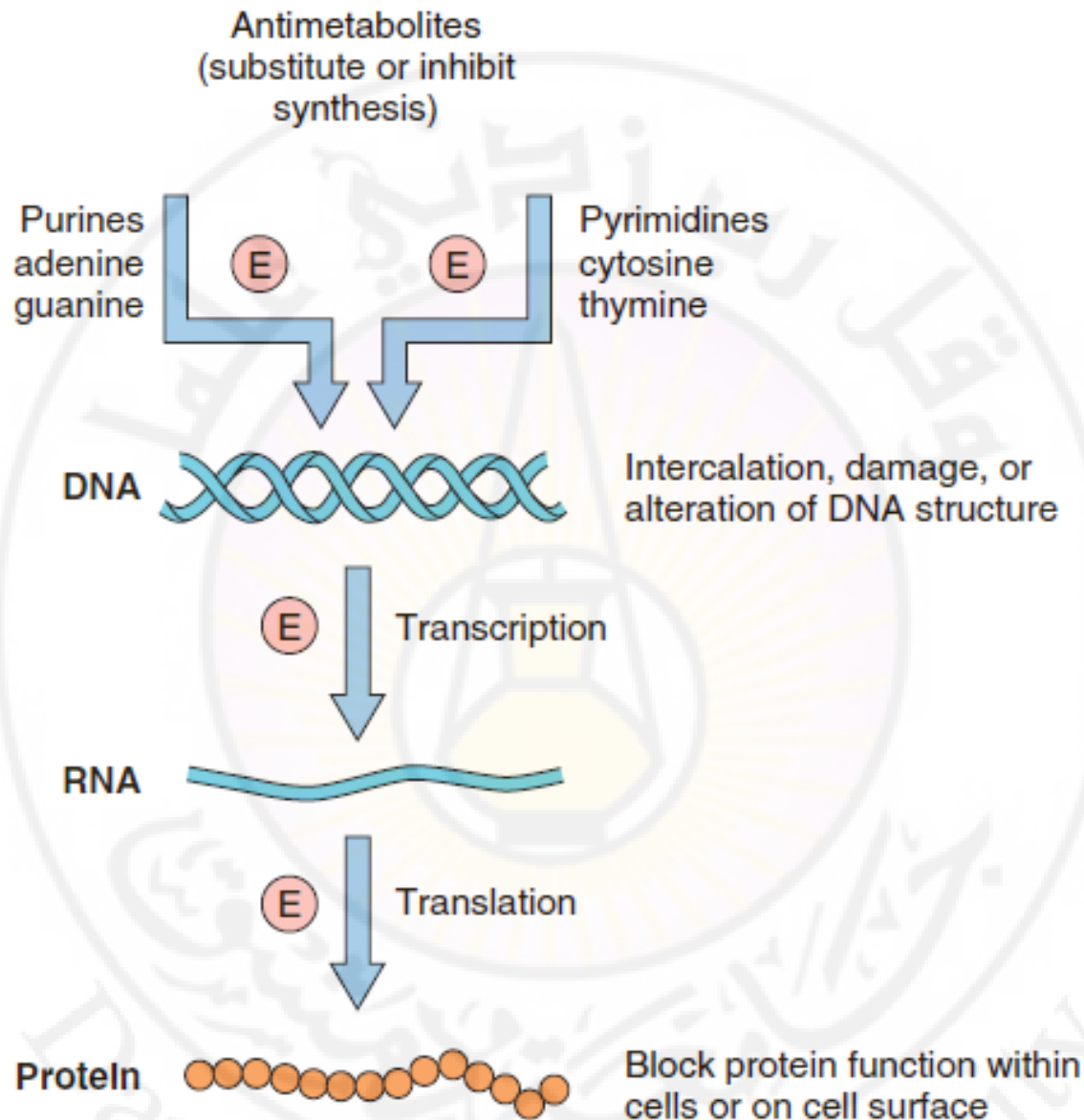


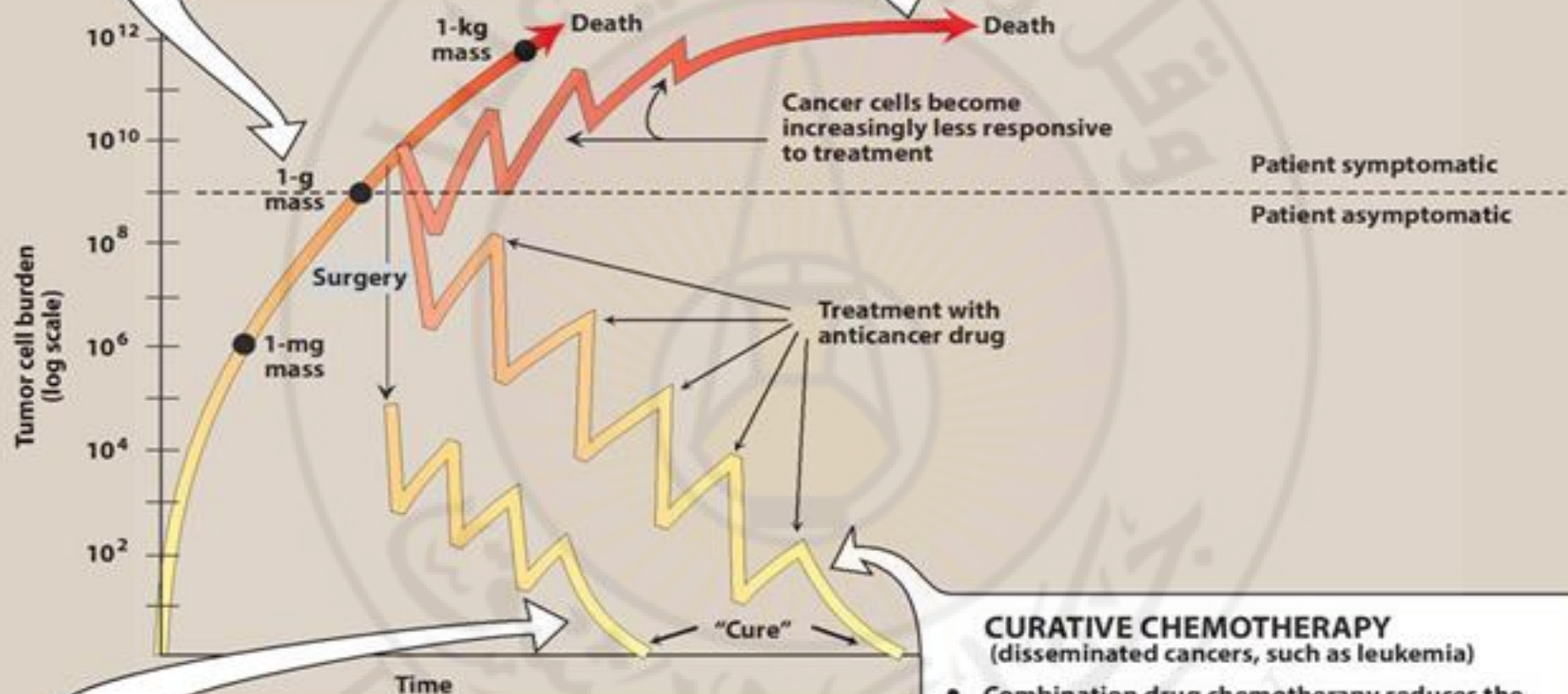
FIG. 68.3 Basic Mechanisms by Which Antineoplastic Drugs Selectively Kill Tumor Cells. *E* represents enzymes, some of which are inhibited by these drugs. Inhibition of DNA or RNA synthesis, production of miscoded nucleic acids, and formation of modified proteins are key mechanisms of action for many of these drugs.

SIGNIFICANCE OF A 1-g TUMOR MASS

- A total of 10^9 cells is the smallest tumor burden that is physically detectable.
- These 1 billion cells represent a tumor weighing about 1 g or about the size of a small grape.
- Clinical symptoms usually first appear at this stage.

PALLIATIVE CHEMOTHERAPY

- Initial remissions are transient, with symptoms recurring between treatments.
- Survival is extended, but the patient eventually dies of the disease.



CURATIVE CHEMOTHERAPY (solid tumors such as testicular carcinoma)

- Tumor burden is initially reduced by surgery and/or radiation.
- Treatment of occult micrometastases continues after clinical signs of cancer have disappeared.

CURATIVE CHEMOTHERAPY (disseminated cancers, such as leukemia)

- Combination drug chemotherapy reduces the chance of drug resistance.
- Each drug is chosen to have a different cellular site of action or different cell cycle specificity.
- Each drug is chosen to have a different organ toxicity.

Figure 35.3

Effects of various treatments on the cancer cell burden in a hypothetical patient.

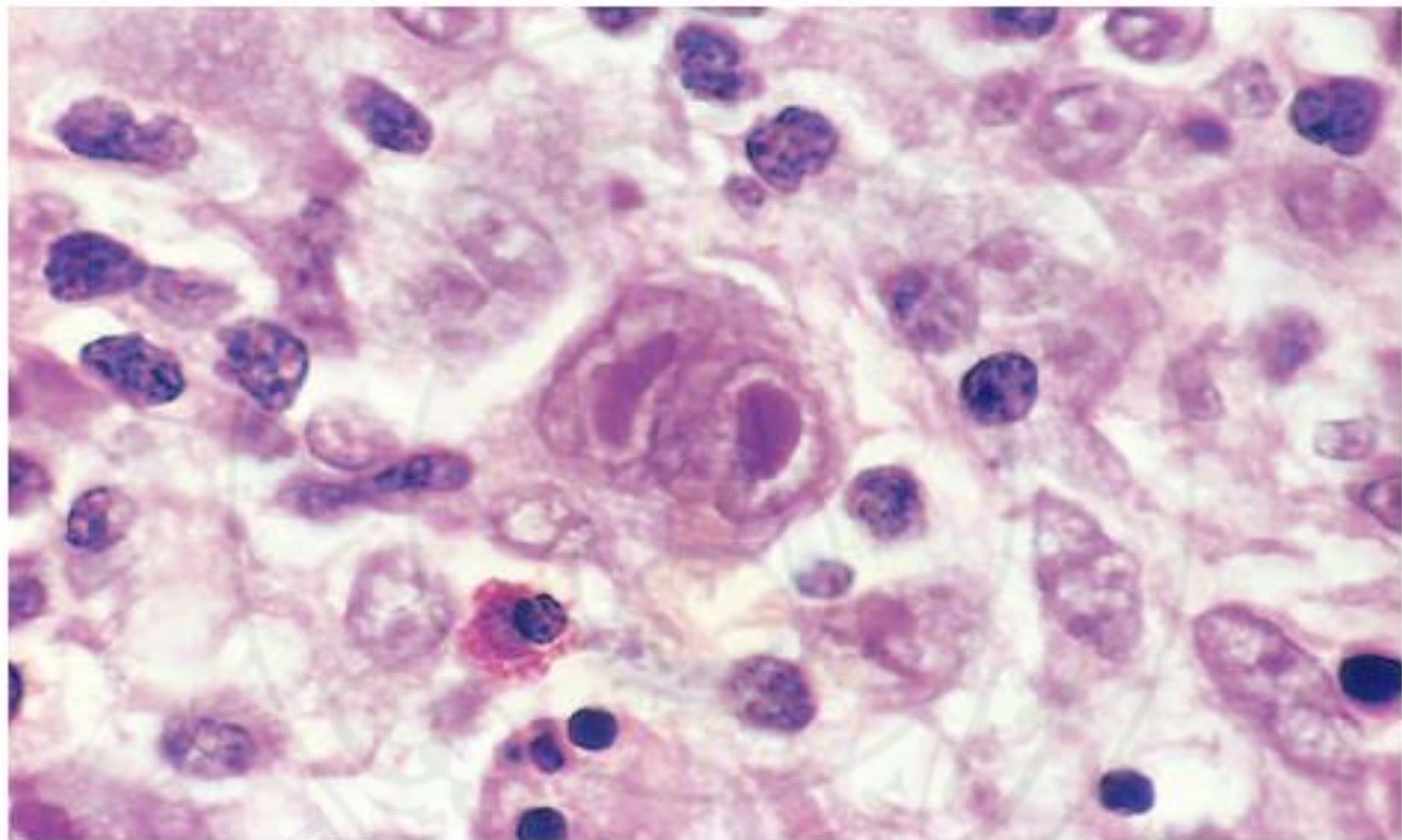


Fig. 12.20 Hodgkin lymphoma—lymph node. A binucleate Reed-Sternberg cell with large, inclusion-like nucleoli and abundant cytoplasm is surrounded by lymphocytes, macrophages, and an eosinophil. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

mediastinal مَنَصِفِي , contiguity تَجَاوُر

Table 12.9 Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, paraaortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal involvement uncommon	Extranodal involvement common

HODGKIN'S LYMPHOMA

PATHOPHYSIOLOGY

- Current hypotheses indicate that B-cell transcriptional processes are disrupted, which prevent expression of B-cell surface markers and production of immunoglobulin messenger RNA. Alterations in the normal apoptotic pathways favor cell survival and proliferation.
- Malignant Reed-Sternberg cells overexpress nuclear factor- κ B, which is associated with cell proliferation and anti-apoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor- κ B. Epstein- Barr virus is found in many, but not all, HL tumors.

CLINICAL PRESENTATION

- Most patients with HL present with a painless, rubbery lymph node. Adenopathy is usually localized to the cervical region but can also occur in the mediastinal, hilar, and retroperitoneal regions.
- Constitutional, or “B,” symptoms (e.g., fever, night sweats, weight loss, and pruritus) are present at diagnosis in approximately 25% of patients with HL.

DIAGNOSIS AND STAGING

- Diagnosis requires the presence of Reed-Sternberg cells in the lymph node biopsy.
- Staging is performed to provide prognostic information and to guide therapy. Clinical staging is based on noninvasive procedures such as history, physical examination, laboratory tests, and radiography. Pathologic staging is based on biopsy findings of strategic sites (e.g., muscle, bone, skin, spleen, abdominal nodes) using an invasive procedure (e.g., laparoscopy).
- Approximately half of the patients have localized disease (stages I, II, and IIE). The other half has advanced disease at diagnosis, of which 10% to 15% is stage IV.
- Prognosis predominantly depends on age and stage; patients older than 65 to 70 years are 50% as likely to be cured as younger patients. Patients with limited stage disease (stages I to II) have a 90% to 95% cure rate, whereas those with advanced disease (stages III to IV) have a 65% to 75% cure rate.

TREATMENT SUMMARY

- The treatment goal for HL is to maximize curability while minimizing treatment-related complications.
- Treatment options include radiation therapy, chemotherapy, or both (combined-modality therapy). The therapeutic role of surgery is limited, regardless of stage.
- Combination chemotherapy is the primary treatment modality for most HL patients.
- Radiation therapy is an integral part of treatment and can be used alone for selected patients with early-stage disease, although most patients will receive chemotherapy and radiation. Involved-field radiation therapy targets a single field of HL. Extended-field or subtotal nodal radiation targets the involved field and an uninvolved area. Total nodal radiation therapy targets all areas.
- Long-term complications of radiotherapy, chemotherapy, and chemoradiotherapy include gonadal dysfunction, secondary malignancies, and cardiac disease. Patients treated for HL are at increased risk of developing leukemia, GI tumors, lung cancer, and breast cancer.

Hand Book

Introduction

Hodgkin's disease (HD) is a malignant lymphoma. It is distinguished from non-Hodgkin's lymphoma on the basis of its epidemiology, pathology, anatomic progression of nodal involvement, response to therapy, and outcome. The Reed–Sternberg cell is the distinctive cell in H D. There is increasing evidence for a viral etiology for this condition.

Definition

Hodgkin's disease is a malignant lymphoma whose **hallmark is the Reed–Sternberg cell**. This is a **giant, multinucleated cell, usually a transformed B cell**.

≡

Olaparib for the treatment of ovarian cancers, which have lost the brain cancer resistance protein 1 (**BRCA1**)-mediated homologous repair process for double-strand DNA breaks, as shown in Fig. 67.4.

multidrug resistance protein 1 (MRP1) and **breast cancer resistance protein (BCRP)**, have also been implicated to play a role in multidrug resistance.

Table 55-1. An overview of anticancer drugs

Type	Group	Examples	Main mechanism
Alkylating and related agents	Nitrogen mustards	Cyclophosphamide, ifosfamide, chlorambucil, melphalan, estramustine,	Intrastrand cross-linking of DNA
	Nitrosoureas	Lomustine, carmustine,	
	Platinum compounds	Carboplatin, cisplatin, oxaliplatin	
	Other	Busulfan, treosulfan, thiotepa, dacarbazine, procarbazine, temozolamide	
Antimetabolites	Folate antagonists	Methotrexate, raltitrexed, pemetrexed	Blocking the synthesis of DNA and/or RNA
	Pyrimidine pathway	Fluorouracil, capecitabine, cytarabine, gemcitabine, tegafur	
	Purine pathway	Fludarabine, cladribine, mercaptopurine, tioguanine, pentostatin, clofarabine, nelarabine	
Cytotoxic antibiotics	Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin, (mitoxantrine), (amascrine)	Multiple effects on DNA/RNA synthesis and topoisomerase action
	Other	Bleomycin, dactinomycin, mitomycin	
Plant derivatives	Taxanes	Paclitaxel, docetaxel	Microtubule assembly; prevents spindle formation
	Vinca alkaloids	Vinblastine, vincristine, vindesine, vinorelbine	
	Campothecins	Irinotecan, topotecan, trabectedin	Inhibition of topoisomerase
Hormones/antagonists	Other	Etoposide	
	Hormones/analogues	Diethylstilbestrol, ethinyloestradiol, medroxyprogesterone, megestrol, norethisterone, goserelin, leuporelin, triptorelin, lanreotide, octreotide	Act as physiological antagonists, antagonists or hormone synthesis inhibitors to disrupt hormone-dependent tumour growth
	Antagonists	Tamoxifen, toremifene, fulvestrant, cyproterone, flutamide, bicalutamide	
Protein kinase inhibitors	Aromatase inhibitors	Anastrozole, letrozole, exemestane	Inhibition of kinases involved in growth factor receptor transduction
	Tyrosine kinase inhibitors	Dasatinib, erlotinib, imatinib, nilotinib, sunitinib	
	Pan kinase inhibitors	Sorafenib	
Monoclonal antibodies	Anti-EGF, EGF-2	Panitumumab, trastuzumab	Blocks cell proliferation
	Anti-CD20/CD52	Rituximab, alemtuzumab	Inhibition of lymphocyte proliferation
	Anti-VEGF	Bevacizumab	Prevents angiogenesis

Drugs in parentheses have similar pharmacological actions but are not necessarily chemically related.

page 677
page 678

The main anticancer drugs can be divided into the following general categories:

- **Cytotoxic drugs.** The mechanism of action of these drugs is discussed more fully below and summarised in Table 55.1; they include:
 - - *alkylating agents* and related compounds, which act by forming covalent bonds with DNA and thus impeding replication
 - - *antimetabolites*, which block or subvert one or more of the metabolic pathways involved in DNA synthesis
 - - *cytotoxic antibiotics*, i.e. substances of microbial origin that prevent mammalian cell division
 - - *plant derivatives* (vinca alkaloids, taxanes, campothecins): most of these specifically affect microtubule function and hence the formation of the mitotic spindle.
- **Hormones**, of which the most important are steroids (e.g. glucocorticoids, oestrogens and androgens) as well as drugs that suppress hormone secretion or antagonise hormone action.
- **Monoclonal antibodies:** these are generally only of use in particular types of cancer.
- **Protein kinase inhibitors:** these drugs inhibit protein (usually tyrosine) kinases that transduce growth signals in rapidly dividing cells. They have a rather restricted use.
- **Miscellaneous agents** that do not easily fit into the above categories.

The clinical use of anticancer drugs is the province of the specialist, who selects treatment regimens appropriate to the patient with the objective of curing, prolonging life or providing palliative therapy.² There are over 80 drugs available in the UK, which are often used in combination. Here we discuss mechanisms of action and the main unwanted effects of commonly used anticancer agents. A recent

Difficulty level: Easy

8. A 61-year-old woman with advanced Hodgkin lymphoma began chemotherapy with the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen. Which of the following molecular actions most likely mediated the therapeutic effect of doxorubicin in the patient's disease?

- A. It intercalates between DNA strands and inhibits topoisomerase II.
- B. It prevents microtubule disassembly into tubulin monomers.
- C. It prevents assembly of tubulin dimers into microtubules.
- D. It alkylates nucleophilic groups on DNA bases.
- E. It blocks the synthesis of both ribonucleotides and deoxynucleotides.

Learning objective: Explain the mechanism of anticancer action of doxorubicin.

8. A **Doxorubicin** is an anthracycline antibiotic, thus the *A* in the ABVD acronym; alternatively, the *A may be considered to stand for Adriamycin*, a brand name for doxorubicin. These anticancer drugs likely act with multiple mechanisms, including intercalation between adjacent base pairs of DNA, thus causing blockade of DNA replication; blockade of topoisomerase II, the enzyme that catalyzes DNA repair (it breaks and then reseals DNA strands); and generation of free radicals that can oxidize DNA bases. The end result of these multiple mechanisms is cell apoptosis.

- B This is the mechanism of action of **taxanes**.
- C This is the mechanism of action of **vinca alkaloids**.
- D This is the mechanism of action of **alkylating drugs**.
- E This is the mechanism of action of **methotrexate**.

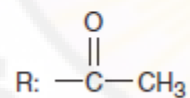
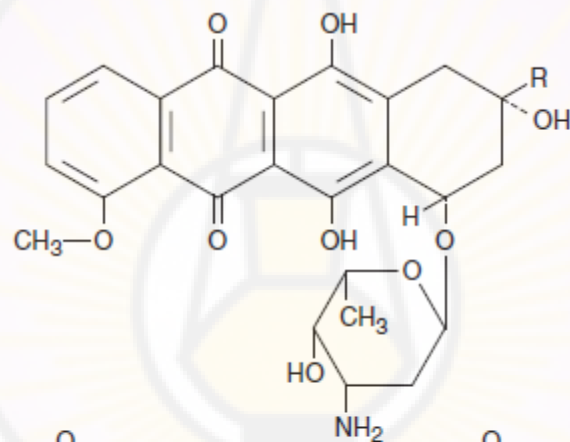
H. The mechanism of action of doxorubicin, daunorubicin, and their analogues : intercalate between bases in double-stranded DNA, poison DNA topoisomerase II, generate semiquinone and oxygen-free radicals, and possibly disrupt the fluidity of the cell membrane.

تُثَقِّم بين الأُسُس في الدنا المزدوج —الطاق ، تسمم توبوأيزوميراز— II الدنا ، تولد نصف كينون وجذور أكسجين حرّة . ربما أيضاً تعرقل سيولة الغشاء الخلوي . للتوبوأيزوميراز — دور في تضاعف الدنا وضروري لتفريق الكروموزوم ..

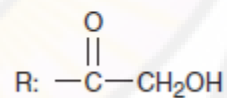
As illustrated in Fig. 68.10, the poisoning of DNA topoisomerase II is thought to constitute the major cytotoxic activity of these drugs.

Topoisomerase II is an enzyme that plays an important role in DNA replication and is essential for chromosome segregation التفرقة. It

catalyzes the uncoiling and unlinking of both strands of double-stranded DNA to modify DNA coiling and the intertwining of DNA duplexes. Doxorubicin and analogues poison the enzyme by stabilizing a covalent topoisomerase II-DNA reaction intermediate, which prevents the protein-linked DNA breaks from rejoining, ultimately leading to cell death.



Daunorubicin



Doxorubicin

Damascus University

Difficulty level: Easy

21. A 59-year-old woman with inoperable غير صالح للعملية lung cancer had been receiving combination chemotherapy. Lab tests revealed the following plasma levels: creatinine 5.5 mg/dL (normal 0.6–1.2 mg/dL), blood urea nitrogen (BUN) 45 mg/dL (normal 7–18 mg/dL), Mg^{2+} 0.2 mmol/L (normal 1.5–2.0 mmol/L). Which of the following drugs most likely caused these lab results?

A. Fluorouracil B. Doxorubicin C. Vincristine D. Cisplatin E. Paclitaxel

Learning objective: Describe the adverse effects of cisplatin.

Which of the following drugs to be used as a methotrexate antidote ?

A. Vitamin B12 B. Pyridoxine C. Folic acid D. Vitamin B3 E. Leucovorin

21. D The patient's lab results suggest the diagnosis of renal failure. Cisplatin is the anticancer drug with the highest risk of nephrotoxicity, and hypomagnesemia is the most common electrolyte abnormality caused by cisplatin. However, the routine use of hydration and diuresis has largely reduced cisplatin-induced nephrotoxicity.

A–C, E These drugs very rarely cause nephrotoxicity.

Damascus University

V. MICROTUBULE INHIBITORS. The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity. The microtubule inhibitors are summarized in Figure 35.21.

خامساً. مثبطات الأنبيبيات (iv):

MICROTUBULE INHIBITORS

Taxene derivatives

Paclitaxel

Docetaxel

Vinca alkaloids

Vincristine

Vinblastine

Vinorelbine

مغزل الانقسام ضروري لتقاسم متساوي للدنا في الخليتين البنيتين اللتان تتكوّنان عند انقسام خلية حقيقية النواة ويتكوّن من مجموعة من الأنبيبيات المُركّبة من توبولين (البروتين المكون للأنبيبيات الخلوية) وكروماتين .

تستعمل مواد مشتقة—من نباتات مضادة للسرطان تعرقل هذه العملية بتأثيرها على التوازن بين الأشكال المُبلّمة وغير المُبلّمة للأنبيبيات ، مسببةً بالتالي سُميّةً للخلايا . مثبطات الأنبيبيات ملخصة في الشكل ٣٥ . ٢١ .

أ. **Vincristine** و **vinblastine** (قلوانيات العنقائية) :
 مشتقان من نبات العنقائية .. الـ **vinorelbine** أقل سمية
 عصبية ..

آلية الفعل : ترتبط مع التوبولين ، مما يعرقل جميع
 النبببات المجهرية وبلمرتها ، خصوصاً المكتنفة في مغزل
 الانقسام الخيطي . يؤدي هذا إلى توقف الانقسام الخيطي في
 مرحلة التنصيف—م وموت الخلية (الشكل ٣٥ . ٢٢)

نوعية—لدورة الخلية ونوعية—الطور ، تعيق الانقسام
الفتيلي في الطور—م (مرحلة التنصيف في الانقسام الخيطي
metaphase) .

يستعمل الفينكريستين لمعالجة ابيضاض الأرومات اللمفية
 الحاد للأطفال و وَرَمٌ ويلمز (في الكلية عند الأطفال) و
 ساركومة يُونينغ (في العظام) .. فعاليته المثبطة للنقي خفيفة .

يعطى vinblastine مع بليومييسين و سيسبلاتين في سرطانة
 الخصية النقيلية وفي لمفوما هودجكن وغير الهودجكنية

يسبب الـ VX اعتلال أعصاب محيطية أكثر . ينبغي عدم

إعطائهما داخل القِراب (هذا الخطأ قد يسبب الموت ،

ينبغي التحذير النوعي في تعليمات الإعطاء) . *

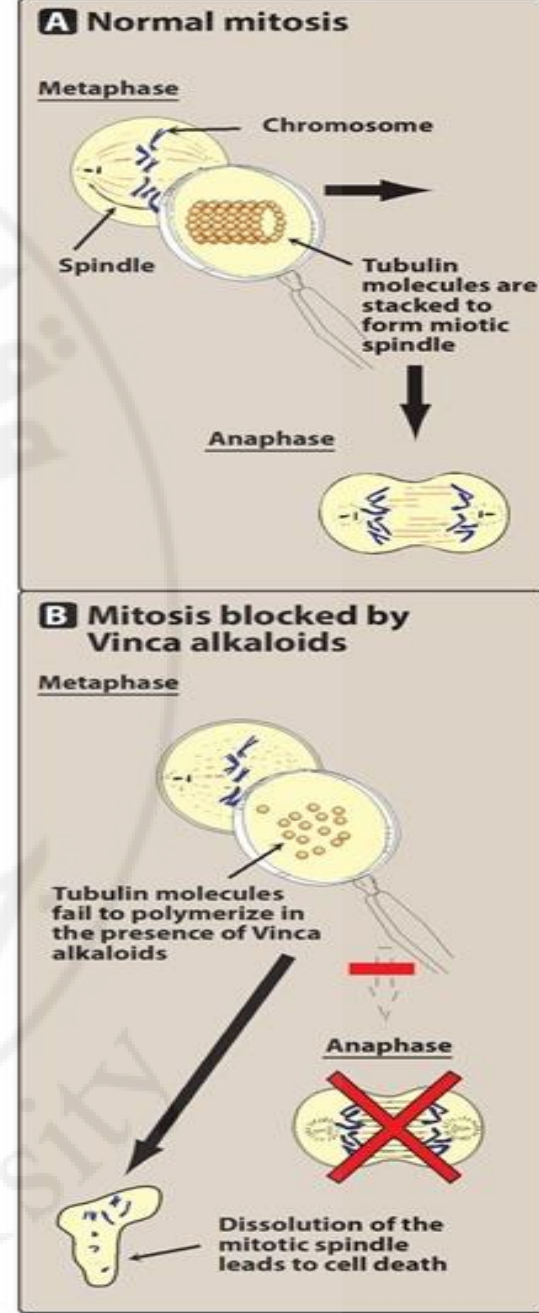
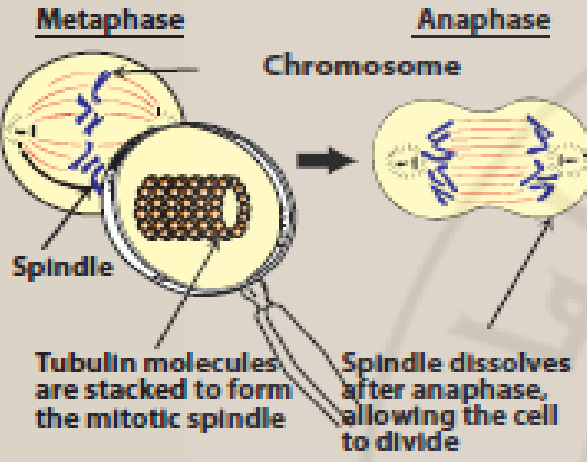


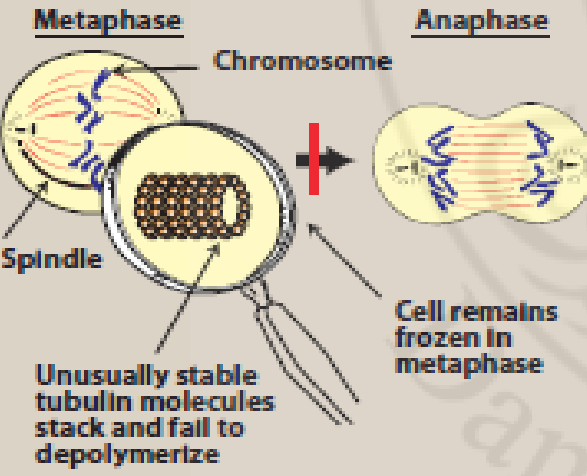
Figure 35.22

Mechanism of action of the microtubule inhibitors.

A Normal mitosis



B Mitosis blocked by paclitaxel



ب. Paclitaxel و docetaxel : الـ Paclitaxel أول أعضاء التاكسان .. نصف صناعي من طلائع في إبر أنواع نبات طقسوس المحيط الهادي أو الهملالي (شجرة دائمة الخضرة من الفصيلة الصنوبرية) .. اشتق منه الـ docetaxel الأقوى . جيد لسرطان المبيض المتقدم وسرطان الثدي النقيلي ... الثاني لسرطانات البروستاتة والثدي والهضم ..

١. آلية الفعل : فعّالان في الطور—م ، بخلاف قلوانيات العنقائية يعززان تثبيت البوليمر بدلاً من فصل التجمع ، مؤديان إلى تراكم الأنابيبات على نحو ثابت غير وظيفي (الشكل ٣٥ . ٢٣) فلا يحدث دمج عناصر الصبغي فتموت الخلية .

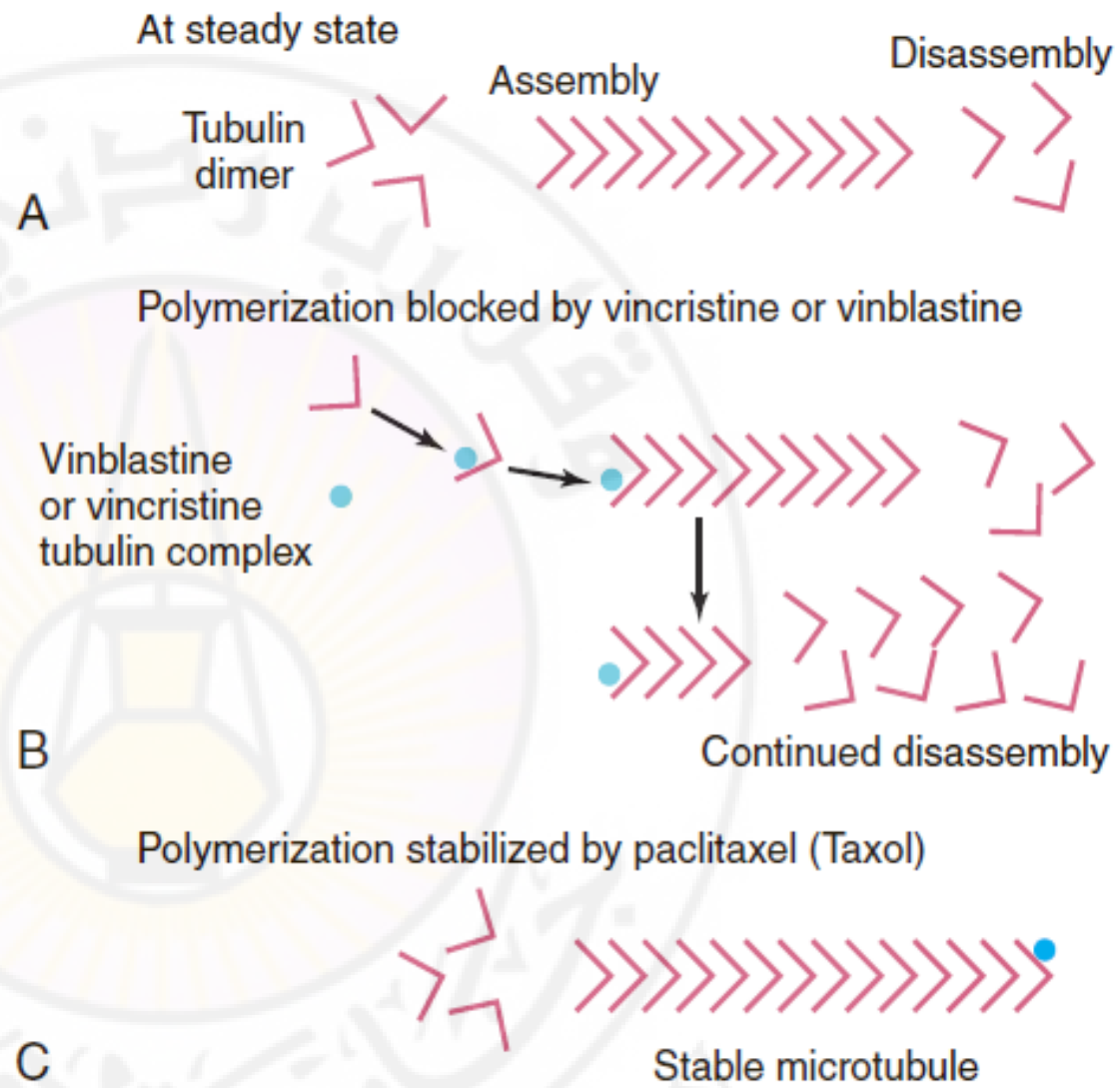
التأثيرات الضائرة : تتضمن السمّيات المحددة—بالجرعة للدوائين قلّة العدلات وقلّة الكريات البيض . اعتلال الأعصاب المحيطية شائع مع التاكسانات .

{ملاحظة : بسبب فرط التحسس الخطير (متضمناً عسر النفس والشرى ونقص الضغط) ينبغي استباق المعالجة بالباكليتاكسيل بإعطاء ديكساميثازون وديفينهيدرامين ومناهض لمستقبلة الهيستامين—٢ } . *

Figure 35.23
Paclitaxel stabilizes microtubules, rendering them nonfunctional.

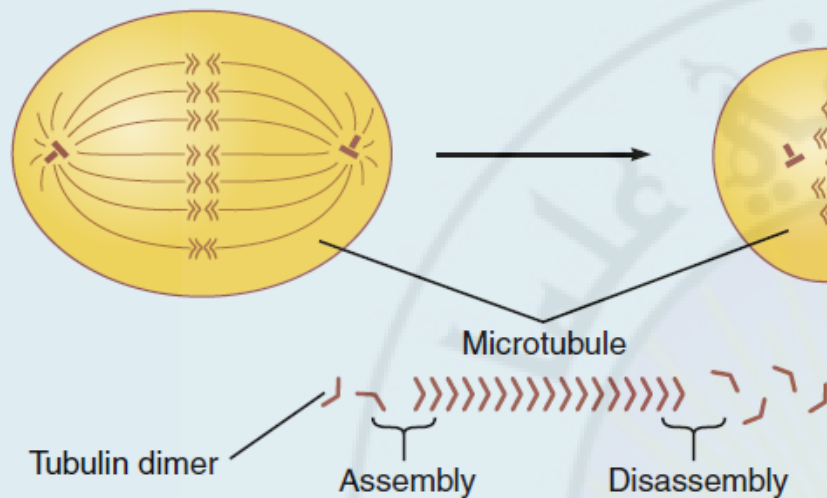
FIG. 68.11 Microtubule

Dynamics in the Presence of Vincristine, Vinblastine, or Paclitaxel. A dynamic steady state exists, with microtubule assembly occurring at one end and disassembly at the other (A). Vincristine and vinblastine (B) bind to tubulin dimers and block polymerization, allowing disassembly to predominate. In contrast, paclitaxel (C) blocks disassembly, causing stable microtubules to form even in the absence of normally essential cofactors. Cells treated with any of these agents are blocked in mitosis.

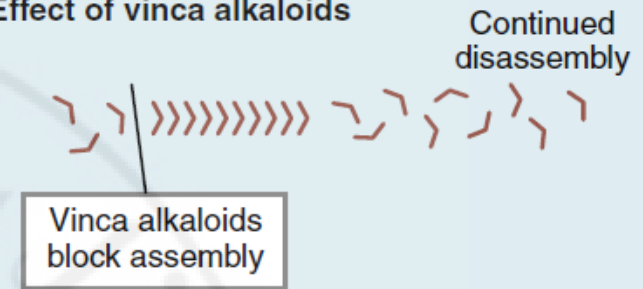


الشكل ٦٨. ١١ : الديناميكيات النببية المجهرية في وجود الفينكريستين والفينبلاستين أو الباكليتاكسيل . ثمة حالة ثبات ديناميكية ، تتمثل بتجمُّع النببيات المجهرية من جهة وانفصال هذا التجمع من الجهة الثانية (أ) . يرتبط الفينكريستين والفينبلاستين (ب) بمثنويات توبولين ويحصران البلمرة ، سامحين بأن يكون الانفصال سائداً . على النقيض من هذا ، يحصر الباكليتاكسيل (ج) الانفصال ، مسبباً تكون نببيات مجهرية ثابتة حتى في غياب تميمات العوامل cofactors الضرورية الطبيعية . تثبُّط الخلايا المعالجة بأيٍّ من هذين الدوائين في الانقسام الخيطي .

A Normal mitosis



B Effect of vinca alkaloids



C Effect of taxanes



Fig. 45.5 Mechanisms of action of mitotic inhibitors. (A) In normal mitosis, the mitotic spindle is formed by microtubules that continuously undergo assembly and disassembly as a result of tubulin polymerization and depolymerization, respectively. (B) Vincristine and other vinca alkaloids bind to tubulin and prevent the polymerization of tubulin dimers. (C) Paclitaxel and other taxanes bind to tubulin, stabilize the tubulin polymer, and thereby prevent depolymerization. As with vinca alkaloids, taxanes cause metaphase arrest.

B. Cytostatics: inhibition of mitosis

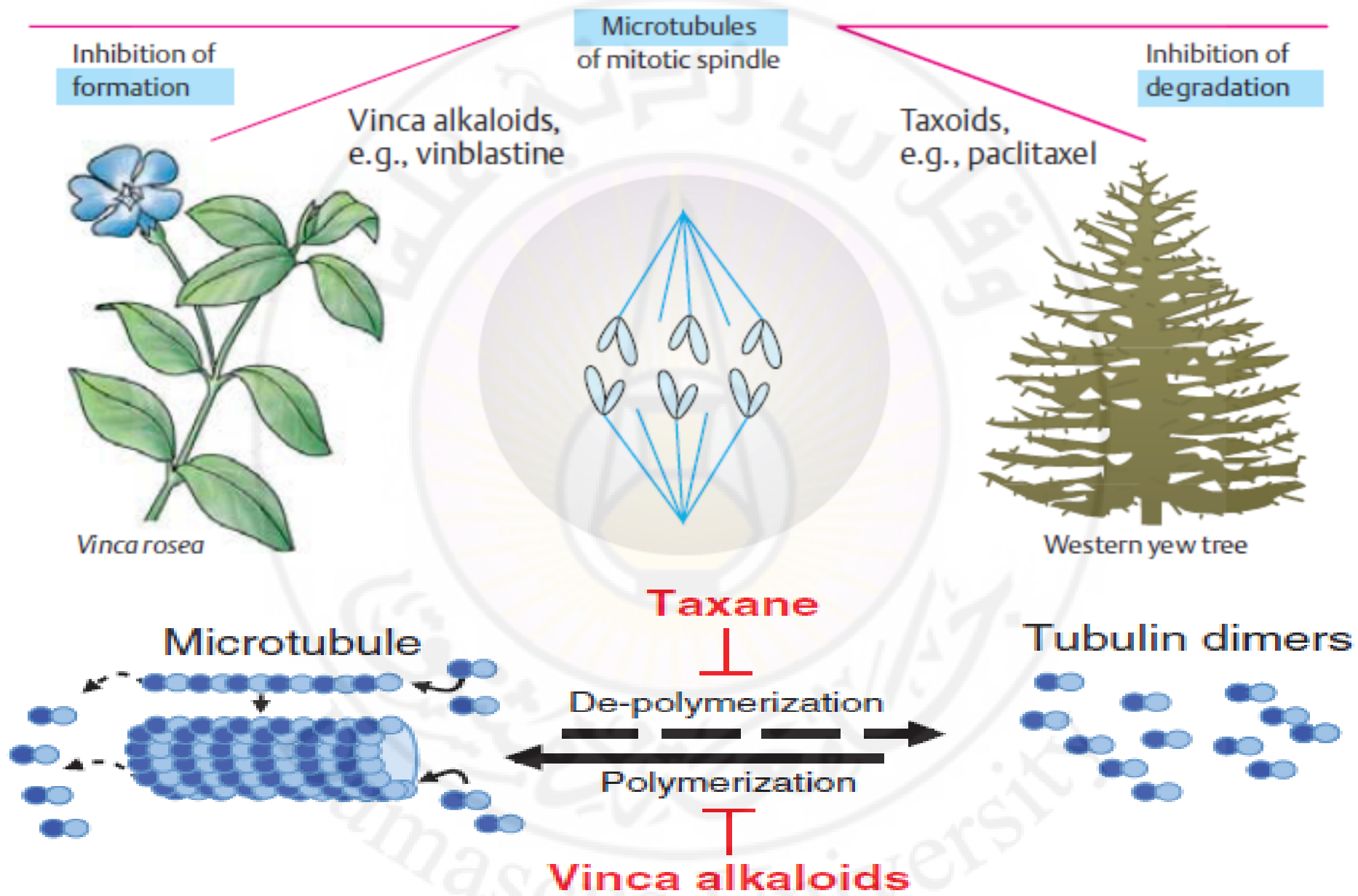


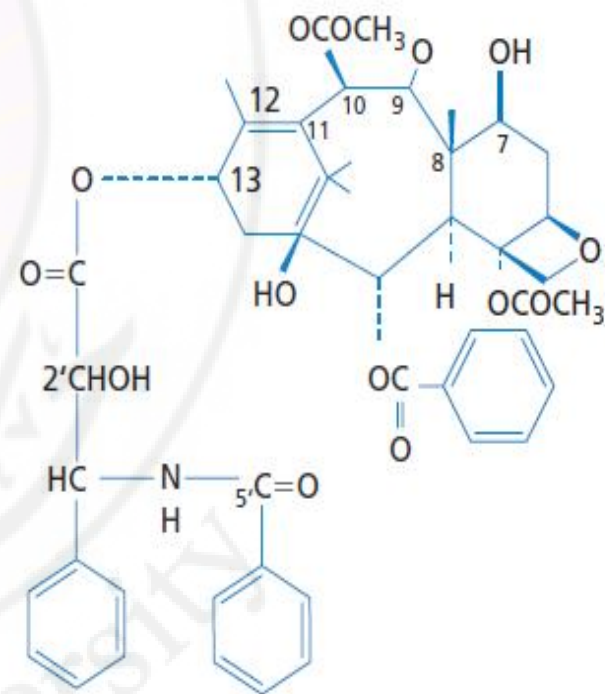
Figure 66–10 *Inhibitors of microtubular function.*



(a)



(b)



(c)

Figure 48.7: *Taxus brevifolia* (a, b), the source of paclitaxel. The chemical structure is shown in panel (c). ((a) Source: Pacific Yew (*Taxus brevifolia*) O'Daniel Tigner, Canadian Forest Tree Essences, provided courtesy of Tree Canada Foundation. (b) © Natural History Museum, London. Reproduced with permission.)

G G : Two classes of **courtesy** (I and II) mediate DNA strand breakage and resealing.

TOPOISOMERASE INHIBITORS
Photophyllam derivatives
Topoisomerase-II inhibitors
<i>Etoposide</i>
<i>Tiniposide</i>
Topoisomerase-I inhibitors
<i>Topotecan</i>
<i>Irinotecan</i>

VI. TOPOISOMERASE INHIBITORS.

These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA (Figure 35.28).

- A. Camptothecins (topoisomerase II inhibitors) Camptothecins are plant alkaloids originally isolated from the Chinese tree *Camptotheca*. *Irinotecan* and *topotecan* are semisynthetic derivatives of *camptothecin*. *Topotecan* is used in *metastatic ovarian cancer* when primary therapy has failed and also in the treatment of small cell lung cancer. *Irinotecan* is used with 5-FU and leucovorin for the treatment of colorectal carcinoma.

سادساً. مثبطات التوبوآيزوميراز : تثبط إنزيمات التوبوآيزوميراز (التي تنقص فرط اللفاف للدنا) (الشكل ٣٥ (28).

أ. الـ Camptothecins (مثبطات الـ

topoisomerase-I) : قلوانيات نباتية من شجرة صينية (كامبتوثيكا) . الـ *Irinotecan* والـ *topotecan* مشتقان نصف صناعيان للـ

camptothecin . يستعمل الأول لسرطان المبيض النقيلي كخط ثاني ولمعالجة سرطان الرئة الصغير الخلايا . الثاني مع الـ 5-FU والـ leucovorin لمعالجة سرطانة القولون والمستقيم .

1. Mechanism of action: These drugs are S-phase specific and inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 35.29). SN-38 (the active metabolite of irinotecan) is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks. 2. Adverse effects: Bone marrow suppression, particularly neutropenia is the dose-limiting toxicity for topotecan. Frequent blood counts should be performed in patients receiving this drug. Myelosuppression is also seen with irinotecan. Acute and delayed diarrhea with irinotecan may be severe and require treatment with atropine during the infusion or high doses of loperamide in the days following the infusion.

آلية الفعل : الـ Topotecan والـ irinotecan تثبط

التوبوأيزوميراز — ١ الحاسم للدنا أثناء التضاعف والانتساخ . لهذا ، فعلها السام للخلية معتمد الطور — س . يسبب هذا الإنزيم تعريّيات مفردة الطاق استرخائية/مفكوكة عابرة في الدنا المزدوج ليسمح بقك/استرخاء الدنا أو عدم لّفه . هذه الأدوية تثبت المرحلة المتوسطة من تفاعل الإنزيم — الدنا التساهمي لتمنع إعادة وصل الدنا فتثبط تضاعفه .

١. التأثيرات الضائرة : كبت نقي العظم ، خصوصاً قلة العدلات المعتمدة — الجرعة للتوبوتيكان . يلاحظ تثبيط النقي أيضاً مع الإرينوتيكان ،

الإسهال الحاد والمؤجل قد يكون شديد ويتطلب أتروبين أثناء تسريبه أو مع الجرعات الكبيرة أو لوبيراميد في الأيام التالية للتسريب .

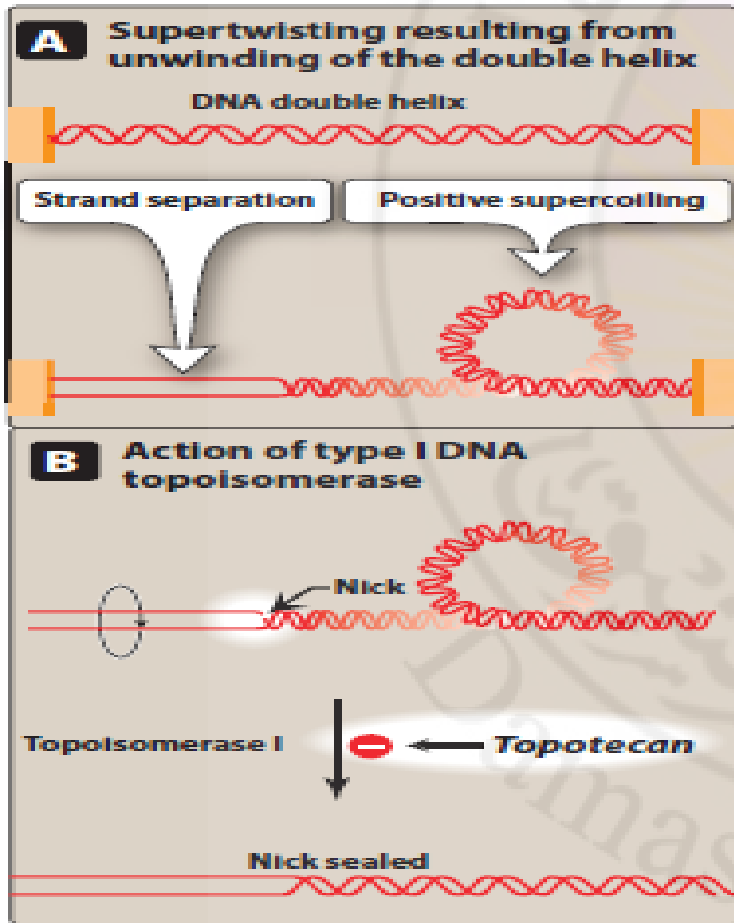


Figure 35.29
Action of type I DNA topoisomerases.

B. Etoposide (topoisomerase I inhibitors) *Etoposide is a semisynthetic derivative of the plant alkaloid, podophyllotoxin. This agent blocks cells in the late S- to G2 phase of the cell cycle, and the major target is topoisomerase II. Binding of the drug to the enzyme–DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 35.30). and in combination with bleomycin and cisplatin for testicular carcinoma. Etoposide finds its major clinical use in the treatment of lung cancer Etoposide may be administered either IV or orally. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity. Teniposide is another derivative administered by the intravenous route having a longer terminal half-life compared to etoposide. The mechanism of action is similar to that of etoposide. It is used for the refractory. ALL in children. Apart from GI side effects, myelosuppression has also been associated with its usage.*

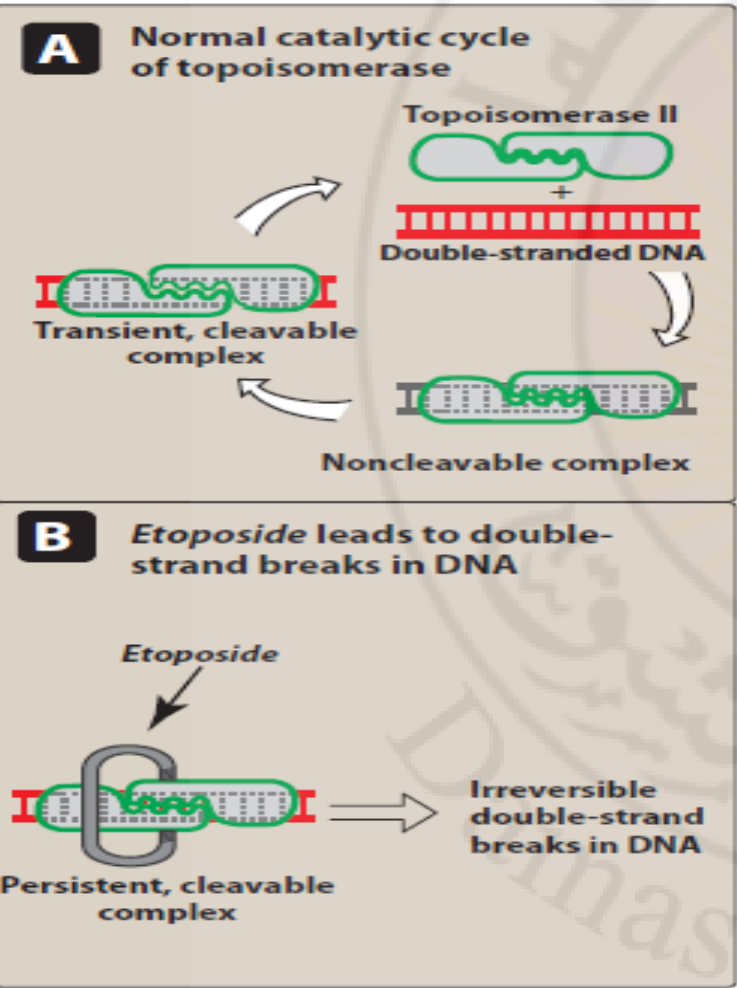


Figure 35.30
Mechanism of action of etoposide.

ب. (فموي ووريدي) **Etoposide** (مُثَبِّط) **التوبوآيزوميراز-II** : مشتق نصف صناعي للقلواني النباتي الـ podophyllotoxin (بودوفيلوتوكسين سم نباتي المنشأ). يحصر الخلايا في نهاية الطور—س إلى الطور—ج ٢ من الدارة الخلوية ، **التوبوزيد** يكوّن معقد مع التوبوآيزوميراز—٢ ، المسؤول عن قطع وإعادة وصل الدنا المضاعف الطاق مؤدياً إلى تثبيط النشاط الوظيفي للتوبوآيزوميراز—٢ مع تثبيط صنع الدنا ووظيفته .

(الشكل ٣٥ . ٣٠) .

لسرطان الرئة وبالتوليف مع بليوميسين وسيسبلاتين لسرطانة الخصية .

يسبب تثبيط نقي-محدد بالجرعة (قلة البيض) .

الـ **Teniposide** وريدي **يثبط النقي**..

ALKYLATING AGENTS

Nitrogen mustards

Mechloréththamine

Cyclophosphamide

Ifosfamide

Chlorambucil

Melphalan

Bendamustine

Ethyleneimines

Altretamine

Thiotepa

Alkyl sulfonates

Busulfan

Nitrosoureas

Carmustine

Lomustine

Streptozotocin

Triazine

Decarbazine

Temozolomide

Methylhydrazine

Procarbazine

{{ Alkylating agents all work by adding an alkyl group to DNA. }}

These drugs all introduce alkyl group into nucleophilic sites with covalent bonds . There are many sites of alkylation, but the degree of deoxyribonucleic acid (DNA) alkylation correlate with the cytotoxicity of the drugs. these drugs are not cycle specific. They are prone to cause local tissue necrosis and damage .

سابعاً . العوامل المؤلّكة (الشكل ٣٥ . ١٧) :

{{العوامل المؤلّكة تعمل بإضافة مجموعة ألكيل إلى الدنا (ألكلة الدنا)}}

كل هذه الأدوية تُدخل مجموعة ألكيل في مقرّات أليفة للنواة بروابط تساهمية (تأثيراتها السامة للخلية بارتباطها تساهمياً بمجموعات أليفة النواة) .

هذه الأدوية ليست نوعية لدورة الخلية .

قد تسبب نخر وضرر موضعي للنسيج .

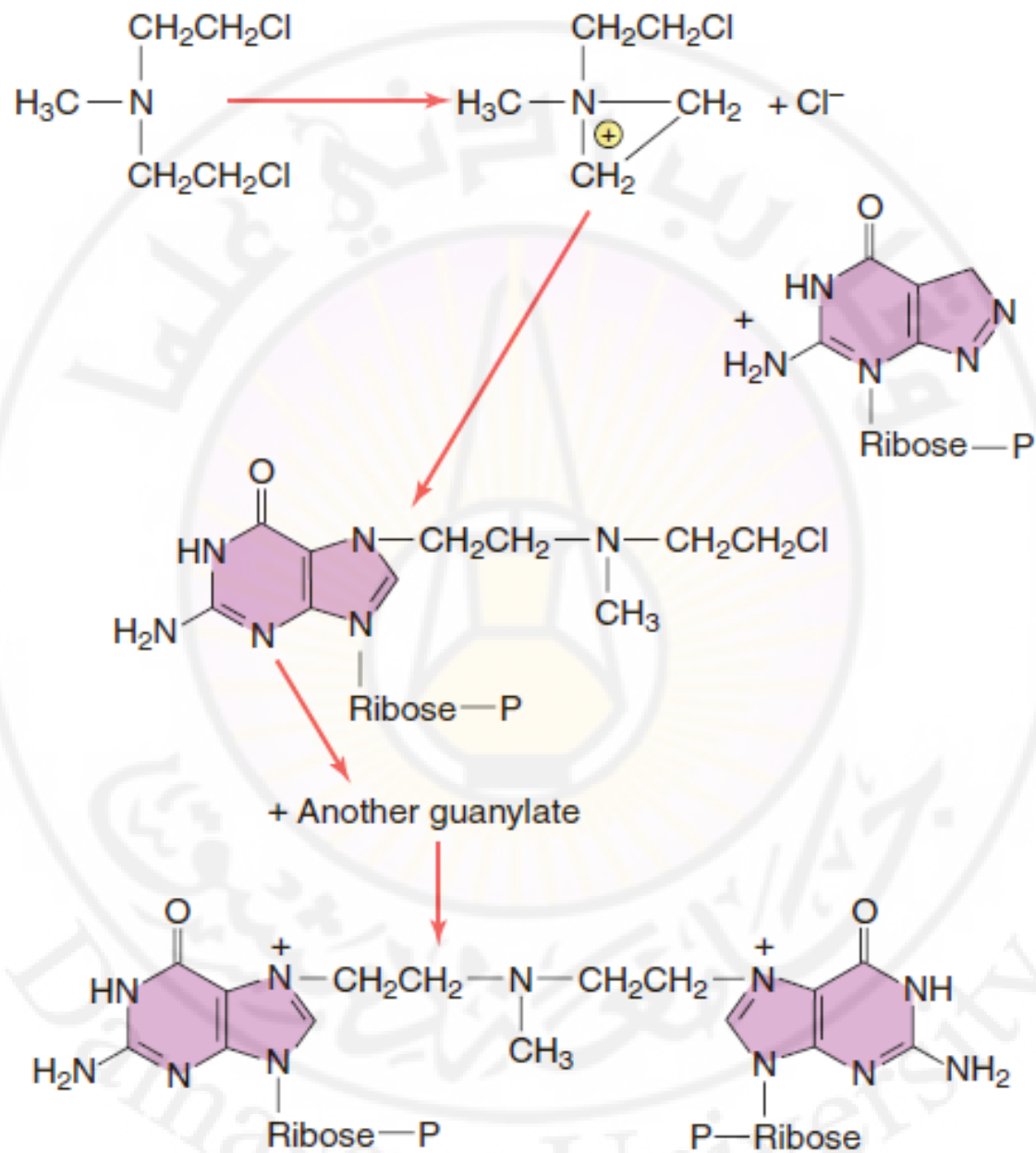


FIG. 68.5 DNA Alkylation by Mechlorethamine. Shown is the positively charged intermediate ion and its covalent attachment to the N-7 position of two deoxyguanylate nucleotides of DNA.

G = Guanine

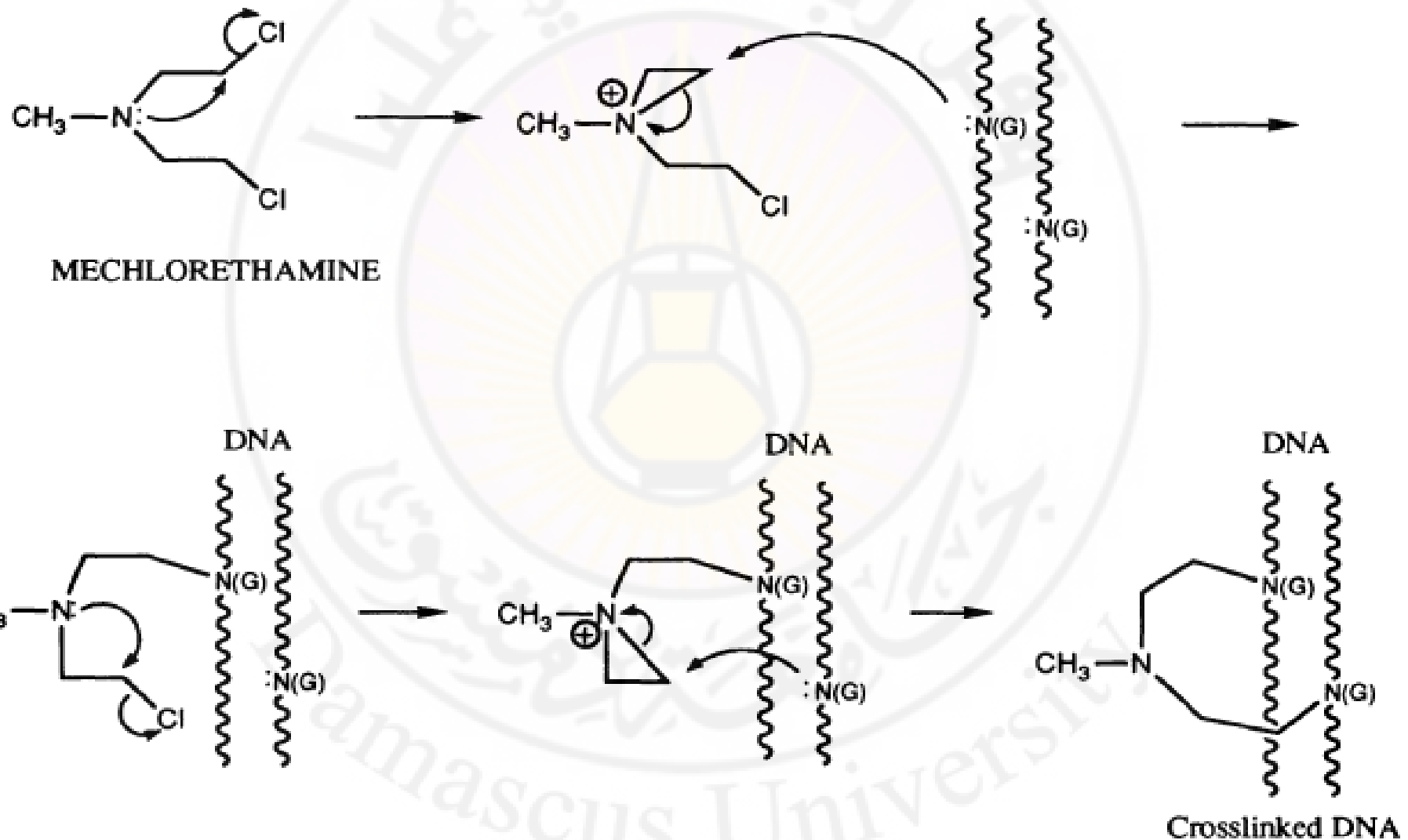


Fig. 6.10 Alkylation of DNA by the nitrogen mustard compound, mechlorethamine.

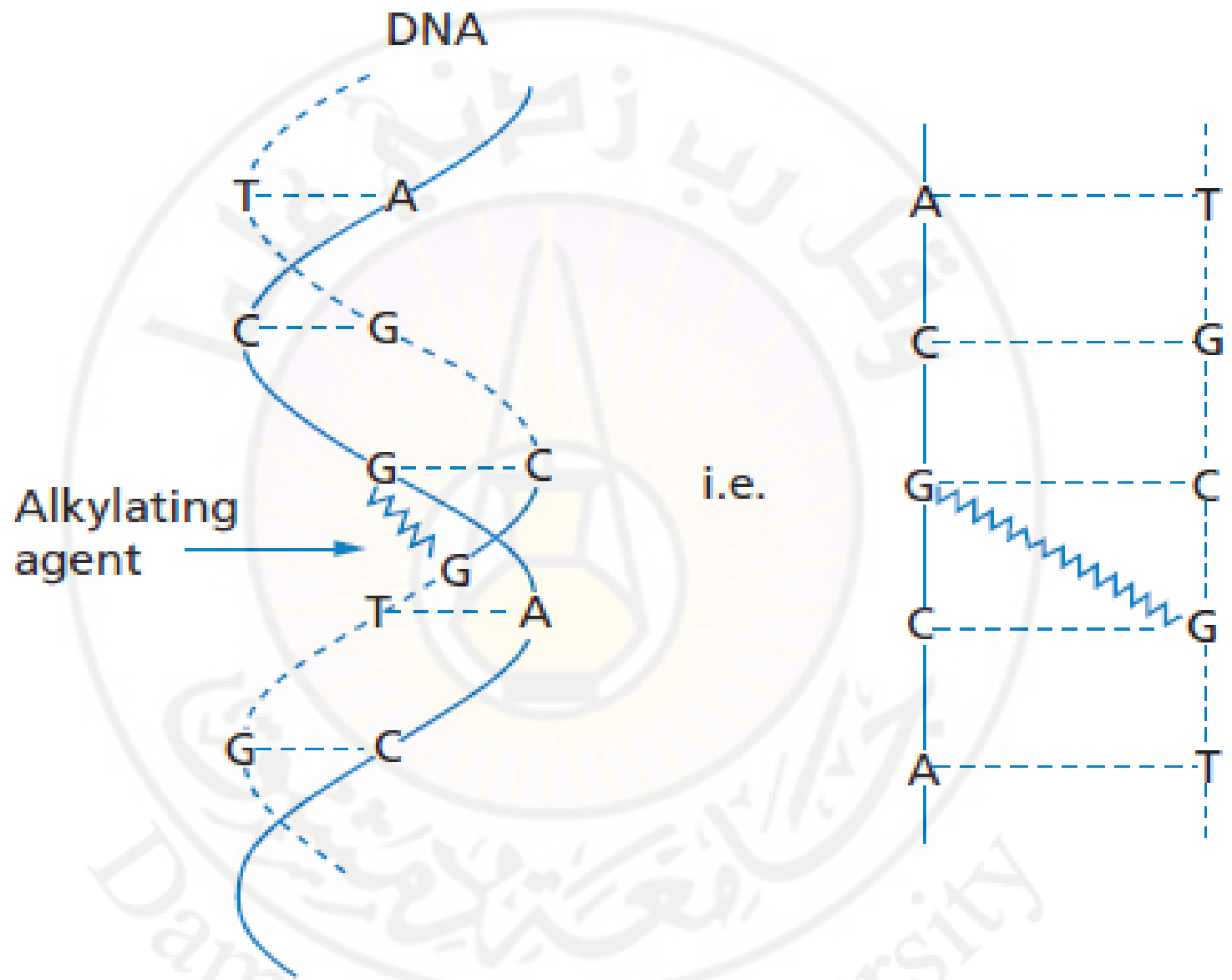
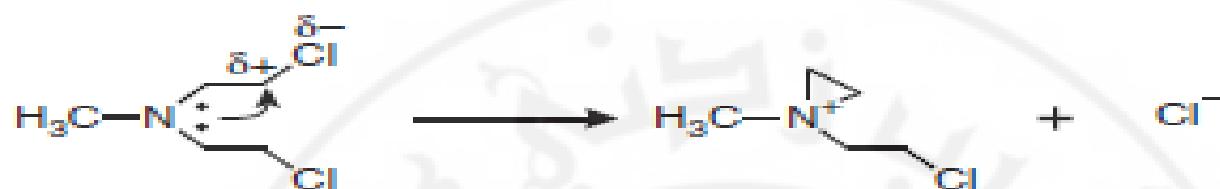


Figure 48.4: Mechanism of intramolecular bridging of DNA by alkylating agents. A, adenine; C, cytosine; G, guanine; T, thymidine.

A**Activation****B****Nucleophilic attack of unstable aziridine ring by electron donor**

($-\ddot{\text{S}}\text{H}$ of protein, $-\ddot{\text{N}}-$ of protein or DNA base, $=\ddot{\text{O}}$ of DNA base or phosphate)

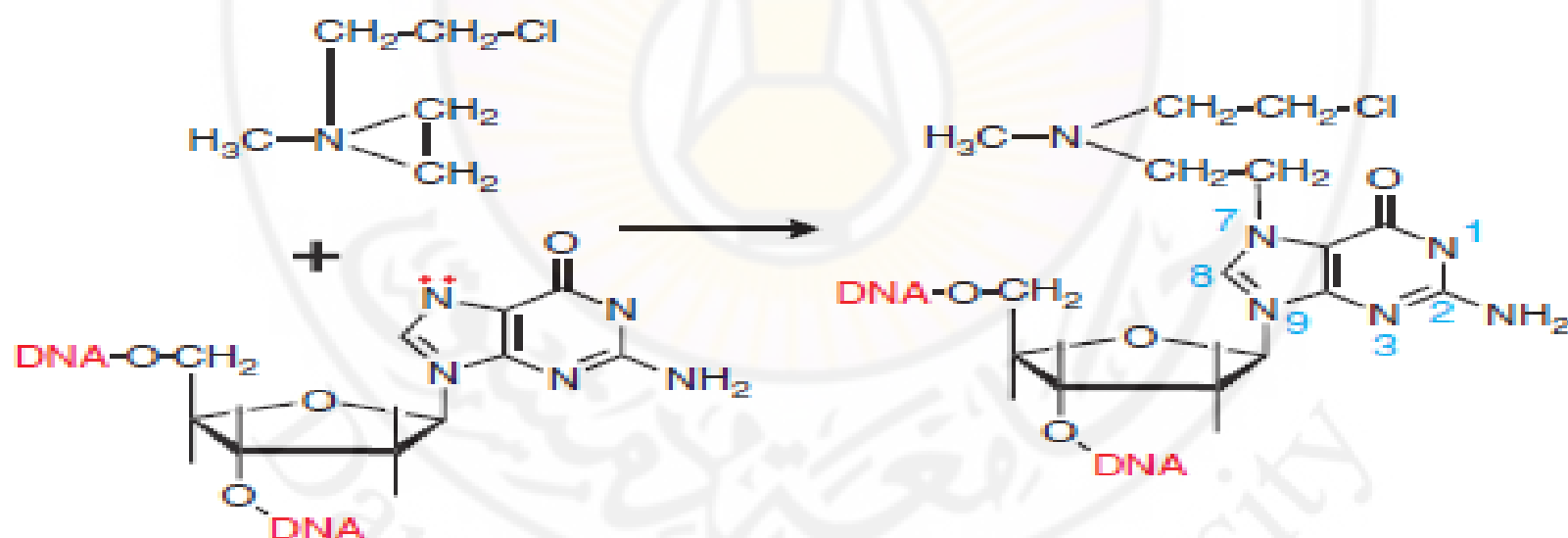
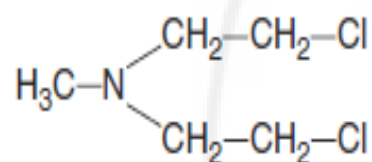
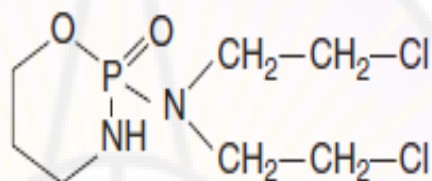


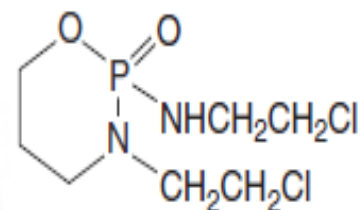
Figure 66–1 Mechanism of action of alkylating agents of mechlorethamine, a prototypic nitrogen mustard. **A.** Activation reaction. **B.** Alkylation of N7 of guanine. With bifunctional drugs such as nitrogen mustards (see Figure 66–2), the second 2-chloroethyl side chain can undergo a similar activation cross-link of two nucleic acid chains or a nucleic acid to a protein.



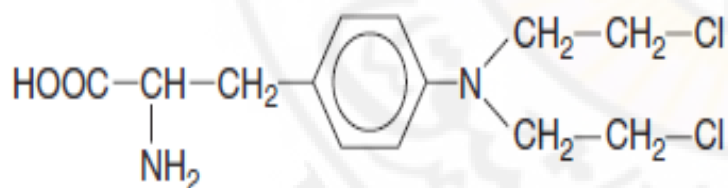
MECHLORETHAMINE



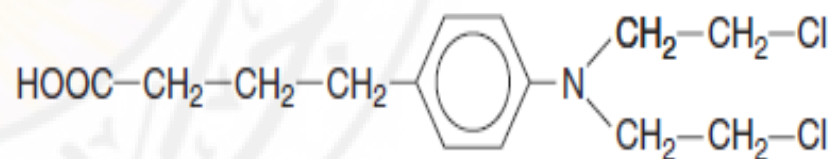
CYCLOPHOSPHAMIDE



IFOSFAMIDE



MELPHALAN



CHLORAMBUCIL

Figure 66-2 Nitrogen mustards employed in therapy.

Nitrogen mustards: chlorambucil ; cyclophosphamide; ifosfamide;
mechlorethamine (nitrogen mustard) ; melphalan

Nitrosoureas: carmustine ; lomustine

Other alkylating agents: busulphan; carboplatin; cisplatin; oxaliplatin
dacarbazine; temozolomide; thiopeta

The nitrosoureas are easy to recognize because of the “-mustine” ending on their names.
They are lipid soluble and therefore cross into the central nervous system (CNS).
They have found use in the treatment of brain tumors..

أ. الخَردل النِّتْرُوجِينِيَّة :

chlorambucil ; cyclophosphamide; ifosfamide; mechlorethamine ;
melphalan

ب. مَرَكَّبَات النِّتْرُوزُوِيُورِيَا : carmustine ; lomustine
ج. عوامل مؤلِّكة إِضَافِيَّة :

busulphan; carboplatin; cisplatin; oxaliplatin; dacarbazine;
temozolomide; thiopeta

تتميز مَرَكَّبَات النِّتْرُوزُوِيُورِيَا بِالنِّهَآيَةِ “-mustine” . ذَوَابَةِ فِي الشَّحْم فَتَعْبُرُ إِلَى الْ-
CNS . تَسْتَعْمَلُ فِي مَعَالَجَةِ أَوْرَامِ الدِّمَاغِ .

Alkylating Agents

Mechlorethamine

Chlorambucil

Cyclophosphamide

Bendamustine (consisting of a purine benzimidazole ring and a nitrogen mustard moiety.)

Melphalan

Thiotepa

Busulfan

Carmustine

Lomustine

Altretamine

Forms DNA crosslinks, resulting in inhibition of DNA synthesis and function

تُكوّن وصلات متصالبة للدنا ، مسببة تثبيط تصنيع الدنا ووظيفته .

Procarbazine 1

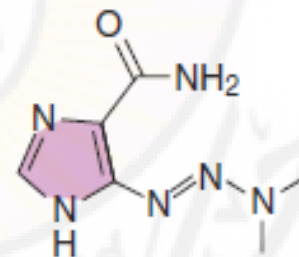
Dacarbazine 2

Temozolomide 1

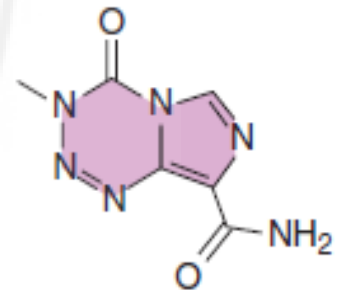
Methylates DNA and inhibits DNA synthesis and function

تُمَثِّل الدنا وتثبط تصنيعه ووظيفته .

Triazines



Dacarbazine



Temozolomide

TABLE 54-2 Alkylating agents and platinum analogs: Clinical activity and toxicities.

Alkylating Agent	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency
Chlorambucil	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Cyclophosphamide	Same as above	Breast cancer, ovarian cancer, non-Hodgkin's lymphoma, CLL, soft tissue sarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma	Nausea and vomiting	
Bendamustine	Same as above	CLL and non-Hodgkin's lymphoma	Nausea and vomiting	
Melphalan	Same as above	Multiple myeloma, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; rarely interstitial lung disease and interstitial nephritis
Thiotepa	Same as above	Breast cancer, ovarian cancer, superficial bladder cancer	Nausea and vomiting	
Busulfan	Same as above	CML	Nausea and vomiting	
Carmustine	Same as above	Brain cancer, Hodgkin's and non-Hodgkin's lymphoma	Nausea and vomiting	
Lomustine	Same as above	Brain cancer	Nausea and vomiting	

تابع للجدول السابق

Altretamine	Same as above	Ovarian cancer	Nausea and vomiting	Myelosuppression, peripheral neuropathy, flu-like syndrome
Temozolomide	Methylates DNA and inhibits DNA synthesis and function	Brain cancer, melanoma	Nausea and vomiting, headache and fatigue	Myelosuppression, mild elevation in liver function tests, photosensitivity
Procarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's and non-Hodgkin's lymphoma, brain tumors	Central nervous system depression	Myelosuppression, hypersensitivity reactions
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function	Hodgkin's lymphoma, melanoma, soft tissue sarcoma	Nausea and vomiting	Myelosuppression, central nervous system toxicity with neuropathy, ataxia, lethargy, and confusion
Cisplatin	Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, cholangio-carcinoma, gastroesophageal cancer, head and neck cancer, ovarian cancer, germ cell cancer	Nausea and vomiting	Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction
Carboplatin	Same as cisplatin	Non-small cell and small cell lung cancer, breast cancer, bladder cancer, head and neck cancer, ovarian cancer	Nausea and vomiting	Myelosuppression; rarely peripheral neuropathy, renal toxicity, hepatic dysfunction
Oxaliplatin	Same as cisplatin	Colorectal cancer, gastroesophageal cancer, pancreatic cancer	Nausea and vomiting, laryngopharyngeal dysesthesias	Myelosuppression, peripheral sensory neuropathy, diarrhea

VIII. ANTIMETABOLITES. Antimetabolites are structurally related to normal compounds that exist within the cell (Figure 35.8). They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase and are, therefore, cell cycle-specific.

ANTIMETABOLITES
Folate antagonists
<i>Methotrexate</i>
<i>Pemetrexed</i>
<i>Pralatrexate</i>
Purine antagonists
<i>6-Mercaptopurine</i>
<i>6-Thioguanine</i>
<i>Azathioprine</i>
<i>Fludarabine</i>
<i>Cladribine</i>
Pyrimidine antagonists
<i>Fluorouracil (5-FU)</i>
<i>Capecitabine</i>
<i>Floxuridine</i>
Cytidine analogs
<i>Cytarabine</i>
<i>Azacytidine</i>
<i>Gemcitabine</i>

ثامناً. مضادات الاستقلاب : متعلقة كيميائياً بالمرکبات الطبيعية الموجودة ضمن الخلية .

تتداخل مع توافر طلائع البورين أو البيريميدين النوكليوتيدية ،
إما بتثبيط تصنيعها أو بالتنافس معها في تصنيع الدنا أو الرنا } - تتنافس على مقرّات إرتباط على إنزيمات أو تُضمّن في الدنا أو الرنا . تفيد خصوصاً إذا ارتبطت بإنزيم ذو تأثير مهم على طرق تؤدي للتضاعف ، خصوصاً الـ **thymidylate synthase (TS)** .

تأثيراتها السامة للخلية الأعظمية في الطور —س ولهذا هي
نوعية —لدورة الخلية . < < <

TABLE 54-3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, nausea and vomiting, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase.

{{ Methotrexate competitively inhibits dihydrofolate reductase. }}

Remember this pathway from folate antagonists. Methotrexate inhibits the binding of folic acid to the enzyme. It therefore inhibits DNA synthesis by inhibiting thymidylate synthesis. Cellular uptake of methotrexate is by a carrier-mediated active transport. Cellular resistance to methotrexate is presumably caused by decreased transport into the cell. This can be overcome by using high doses .

{يثبط الميتوتريكسات تنافسياً الـ {dihydrofolate reductase

يثبط الميتوتريكسات ارتباط حامض الفوليك بالإنزيم . بالتالي يثبط تصنيع الدنا بتنشيط الـ (TS) thymidylate synthesis. يجري أخذ الميتوتريكسات إلى الخلايا بنقل فعال متواسط—ب حامل . إذ تحدث مقاومة الميتوتريكسات بتنقيص نقله إلى الخلية . يمكن التغلب على هذا باستعمال جرعات كبيرة .

{يوفر اللوكوفورين فولات مُرجعة لينقذ الخلايا الطبيعية من فعل الميتوتريكسات}

يوفر اللوكوفورين خلايا فيها فولات مُرجعة مما يتجاوز الإنزيم المثبّط .

{يستعمل الميتوتريكسات لمعالجة الصدفية والتهاب المفاصل الروماتويدي الوخيم وفي معالجة ضرب واسع من السرطان . يمكن إعطاؤه داخل القراب} .

تُحاكي الأدوية الإضافية في هذا الصنف البورين أو البيريميدينات أو السيتيدين .
تُضمّن في الدنا النامي أثناء انقسام الخلية وتُحصر تضاعف الدنا . لهذا هي فعالة أكثر في الخلايا المنقسمة .

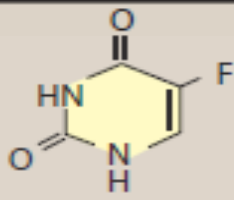
يجب تنشيط (فسفرة) هذه المضاهئات (المشابهات) لكي تكون فعالة .
قارن هذا التنشيط مع تنشيط مضادات الفيروسات .

D. 5-Fluorouracil (pyrimidine antagonists)

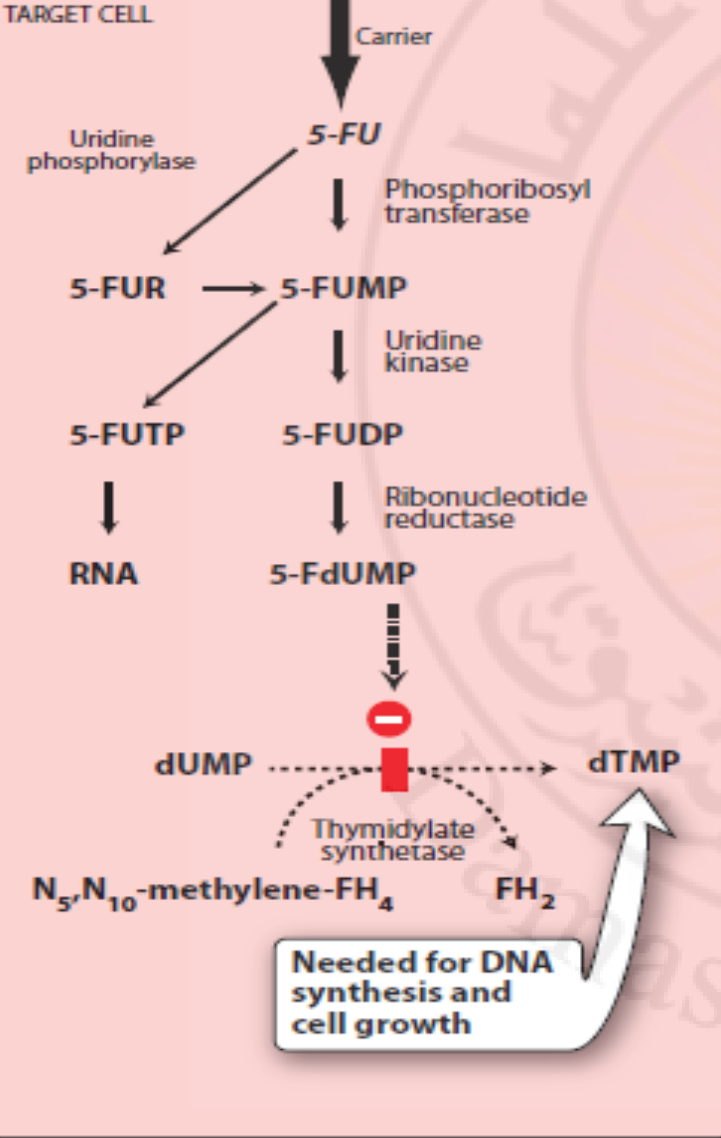
5-Fluorouracil (5-FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The **fluorine** interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

د. الـ (pyrimidine antagonists) (5-Fluorouracil (5-FU) : مشابه (مضاهي) للبيريميدين ، .. يتداخل الفلور مع تحوّل حامض الذي أكسي يوريديليك ، فيحرم الخلية من الثيميدين ، أحد الطلائع الضرورية لتصنيع الدنا .

يعالج الأورام الصلبة البطيئة—النمو (مثل كارسينوما القولون والمستقيم والثدي والمبيض والبنكرياس والمعدة . يفيد تطبيقه الموضعي في معالجة الكارسينوما السطحيّة القاعدية الخلايا .



5-Fluorouracil (5-FU)



1. Mechanism of action: 5-FU itself is devoid of cytotoxic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; Figure 35.11), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine-less death" of rapidly dividing cells. [Note: Leucovorin is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition. For example, a standard regimen for advanced colorectal cancer is irinotecan plus 5-FU/leucovorin.] 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S-phase of the cell cycle.

١. آلية الفعل : يدخل الخلية بنظام نقل متواسط —

بحامل ويتحول إلى 5-fluorodeoxyuridine monophosphate [5-FdUMP]; (الشكل ٣٥)، الذي يتنافس مع الـ deoxyuridine monophosphate (dUMP) علي الـ

thymidylate synthase ، مثبتاً فعله بالتالي . إذ ينقص تصنيع الدنا بسبب نقص الثيميدين ، مؤدياً اختلال نمو الخلية و "موت بنقص—الثيميدين" للخلايا السريعة الانقسام .

(ملاحظة : يعطى Leucovorin مع 5-FU ، لأنّ تميم الإنزيم الفولات المختزل مطلوب في تثبيط تصنيع الثيميديلات . مثال ، التدبير المعياري من أجل سرطان القولون والمستقيم هو irinotecan مع 5-FU/leucovorin .) يُضمّن الـ 5-FU أيضاً في الرنا ، وقد كشفت مستويات قليلة في الدنا . في الحالة الأخيرة ، ثمة glycosylase يزيل/يقطع الـ 5-FU ، مخرباً الدنا .

تأثير الـ 5-FU في الطور —س .

مضادات الاستقلاب ANTIMETABOLITES (آليات الفعل) :

Capecitabine , 5-Fluorouracil

تثبط الـ (thymidylat synthase) **TS** ؛
يؤدي تضمين

الـ -5'-5-fluorouridine- triphosphate (FUTP)

في الرنا إلى تغيير في عملية الرنا ،
ويؤدي تضمين

الـ -5-fluorodeoxyuridine- triphosphate (FdUTP)

في الدنا إلى تثبيط تصنيع الدنا ووظيفته

Methotrexate

يثبط الـ (dihydrofolate reductase) **DHFR**

والـ **TS** وتصنيع نوكلئوتيد البورين الجديد

Pemetrexed

يثبط الـ **TS** والـ **DHFR** وتصنيع
نوكلئوتيد البورين.

Cytarabine

يثبط استطالة سلسلة الدنا وتصنيع الدنا وإصلاحه ؛
يثبط الـ ribonucleotide reductase مع إنقاص
تكوين الـ dNTPs (deoxyribonucleotide triphosphate) ؛
يجري تضمين السيتارابين ثلاثي
الفسفات في الدنا .

Gemcitabine

يثبط تصنيع الدنا وإصلاحه ؛ يثبط الـ
reductase ribonucleotide مع إنقاص تكوين
الـ dNTPs ؛ تضمين شكله الثلاثي الفسفات في الدنا
يثبط تصنيع الدنا ووظيفته

Fludarabine , Cladribine

يثبط تصنيع الدنا وإصلاحه ، ويثبط الـ
reductase ribonucleotide ؛ تضمين شكله
الثلاثي الفسفات في الدنا ؛ تحريض الاستماتة .

6-Mercaptopurine (6-MP), 6-Thioguanine

يثبط تصنيع نوكلئوتيد البورين الجديد ؛ تضمين شكل
الدواء الثلاثي الفسفات في الرنا والدنا .

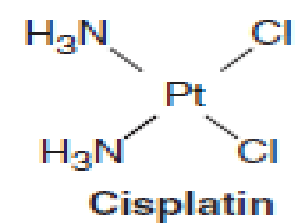
IX. PLATINUM COORDINATION COMPLEXES

A. Cisplatin, carboplatin, and oxaliplatin Cisplatin was the first member of the platinum coordination complex class of anticancer drugs, but because of severe toxicity, carboplatin was developed. The potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly (Figure 35.27) between the two drugs. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. It has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with VBL and bleomycin, ovarian carcinoma in combination with cyclophosphamide , or alone for bladder carcinoma. Carboplatin is used when patients cannot be vigorously hydrated, as is required for cisplatin treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. Oxaliplatin is a closely related analog of carboplatin used in the setting of colorectal cancer.

تاسعاً. المركّبات المتناسقة مع البلاتين :

أ. **Cisplatin** و **carboplatin** و **oxaliplatin** : للسيسبلاتين سمية خلوية تآزرية مع التشعيع ومضادات السرطان . للأورام الصلبة كسرطانة الخصية النقيلية بالتوليف مع VBL و بليوميسن ، وسرطانة المبيض بالتوليف مع سيكلوفسفاميد ، أو وحيداً لسرطانة المثانة .

يستعمل الكربوبلاتين لمن لا يستطيعون الإماهة الشديدة ، المطلوبة مع السيسبلاتين ، أو المعانون من خلل كلوي أو المهيئين للتسمم العصبي أو الأذني .
الأكساليبلاتين مضاهئ للكربوبلاتين يستعمل في سرطان القولون والمستقيم .



1. Mechanism of action: The mechanism of action for these agents is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, *cisplatin persists as the neutral species*, which enters the cell and loses chloride in the low-chloride milieu. It then binds to guanine in DNA, forming inter- and intrastrand cross-links. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G1- and S-phases.

١. **آلية الفعل :** مماثلة لآلية العوامل المؤلفة . يدخل السيسبلاتين الخلية ويفقد الكلوريد في الوسط القليل—الكلوريد . ثم يرتبط بالغوانين في الدنا ، مكوناً اتصالات—متقاطعة بين الطيقان وداخلها ، مما يثبط بوليميراز تضاعف الدنا وبوليميراز تصنيع الرنا .

تسمح الخلية يحصل بأي مرحلة من الدارة ، لكن الخلايا الأكثر عرضة لأفعال هذه الأدوية هي في الطورين س و ج ١ .

3. Adverse effects: Severe, persistent vomiting occurs for at least 1 hour after administration of cisplatin and may continue for as long as 5 days. Premedication with antiemetic agents is required. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be prevented by aggressive hydration. Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus. Unlike cisplatin, carboplatin causes only mild nausea and vomiting, and it is rarely nephro-, neuro-, or ototoxic. The dose-limiting toxicity is myelosuppression. Oxaliplatin has a distinct adverse effect of cold-induced peripheral neuropathy that usually resolves within 72 hours of administration. It also causes myelosuppression and cumulative peripheral neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.

--التأثيرات الضائرة : قيء شديد مستدام لساعة على الأقل بعد إعطاء سيسبلاتين قد يدوم ٥ أيام . يتطلب معالجة مسبقة بمضادات القيء . السمية المقيدة الرئيسة كلوية—معتمدة الجرعة ، مكثفة النبيب الملتف البعيد والقنوات الجامعة للبول . يمكن منعها بالإمهاء الشديدة . تتضمن السميات أيضاً سمعية مع فقد سمع التردد العالي والطنين . يسبب الكربوبلاتين فقط غثيان وقيء خفيفين ، ونادراً تسممات كلوية وعصبية وسمعية . كبت النقي محدد—بالجرعة .

يسبب الأكساليبلاتين اعتلال أعصاب محيطية—محرّض—بالبرد يزول عادةً خلال ٧٢ ساعة من الإعطاء . يسبب أيضاً تثبيط نقي واعتلال أعصاب محيطية تراكمي . ثمة بلغات عن سمية كبدية . قد تسبب هذه الأدوية فرط تحسس يتراوح بين طفح الجلد والتأق .

DRUGS ACTING THROUGH SPECIFIC TARGETS

Angiogenesis inhibitors

Bevacizumab

Sunitinib

Proteasome inhibitor

Bortezomib

EGF receptor inhibitors

Cefitinib

Erlotinib

Cetuximab

Tyrosine protein-kinase inhibitors

Imatinib

Nilotinib

Unarmed monoclonal antibody

Rituximab

Trastuzumab

X. ANTIBODIES. Monoclonal antibodies (Figure 35.31) are an active area of drug development for anticancer therapy and other non-neoplastic diseases, because they are directed at specific targets and often have different adverse effect profiles as compared to traditional chemotherapy agents. [Note: Monoclonal antibodies also find application in a number of other disorders, such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis.] All of these agents are administered intravenously, and infusion-related reactions are common.

XI. TYROSINE KINASE INHIBITORS. The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division. [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylation of signaling proteins. They have been implicated in the development of many neoplasms.] The tyrosine kinase inhibitors are administered orally, and these agents have a wide variety of applications in the treatment of cancer (Figure 35.32).

عاشراً. الأضداد : الأضداد وحيدة النسيلة **(الشكل ٣٥ . ٣١)** فعالة موجهة نحو أهداف نوعية .. كلها تعطى في الوريد والتفاعلات المتعلقة بالتسريب شائعة

إحدى عشر. مثبطات التيروسين كيناز : (فموية، الشكل ٣٥ . ٣٢):
هذه الإنزيمات مكثفة في نقل تحاسّ الإشعاع وانقسام الخلية .
(ملاحظة : ٥٠ **تيروزين كيناز على الأقل** تتوسط نمو الخلية وانقسامها بواسطة فسفرة بروتينات الإشعاع . **متورطة في تطور أورام كثيرة**).

يسبب الـ **Imatinib** كبت نقى واحتباس سوائل و CHF والـ **Nilotinib** تثبيط نقى وإطالة كيو—ت وسمية كبدية . **Sunitinib**

Figure 35.31. Summary of monoclonal antibodies. BP = blood pressure; CBC = complete blood count; **EGFR** = epidermal growth factor receptor; **HER2** = human epidermal growth factor receptor protein 2; GI = gastrointestinal; LVEF = left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy اعْتِلَالُ بَيضَاءِ الدِّمَاغِ العَدِيدُ البَوَرِّ المُتَرَقِّي; TLS = tumor lysis syndrome; **VEGF** = vascular endothelial growth factor. ; TLS = tumor lysis syndrome; **PML** = progressive multifocal leukoencephalopathy

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS
<i>Bevacizumab</i>	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding
<i>Cetuximab</i>	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea
<i>Rituximab</i>	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal Infusion reaction, TLS, mucocutaneous reactions, PML
<i>Trastuzumab</i>	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, Infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting

Drug	Mechanism of Action ¹	Clinical Applications ¹	Acute Toxicity	Delayed Toxicity
Bortezomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF-κB signaling pathway	Multiple myeloma, mantle cell lymphoma	Nausea and vomiting, fever	Peripheral sensory neuropathy, diarrhea, orthostatic hypotension, fever, pulmonary toxicity, reversible posterior leukoencephalopathy (RPLS), congestive heart failure (CHF), rare cases of QT prolongation
Carfilzomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF-κB signaling pathway; maintains activity in bortezomib-resistant tumors	Multiple myeloma	Fever	Fatigue, cardiac toxicity with CHF and myocardial infarction, myelosuppression, pulmonary toxicity, hepatotoxicity, orthostatic hypotension
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling	Non-small cell lung cancer, pancreatic cancer	Diarrhea	Skin rash, diarrhea, anorexia, interstitial lung disease
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit	CML, gastrointestinal stromal tumor (GIST), Philadelphia chromosome-positive ALL	Nausea and vomiting	Fluid retention with ankle and periorbital edema, diarrhea, myalgias, congestive heart failure
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.	CML	Nausea and vomiting	Diarrhea, fluid retention, myelosuppression, skin rash hepatotoxicity
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer, head and neck cancer (used in combination with radiotherapy), non-small cell lung cancer	Infusion reaction	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer	Infusion reaction (rarely)	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, glioblastoma multiformae	Hypertension, infusion reaction	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, proteinuria

Table 48.10: Monoclonal antibodies used to treat cancer

Drug ^a	Therapeutic use	Pharmacodynamics/pharmacokinetics	Side effects	Additional comments
Alemtuzumab	B-cell lymphoma	Binds to CD52 on neutrophils and lymphs, Causes apoptosis via ADCC. Plasma $t_{1/2}$ = 12 days, dose-dependent kinetics	Infusion reactions, opportunistic infections, pancytopenia	Early efficacy in mycosis fungoides and T-cell lymphoma
Bevacizumab	Colorectal and ? lung cancer	Binds to circulating VEGF, inhibits angiogenesis neovascularization, plasma $t_{1/2}$ = mean 20 days (range 11–50)	Hypertension, pulmonary and gastro-intestinal bleeds, proteinuria, cardiac failure	Used as single agent or in combinations in colorectal cancer. It improves median survival by 5 months
Cetuximab	Colorectal and pancreatic and NSCL and ? breast cancer	Targets EGFR (Erb-1), inhibits EGFR-mediated signal transduction. Plasma $t_{1/2}$ = 3–8 days	Infusion reactions, skin rashes – 75%, electrolyte losses	Prolongs survival in colon cancer
Gemtuzumab	Acute myeloid leukaemia	Targets CD33 on T cells, plasma $t_{1/2}$ = 10–20 days	Infusion reactions, bone marrow suppression, VOD and skin rash	
Rituximab ^b	B-cell lymphoma and CLL (also used for ITP)	Binds to CD20 on B-cells and activates TK, c-myc and MHC class II molecules, plasma $t_{1/2}$ = 10–14 days	Infusion reactions: fever, rash, dyspnoea, delayed neutropenia	

^aDosing of all monoclonal antibodies is intravenous. Usually a loading dose is followed by weekly or biweekly treatments.

^bRadioisotope labelled versions of other antibodies to the same target are available.

ADCC, antibody-directed cellular cytotoxicity; EGFR, epidermal growth factor receptor; CLL, chronic lymphatic leukaemia; ITP, idiopathic thrombocytopenia; NSCL, non-small cell lung; TK, tyrosine kinase; VEGF, vascular endothelial growth factor; VOD, vascular occlusive disease.

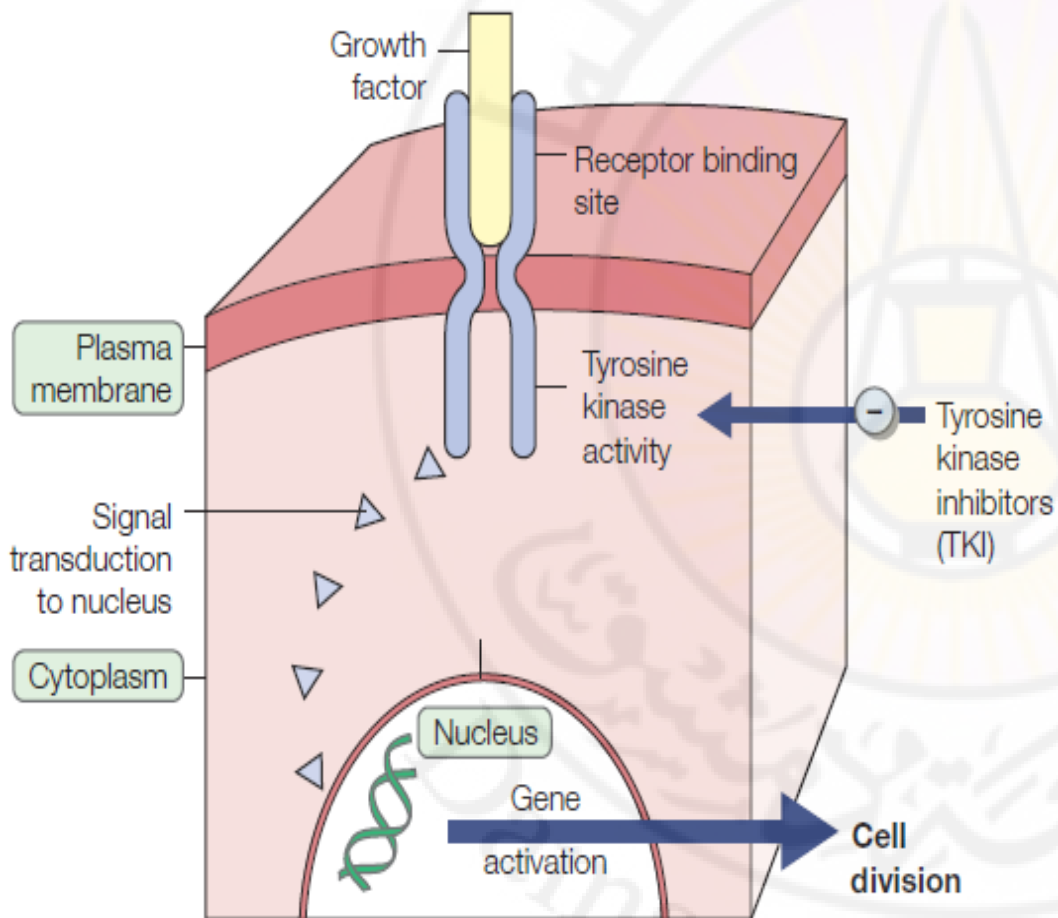


Figure 48.8: Inhibitory effect of tyrosine kinase inhibitors on cell proliferation. (Redrawn with permission from Gardiner-Caldwell communications Ltd.(©1999).)

XII. IMMUNOTHERAPY. The goal of immune checkpoint inhibitors is to block the checkpoint molecules, such as the **programmed- death (PD-1)** receptor, that normally help to keep the immune system in check. By blocking these molecules, the immune system is better able to attack the tumor and cause destruction. The two most commonly used checkpoint inhibitors are pembrolizumab and nivolumab .The adverse reaction profiles of these agents consist of potentially severe and even fatal immune-mediated adverse events. This is because turning off the immune checkpoints allows attack of the tumor, but can also lead to unchecked autoimmune response to normal tissues. Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism. Patients should be closely monitored for the potential development of signs and symptoms of toxicity and promptly treated with corticosteroids if necessary.

إثنا عشر. المعالجة المناعية : الـ pembrolizumab و nivolumab :
يسبب إحصار جزيئات مثل مستقبلات الموت—المبرمج (**PD-1**) المعبرة على الخلايا
التائية والتي تتواسط آلية لهروب الورم من المناعة (بوساطة تعبير اللجين—١ لمستقبلات
الموت المبرمج "PD-L1") . إذ أن إحصار هذه الجزيئات يجعل جهاز المناعة (الخلايا
التائية) أكثر قدرة على مهاجمة الورم وتخريبه.. (**nivolumab** يثبط الـ PD-L1 ، و
pembrolizumab يحصر الـ PD-1).

تتضمن التأثيرات الضائرة إسهال والتهاب قولون ورئة وكبد وكلية وتسمم جلد (طفح وخيم) وسمية عصبية واعتلالات صمّاوية مثل نقص أو فرط الدرق .

XIII. MISCELLANEOUS AGENTS

A. Abiraterone acetate. *Abiraterone [ab-er-AT-er-own] acetate is an oral agent used in the treatment of metastatic castration-resistant prostate cancer. Abiraterone acetate is used in conjunction with prednisone to inhibit the CYP17 enzyme (an enzyme required for androgen synthesis), resulting in reduced testosterone production. Coadministration with prednisone is required to help lessen the effects of mineralocorticoid excess resulting from CYP17 inhibition. Hepatotoxicity may occur, and patients should be closely monitored for hypertension, hypokalemia, and fluid retention. Joint and muscle discomfort, hot flushes, and diarrhea are common adverse effects with this agent.*

ثلاثة عشر. أدوية متنوعة :

أ. **Abiraterone acetate** : فموي يعالج سرطان البروستاتة النقيلي المقاوم—لإستئصال الغُدِّ التَّنَاسُلِيَّة/الخِصَاء . مع بريدينزون لتثبيط CYP17 المصنع للأندروجين فينقص إنتاج التستوستيرون . مشاركته مع بريدينزون ليققل تأثيرات زيادة القشرانيات المعدنية الناجمة عن تثبيط CYP17 .

قد يسبب تسمم الكبد وفرط الضغط ونقص بوتاسيوم الدم واحتباس السوائل . يشيع حدوث هبات الحرارة وإسهال وعدم راحة المفاصل والعضل .

B. Immunomodulating agents. Thalidomide , lenalidomide , and pomalidomide are oral agents used in the treatment of multiple myeloma. Their exact mechanism of action is not clear, but they possess antimyeloma properties including antiangiogenic, immune-modulation, anti-inflammatory, and anti-proliferative effects. These agents are often combined with dexamethasone or other chemotherapeutic agents. Adverse effects include, thromboembolism, myelosuppression, fatigue, rash, and constipation. Thalidomide was previously given to pregnant women to prevent morning sickness. However, severe birth defects were prevalent in children born to mothers who used thalidomide. Lenalidomide and pomalidomide are structural variants of thalidomide and because of their structural similarities, these drugs are contraindicated in pregnancy.

ب. الأدوية المحورة/المعدلة للمناعة : Thalidomide و lenalidomide و pomalidomide فموية لمعالجة الورم النقي المتعدد ..

ذات خواص مضادة لورم النقي متضمنة تأثيرات مضادة لتولد الأوعية ومحورة/معدلة للمناعة ومضادة للالتهاب ومضادة للتكاثر .

تولف مع دكساميثازون أو غيرها .

تتضمن تأثيراتها الضائرة انصمام خثري وكبت نقي وتعب وطفح وإمساك .

ممنوعة الاستعمال في الحمل .

C. Proteasome inhibitors. Bortezomib ,ixazomib ,and carfilzomib , are proteasome inhibitors commonly used as the backbone therapy in the treatment of multiple myeloma. These agents work by inhibiting proteasomes, which in turn prevents the degradation of pro-apoptotic factors, thus leading to a promotion in programmed cell death (apoptosis). Malignant cells readily depend on suppression of the apoptotic pathway; therefore, proteasome inhibition works well in multiple myeloma. Bortezomib can be administered IV, but the subcutaneous route is preferred because it is associated with less neuropathy. Other adverse effects include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation. Patients should receive antiviral prophylaxis if they are receiving therapy with bortezomib. Ixazomib is an oral agent with an adverse effect profile similar to bortezomib. Carfilzomib is administered intravenously, and common adverse effects include myelosuppression, fatigue, nausea, diarrhea, and fever. “Chemo Man” is a useful tool to help remember the most common toxicities of these drugs (Figure 35.33).

ج. مثبطات البروتيزوم : **Bortezomib** (iv,sc) و **ixazomib** فموي و (iv) **carfilzomib** معالجة أساسية لورم النقي المتعدد .

بتثبيطها البروتيزومات تمنع تدرك عوامل مؤيدة للاستماتة ، فتؤدي لتعزيز موت الخلية المبرمج . الخلايا الخبيثة تعتمد على تثبيط طريق الاستماتة ؛ لهذا فمثبطات البروتيزوم تعمل جيداً في ورم النقي المتعدد . (Cancer cells use the proteasome to degrade proapoptotic proteins) .

يسبب البورتيزوميب والثاني سمية عصبية وتثبيط نقي وإسهال و غثيان وتعب و تنشيط الهربس النطاقي (ينبغي إعطاء المرضى مضاد فيروس للوقاية) . الثالث يثبط النقي ويسبب غثيان وتعب وإسهال وحمى .

الباقى للأطلاع

12. A 53-year-old woman recently diagnosed with gouty arthritis started a treatment with a drug that inhibits leukocyte migration and phagocytosis secondary to inhibition of tubulin polymerization. Which of the following drugs did the patient most likely take?
- | | | |
|-----------------|---------------|---------------|
| A. Indomethacin | B. Prednisone | C. Colchicine |
| D. Allopurinol | E. Probenecid | F. Piroxicam |

Difficulty level: Easy

8. A 61-year-old woman with advanced Hodgkin lymphoma began chemotherapy with the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen. Which of the following molecular actions most likely mediated the therapeutic effect of doxorubicin in the patient's disease?
- A. It intercalates between DNA strands and inhibits topoisomerase II.
 - B. It prevents microtubule disassembly into tubulin monomers.
 - C. It prevents assembly of tubulin dimers into microtubules.
 - D. It alkylates nucleophilic groups on DNA bases.
 - E. It blocks the synthesis of both ribonucleotides and deoxynucleotides.

Learning objective: Explain the mechanism of action of colchicine.

12. C Colchicine can be used to stop an acute gout attack or, most often, for the prevention of further attacks, as in this case. The drug binds to the intracellular protein, tubulin, thereby preventing its polymerization into microtubules and thus blocking mitosis in metaphase. Cells with the highest rate of division are affected early. Granulocyte migration into the inflamed area and phagocytosis of urate crystals by macrophages are inhibited, thus relieving the pain and inflammation of gouty arthritis. These actions are specific, and the drug is devoid of general analgesic or antiinflammatory effects.
- A, B, F These drugs are effective in gouty arthritis but have different mechanisms of actions.
- D, E These drugs can decrease the risk of gout attacks by decreasing the urate pool, not by inhibiting tubulin polymerization.

Learning objective: Explain the mechanism of anticancer action of doxorubicin.

8. A **Doxorubicin** is an anthracycline antibiotic, thus the *A* in the ABVD acronym; alternatively, the *A may be considered to stand for Adriamycin*, a brand name for doxorubicin. These anticancer drugs likely act with multiple mechanisms, including intercalation between adjacent base pairs of DNA, thus causing blockade of DNA replication; blockade of topoisomerase II, the enzyme that catalyzes DNA repair (it breaks and then reseals DNA strands); and generation of free radicals that can oxidize DNA bases. The end result of these multiple mechanisms is cell apoptosis.

B This is the mechanism of action of **taxanes**.

C This is the mechanism of action of **vinca alkaloids**.

D This is the mechanism of action of **alkylating drugs**.

E This is the mechanism of action of **methotrexate**.

===

Difficulty level: Easy

21. A 59-year-old woman with inoperable غير صالح للعملية lung cancer had been receiving combination chemotherapy. Lab tests revealed the following plasma levels: creatinine 5.5 mg/dL (normal 0.6–1.2 mg/dL), blood urea nitrogen (BUN) 45 mg/dL (normal 7–18 mg/dL), Mg^{2+} 0.2 mmol/L (normal 1.5–2.0 mmol/L). Which of the following drugs most likely caused these lab results?

- A. Fluorouracil B. Doxorubicin C. Vincristine D. Cisplatin
E. Paclitaxel

Difficulty level: Easy

26. A 10-year-old boy suffering from acute lymphoblastic leukemia started maintenance therapy that included high dose methotrexate. Two weeks later, a blood test with differential showed a white blood cell count of 1800/mm³ (normal 4500–11,000/mm³). The oncologist believed the result was related to an excessive dose of methotrexate and ordered an antidote agent. Which of the following drugs would be appropriate for the patient at this time?

- A. Vitamin B12 B. Pyridoxine C. Folic acid
D. Vitamin B3 E. Leucovorin

Learning objective: Describe the adverse effects of cisplatin.

21. D The patient's lab results suggest the diagnosis of renal failure.

Cisplatin is the anticancer drug with the highest risk of nephrotoxicity, and hypomagnesemia is the most common electrolyte abnormality caused by cisplatin. However, the routine use of hydration and diuresis has largely reduced cisplatin-induced nephrotoxicity.

A–C, E These drugs very rarely cause nephrotoxicity.

Learning objective: Identify the drug to be used as a methotrexate antidote.

26. E Leucovorin can be given to counteract the adverse effects that methotrexate has on normal cells. Leucovorin (formyl tetrahydrofolate, also called folinic acid) is accumulated more readily by normal cells than by neoplastic cells. The administration of this drug results in rescue of the normal cells, because the drug bypasses the step in the purine synthesis that is blocked by methotrexate (i.e., dihydrofolate to tetrahydrofolate).

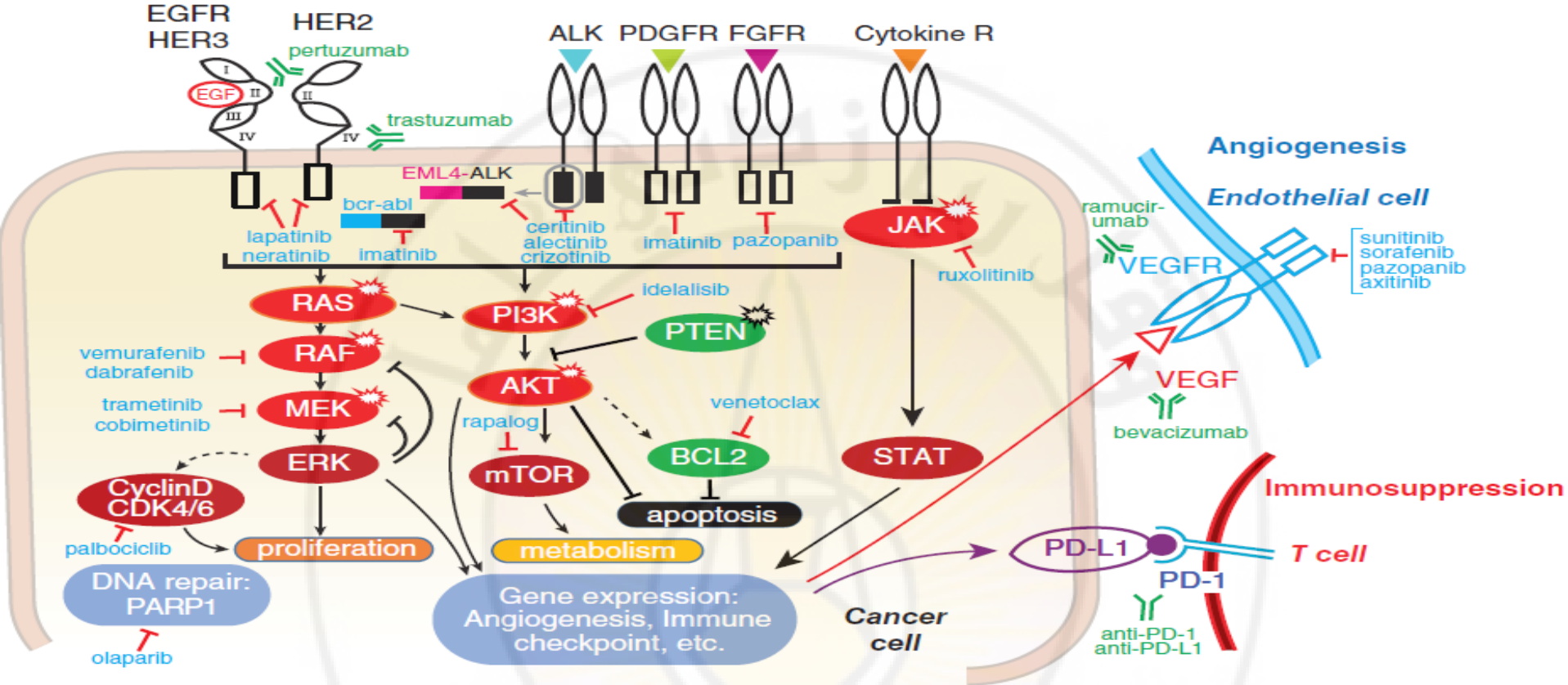


Figure 67–2 Cancer cell signaling pathway and drug targets. Extracellular binding of agonist ligands to transmembrane growth factor receptors causes receptor dimerization and activation of a C-terminal protein kinase that initiates intracellular signaling cascades that regulate gene expression and control cancer cell proliferation, apoptosis, metabolism, and metastasis. Crosstalk between cancer cells and the host stroma (including the vasculature and immune cells) is modulated through the release of angiogenic factors and the expression of immune checkpoint proteins. Cancer cell signaling can be altered through increased expression of receptors (e.g., HER2) or ligands, activating mutations in receptors (e.g., ALK, EGFR, FGFR) or in intracellular kinases (e.g., RAS, RAF, MEK, PI3K, AKT, JAK), gene translocations resulting in activated fusion proteins (e.g., bcr-abl, EML4-ALK), and the loss of function of an inhibitor of a pathway (e.g., the PTEN phosphatase) through mutation, gene deletion, or promoter methylation. Inhibitors are shown acting on three different cells: a cancer cell, an endothelial cell, and a T cell. Antibodies (green) are shown at their extracellular protein targets. Small-molecule inhibitors (in blue) are depicted adjacent to their intracellular target proteins. Proteins within red ellipses provide activating signals, those in green ellipses, inhibitory signals. Star bursts () indicate signaling components in which mutations are common. Figure 67–4 describes mTOR signaling and its inhibition in more detail (see also Figure 35–2).

الباقي للاطلاع

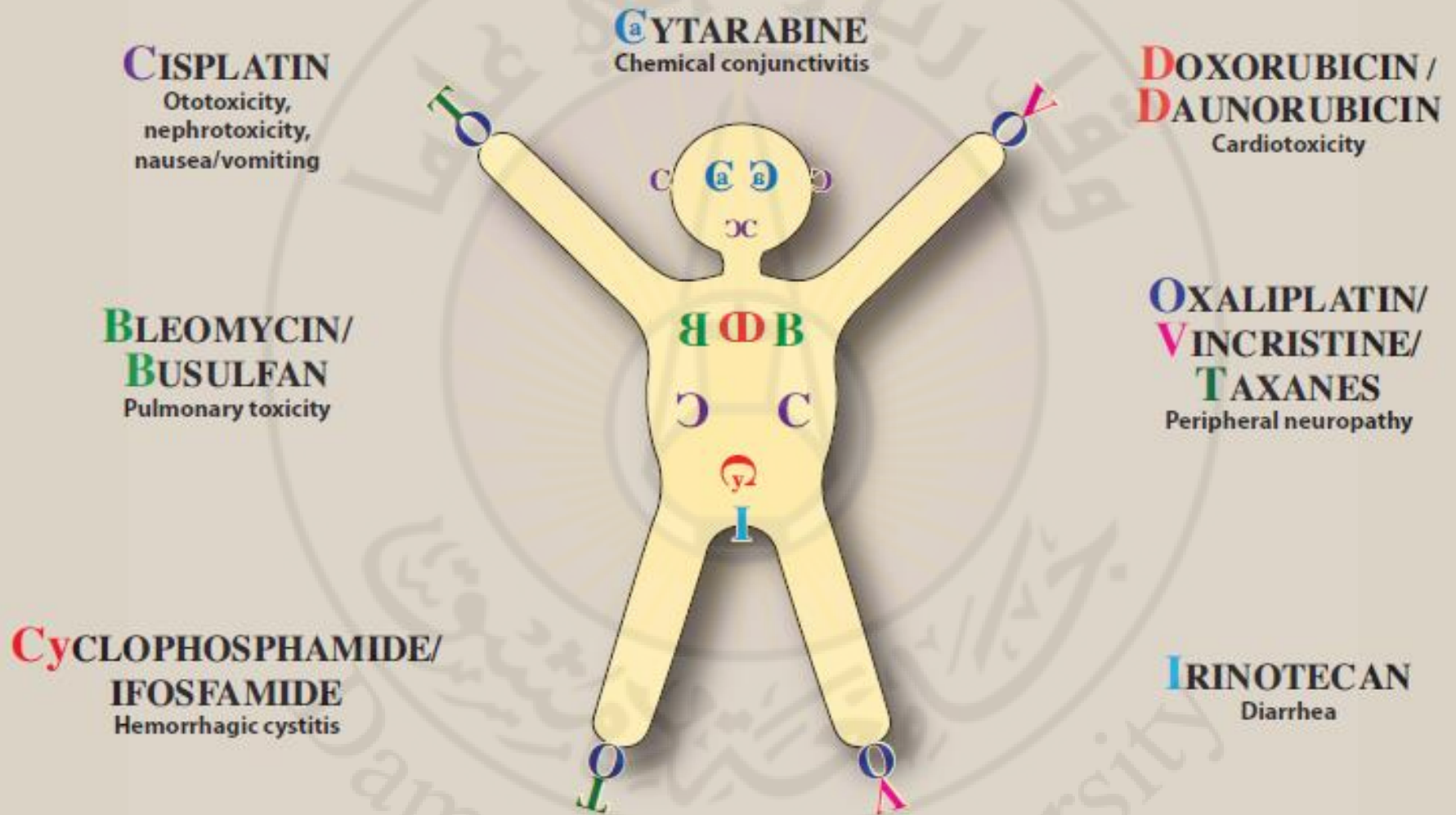


Figure 35.33
Chemo Man—a summary of toxicity of chemotherapeutic agents.

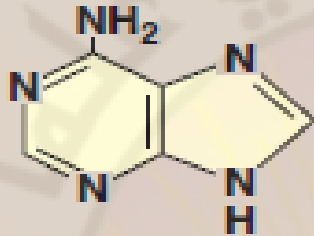
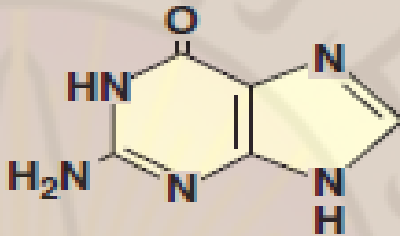
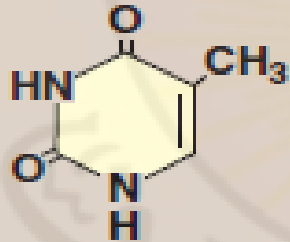
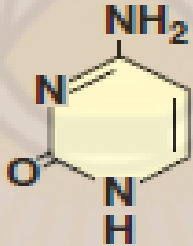
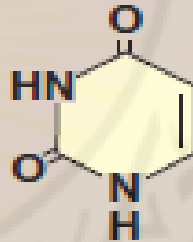
DNA and RNA Purines		
		
Adenine (A)	Guanine (G)	
RNA Pyrimidines		
		
Thymine (T)	Cytosine (C)	Uracil (U)
DNA Pyrimidines		

Figure 22.1
Purines and pyrimidines commonly found in DNA and RNA.

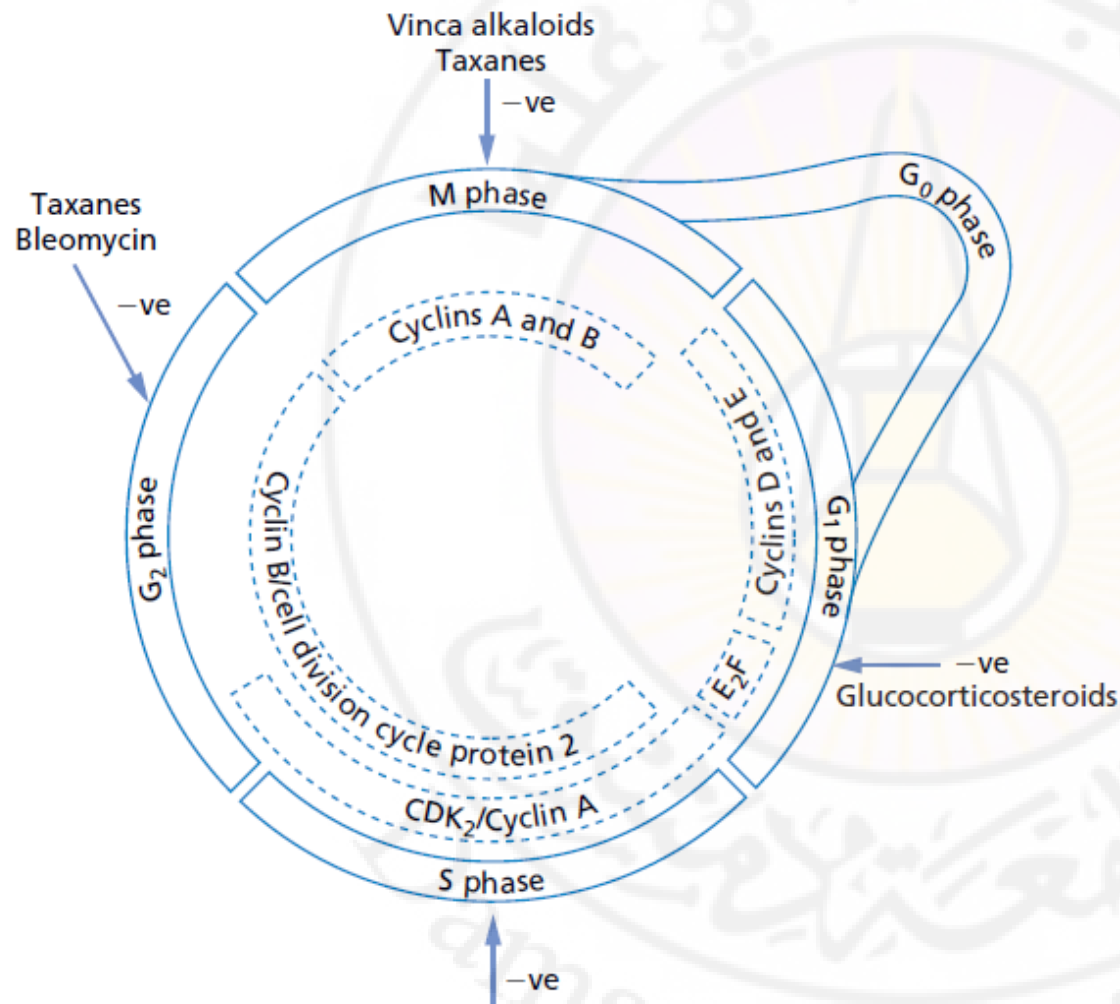


Figure 48.1: The cell cycle regulatory systems and sites of drug actions. 6-MP, 6-mercaptopurine; MTX, methotrexate.

Nitrogen mustards

Mechloreththamine

Cyclophosphamide

Ifosfamide

Chlorambucil

Melphalan

Bendamustine

Ethyleneimines

Altretamine

Thiotepa

Alkyl sulfonates

Busulfan

Nitrosoureas

Carmustine

Lomustine

Streptozotocin

Triazine

Decarbazine

Temozolomide

Methylhydrazine

Procarbazine

Alkylating agents (Figure 35.17) exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, even though they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

سابعاً . العوامل المؤلّكة (الشكل ٣٥ . ١٧) : تأثيراتها السامة للخلية
بارتباطها تساهمياً بمجموعات أليفة النواة على مقومات (بنيات) خلوية
متنوعة . ربما تكون ألكلة الدنا التفاعل السام للخلية الحاسم المميت لخلايا
الورم .

العوامل المؤلّكة لا تميز بين الخلايا الدائرة والمرتاحة ، رغم أنها سامة
أكثر للخلايا السريعة الانقسام .

تستعمل بالتوليف لمعالجة ضرب واسع من السرطانات اللمفاوية والصلبة .
 كلّها مُطَفِّرة و مُسَرِّطنة وقد تسبب خباثات ثانوية مثل ابيضاض حادّ .

Alkylating Agents

Mechlorethamine

Chlorambucil

Cyclophosphamide

Bendamustine (consisting of a purine benzimidazole ring and a nitrogen mustard moiety.)

Melphalan

Thiotepa

Busulfan

Carmustine

Lomustine

Altretamine

Forms DNA crosslinks, resulting in inhibition of DNA synthesis and function

تُكوّن وصلات متصالبة للدنا ، مسببة تثبيط تصنيع الدنا ووظيفته .

Temozolomide

Procarbazine

Dacarbazine

Methylates DNA and inhibits DNA synthesis and function

تُمَثِّل الدنا وتثبط تصنيعه ووظيفته .

أ. Cyclophosphamide و ifosfamide (الخَرَادِلُ)

النَّتْرُوجِينِيَّة) : تتعلق جداً بعوامل الخردل بمشاركتها معظم الآليات الأولى والسميّات . سامّة للخلية فقط بعد توليد جذورها المؤلّكة ، التي تنتج عبر الهدركسلة بالسيتوكروم.

تستعمل منفردة وبالتوليف لمعالجة اللمفومة غير-الهودجكينية والसारcoma وسرطان الثدي .

١. آليّة الفعل : هذان الدواءان يستقلبان إلى الوسطاء المهدركسلة في الكبد بالسيتوكروم (شكل ٣٥. ١٨) التي تستقلب لتكوّن مركّبان فعّالان ،

phosphoramide mustard و acrolein . الخطوة السامة للخلية هي تفاعل الأول مع الدنا .

A. Cyclophosphamide and ifosfamide (nitrogen mustards).

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum and are used as single agents or in combinations in the treatment of a wide variety of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

1. Mechanism of action: *Cyclophosphamide* is the most commonly used alkylating agent. Both *Cyclophosphamide* and *ifosfamide* are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 35.18). The hydroxylated intermediates then undergo metabolism to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

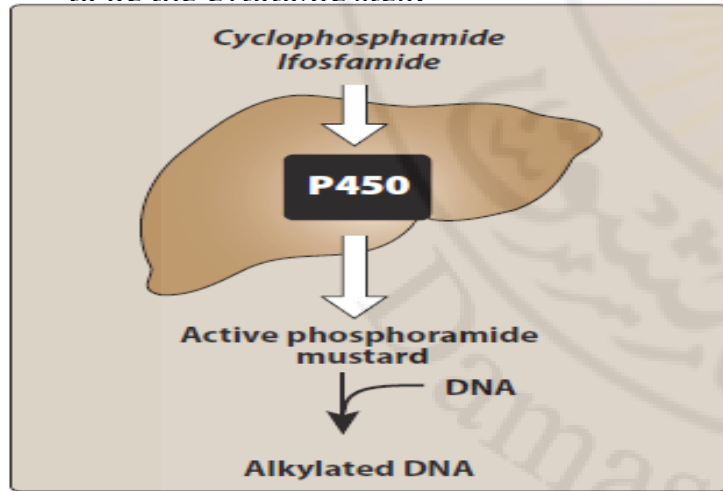


Figure 35.18

Activation of cyclophosphamide and ifosfamide by hepatic cytochrome P450.

3. Adverse effects: A unique toxicity of both drugs is hemorrhagic cystitis, which can lead to fibrosis of the bladder. Bladder toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to toxic metabolites of *ifosfamide*. Adequate hydration as well as IV injection of mesna (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem. Neurotoxicity has been reported in patients on high-dose *ifosfamide*, probably due to the metabolite, chloroacetaldehyde.

B. Nitrosoureas. *Carmustine* and *lomustine* are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

1. Mechanism of action: The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily in cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamylation of amino acids in proteins in the targeted cells.

٣. التأثيرات الضائرة : التهاب المثانة النزفي
سمية فريدة للدوائين ، قد تؤدي إلى تليف المثانة . سببها الـ acrolein في حالة الـ *cyclophosphamide* ومستقلبات سامة في حالة الـ *ifosfamide* . الإمالة الكافية وحقن الـ

2- sodium)mesna (mercaptoethane sulfonate الذي يستعمل المستقلبات السامة يصغر المشكلة .

ثمة تقارير عن سمية عصبية للجرعة الكبيرة من آيفوسفاميد ، ربما بسبب المستقلب chloroacetaldehyde .

ب. مركّبات النيتروزويوريا : Carmustine و lomustine . تعالج أورام الدماغ لنفاذيتها إلى الـ CNS .

١. آلية الفعل : سامة للخلية بألكلة الدنا وثبيط التكرار وتصنيع الرنا والبروتين

C. **Streptozotocin** is an antibiotic brought under this group due to its structure containing methyl nitrososurea group attached to glucose. It is used for the treatment of pancreatic cancer and malignant carcinoid tumors.

1. Mechanism of action: Due to its glucose structure, it has higher affinity for pancreas and in experimental animals it causes diabetes by the destruction of islets of Langerhans.

2. Pharmacokinetics: It shows a very short half-life after intravenous administration of 15 minutes. Only a fraction of drug (20%) is excreted in urine in the unmetabolized form.

3. Adverse effects: Nausea, vomiting, elevation of hepatic enzymes, and renal toxicity are reported. *Streptozotocin should not be combined* with other nephrotoxic agents. It is also reported to cause hematological toxicity in some patients.

ج. الـ **Streptozotocin** : مضاد حيوي يحتوي على مجموعة ميثيل نتروز يوريا متصلة بجلوكوز .

لمعالجة سرطان البنكرياس والأورام السرطانية الخبيثة .

١. آلية الفعل : له الألفة الأكثر للبنكرياس بسبب احتوائه على جلوكوز ويسبب السكري عند حيوانات التجارب بتخريب جزر لانغرهانس .

٢. التأثيرات الضائرة : غثيان وقيء وزيادة إنزيمات الكبد وتسمم الكلية . لا ينبغي توليفه مع أدوية إضافية سامة للكلية . ثمة تقارير عن تسمم دم عند بعض المرضى . *

D. **Procarbazine** (methylhydrazines) is a methylhydrazine derivative used for the treatment of Hodgkin's disease and malignant brain tumors. MOPP is a chemotherapy regimen consisting of mechlorethamine, vincristine, procarbazine, and prednisone. One of the components of MOPP regimen for treating Hodgkin's disease has been now largely replaced with other drugs and regimens.

1. Mechanism of action: Upon administration, *procarbazine is converted* by cytochromes of the liver into a highly reactive alkylating species which in turn methylates DNA. It is extensively metabolized and excreted.

2. Adverse effects: *Procarbazine causes leukopenia and thrombocytopenia.*

Gastrointestinal side effects are very common. It is a weak mono-amino oxidase (MAO) inhibitor and blocks the metabolism of catecholamines. It is highly carcinogenic, mutagenic, and teratogenic and is associated with the risk of developing acute leukemia in patients undergoing treatment with this agent.

د. الـ **Procarbazine** (methylhydrazines): مشتق ميثيل هيدرازين يعالج داء هودجكن وأورام الدماغ الخبيثة . الـ MOPP تدبير علاجي متكوّن من mechlorethamine و vincristine و procarbazine و prednisone ..

١. آلية الفعل : يتحول بالسيتوكروم الكبدي إلى جذور مؤلفة تفاعلية جداً، تُمثّل الدنا ..

٢. التأثيرات الضائرة : قلة البيض والصفائح وتأثيرات جانبية هضمية . مثبط ضعيف للـ MAO فيحصر استقلاب الكاتيكولامين .

مسرطن جداً ومُطفر وماسخ ويترابط مع اختطار تطوير ابيضاض حادّ .

E. Dacarbazine and temozolomide (tiazenes)

Dacarbazine is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). The metabolite is responsible for the alkylating activity of this agent by forming methylcarbonium ions that attack the nucleophilic groups in the DNA molecule. The cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O-6 position of guanine. Dacarbazine has found use in the treatment of melanoma and Hodgkin lymphoma. Temozolomide is related to dacarbazine, because both must undergo biotransformation to an active metabolite, MTIC, which is likely responsible for the methylation of DNA on the O-6 and N-7 position of guanine.

٥. Dacarbazine و temozolomide : داکاربازین عامل مؤکل يستقلب لمركب فعال (methyltriazenoimidazole carboxamide “MTIC”)

الذي يكون methylcarbonium ions تهاجم المجموعات الأليفة التواة في الدنا . سميته للخلايا تعزى لقابلية مستقلبه على مثيلة الدنا في الموضع (O-6) من الغوانين . يستعمل في معالجة الورم الميلانيني (الميلانوم) ولمفوما هودجكين .

الـ temozolomide يتحول أيضاً إلى المستقلب الفعال السابق MTIC الذي يمثل الدنا على الموضع (O-6) و (N-7) للغوانين . يعبر الـ BBB فيستعمل في معالجة أورام الدماغ مثل السرطانة الدبقية (ورم أرومي دبق) glioblastomas و أورام الخلايا النجمية astrocytomas . يستعمل أيضاً في الميلانوما النقيلي . وريدي وفموي ..

F. Other alkylating agents . **Mechlorethamine** was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers. **Melphalan**, a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally. The dose of melphalan is carefully adjusted by monitoring the platelet and white blood cell counts. **Chlorambucil** is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia. **Busulfan** is an oral agent that is effective against chronic granulocytic leukemia. This agent can cause pulmonary fibrosis (“busulfan lung”). Like other alkylating agents, all of these agents are leukemogenic. **Bendamustine** is administered through the intravenous route over a period of 30 minutes which is approved for the treatment of chronic lymphoid leukemia and non-Hodgkin’s lymphoma.

و. عوامل الأكلة إضافية : Mechlorethamine مُنْقَط (خردل نيتروجيني) يسبب قلة اللمفاويات فيستعمل في السرطانات اللمفاوية .

Melphalan مشتق فينيل ألانين لخردل نيتروجيني .. إنه عامل مؤكل ثنائي الوظيفة فموي ..

Chlorambucil عامل مؤكل ثنائي الوظيفة للابيضاض اللمفاوي المزمن .

Busulfan فموي للابيضاض المحبب المزمن . يسبب تليف رئوي “رئة البوسلفان” .
مثل العوامل المؤلكة السابقة هي مُحْدَثَة للابيضاض . يعطى **Bendamustine** بالوريد لمعالجة الابيضاض اللمفاوي المزمن ولمفوما غير الهودجكنية .

VIII. ANTIMETABOLITES. Antimetabolites are structurally related to normal compounds that exist within the cell (Figure 35.8). They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase and are, therefore, cell cycle-specific.

Methotrexate, pemetrexed, and pralatrexate (folate antagonists) The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication. Folic acid is obtained mainly from dietary sources and from food sources produced by intestinal flora. *Methotrexate (MTX), pemetrexed and pralatrexate* [pral-a-TREX-ate] are antifolate agents.

ANTIMETABOLITES
Folate antagonists
<i>Methotrexate</i>
<i>Pemetrexed</i>
<i>Pralatrexate</i>
Purine antagonists
<i>6-Mercaptopurine</i>
<i>6-Thioguanine</i>
<i>Azathioprine</i>
<i>Fludarabine</i>
<i>Cladribine</i>
Pyrimidine antagonists
<i>Fluorouracil (5-FU)</i>
<i>Capecitabine</i>
<i>Floxuridine</i>
Cytidine analogs
<i>Cytarabine</i>
<i>Azacytidine</i>
<i>Gemcitabine</i>

ثامناً. مضادات الاستقلاب : متعلقة كيميائياً بالمركّبات الطبيعية

الموجودة ضمن الخلية. تتداخل مع توافر طلائع البورين
أو البيريميدين النوكليوتيدية ، إمّا بتثبيط تصنيعها أو
بالتنافس معها في تصنيع الدنا أو الرنا .

تأثيراتها السامة للخلية الأعظمية في الطور—س ولهذا
هي نوعية—لدورة الخلية .

أ. الـ **Methotrexate** والـ **pemetrexed** والـ

pralatrexate (مناهضات الفولات) : لحامض الفوليك
دور مهم في تفاعلات استقلابية ضرورية لتكرار الخلية .

مضادات الاستقلاب ANTIMETABOLITES (آليات الفعل) :

Capecitabine , 5-Fluorouracil

تثبط الـ TS(thymidylat synthase) ؛
يؤدي تضمين الـ 5-FUTP
(fluorouridine-5-ptriphosphate)
في الرنا إلى تغيير في عملية الرنا ،
ويؤدي تضمين الـ 5-FdUTP
(fluorodeoxyuridine-5-
triphosphate

) في الدنا إلى تثبيط تصنيع الدنا ووظيفته

Methotrexate

يثبط الـ DHFR(dihydrofolate
reductase) والـ TS وتصنيع نوكلئوتيد
البورين الجديد .

Pemetrexed

يثبط الـ TS والـ DHFR وتصنيع
نوكلئوتيد البورين .

Cytarabine

يثبط استطالة سلسلة الدنا وتصنيع الدنا وإصلاحه ؛
يثبط الـ ribonucleotide reductase مع
إنقاص تكوين الـ
dNTPs(deoxyribonucleotide
triphosphate) ؛ يجري تضمين السيتارابين
ثلاثي الفوسفات في الدنا .

Gemcitabine

يثبط تصنيع الدنا وإصلاحه ؛ يثبط الـ
ribonucleotide reductase مع إنقاص
تكوين الـ dNTPs ؛ تضمين شكله الثلاثي الفوسفات
في الدنا يثبط تصنيع الدنا ووظيفته

Fludarabine , Cladribine

يثبط تصنيع الدنا وإصلاحه ، ويثبط الـ
ribonucleotide reductase ؛ تضمين شكله
الثلاثي الفوسفات في الدنا ؛ تحريض الاستماتة .

6-Mercaptopurine (6-MP), 6-Thioguanine

يثبط تصنيع نوكلئوتيد البورين الجديد ؛ تضمين
شكل الدواء الثلاثي الفوسفات في **الرنا والدنا** .

{{ Methotrexate competitively inhibits dihydrofolate reductase. }}

Remember this pathway from folate antagonists. **Methotrexate inhibits the binding of folic acid to the enzyme. It therefore inhibits DNA synthesis by inhibiting thymidylate synthesis. Cellular uptake of methotrexate is by a carrier-mediated active transport.** Cellular resistance to methotrexate is presumably caused by decreased transport into the cell. This can be overcome by using high doses .

{{ Leucovorin provides reduced folate to “rescue” normal cells from the action of methotrexate. }}

MTX is specific for the S-phase of the cell cycle. *Pemetrexed* is an antimetabolite similar in mechanism to *methotrexate*. However, in addition to inhibiting DHFR, it also inhibits thymidylate synthase and other enzymes involved in folate metabolism and DNA synthesis. *Pralatrexate* is an antimetabolite that also *inhibits DHFR*.

{{ Leucovorin provides reduced folate to “rescue” normal cells from the action of methotrexate. }}

يثبط الميثوتريكسات تنافسياً الـ dihydrofolate reductase

يثبط الميثوتريكسات ارتباط حامض الفوليك بالإنزيم . بالتالي يثبط تصنيع الدنا بـ تثبيط الـ thymidylate synthesis. يجري أخذ الميثوتريكسات إلى الخلايا بنقل فعال متواسط — بحامل . إذ تحدث مقاومة الميثوتريكسات بتقيص نقله إلى الخلية . يمكن التغلب على هذا باستعمال جرعات كبيرة .

الـ MTX نوعي للطور —س .

يوفر اللوكوفورين خلايا فيها فولات مُرجعة مما يتجاوز الإنزيم المَثْبُط .

{ يوفر اللوكوفورين فولات مُرجعة لينقذ الخلايا الطبيعية من فعل الميثوتريكسات }

الـ Pemetrexed مضاد استقلاب مشابه بالآلية ويثبط أيضاً الـ thymidylate synthase

الـ Pralatrexate يثبط الـ DHFR أيضاً .

2. Therapeutic uses: *MTX*, usually in combination with other drugs, is effective against acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, bladder cancer, and head and neck carcinomas. In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease. All patients receiving *MTX* require close monitoring for possible toxic effects. *Pemetrexed* is primarily used in non-small cell lung cancer. *Pralatrexate* is used in relapsed or refractory T-cell lymphoma.

٣--**Adverse effects:** For *MTX* are mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia). *Pemetrexed* and *pralatrexate* should be given with folic acid and vitamin B12 supplements to reduce hematologic and GI toxicities. Pretreatment with corticosteroids to prevent cutaneous reactions is recommended with *pemetrexed*.

٢. الاستعمالات العلاجية : الـ **MTX** فعال بالتوليف مع غيره ضد ابيضاض الدم اللمفاوي الحادّ و لمفومة بيركيت عند الأطفال وسرطان الثدي و سرطانات الرأس والعنق .
الجرعة—القليلة فعالة ضد الصدفية الشديدة والتهاب المفاصل الروماتويدي وداء كرون .
يتطلب المرضى مراقبة التأثيرات السامة .

الـ **Pemetrexed** ضد سرطان الرئة غير—صغير الكريات . الـ **Pralatrexate** للمفوما التائية المعنّدة أو الناكسة .

٣. التأثيرات الضائرة : للميثوتريكسيت (التهاب الغشاء المخاطي وإسهال و **كبت نقي** مع قلة عدلات و صفيحات) . ينبغي إعطاء الـ **Pemetrexed** والـ **pralatrexate** مع حامض الفوليك والفيتامين ب١٢ لإنقاص سمّيات الدم والهضم . يوصى بالمعالجة المسبقة بالكورتيكوستيروئيدات لمنع التفاعلات الجلدية للـ **pemetrexed** .

B. 6-Mercaptopurine (purine antagonists)

6-Mercaptopurine [mer-kap-toe-PYOOOR-een] (6-MP), a purine antimetabolite, is the thiol analog of hypoxanthine. 6-MP and 6-thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: Azathioprine, an immunosuppressant, exerts its cytotoxic effects after conversion to 6-MP.] 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP and its analog, azathioprine, are also beneficial in the treatment of Crohn disease. Adverse effects are noted in Figure 35.8. *Azathioprine is used at an oral dose of 3 to 5 mg/kg/day followed by the maintenance dose of 1 to 2 mg/kg/day.*

ب. الـ **6-Mercaptopurine (purine antagonists)** : مضاد استقلاب بورييني ، هو والـ **6-thioguanine** نافعان لمعالجة المرض الورمي .

(ملاحظة : الـ **Azathioprine** كابيت مناعة سام للخلايا بعد تحوله إلى 6-Mercaptopurine) .

يستعمل **6-Mercaptopurine** للمحافظة على هدأة اببيضاض الأرومات اللمفاوية . هو والأزاثيوبرين ينفعان معالجة داء كرون .

التأثيرات الضائرة : Myelosuppression, immunosuppression, hepatotoxicity

C. Fludarabine [*floo-DARE-a-been*] is the 5'-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma. *Fludarabine is a prodrug, and the phosphate is removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S-phase and affects their function. ...*

ج. الـ **Fludarabine** هو 5'-phosphate of 2-fluoroadenine arabinoside ،
مضاهي للبورين . يعالج الابيضاض اللمفاوي المزمن و ابيضاض الدم الأشعر و
اللمفومة اللاهودجكينية القليل الإيلام .

يُضَمَّن الشكل الثلاثي فسفات في الدنا والرنا . هذا ينقص تصنيعهم في الطور—س
ويحرض الـ apoptosis

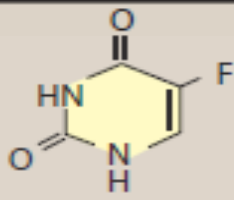
يعطى وريدياً أكثر من فموياً لأنّ الجراثيم المعوية تشطّر السكر لتعطي المستقلب
السام جداً الـ fluoroadenine ..

D. 5-Fluorouracil (pyrimidine antagonists)

5-Fluorouracil (5-FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The **fluorine** interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

د. الـ (pyrimidine antagonists) (5-Fluorouracil (5-FU) : مشابه (مضاهي)
للبيريميدين ، .. يتداخل الفلور مع تحوّل حامض الذي أكسي يوريديليك ، فيحرم الخلية من
الثيميدين ، أحد الطلائع الضرورية لتصنيع الدنا .

يعالج الأورام الصلبة البطيئة—النمو (مثل كارسينوما القولون والمستقيم والثدي والمبيض والبنكرياس والمعدة
.. يفيد تطبيقه الموضعي في معالجة الكارسينوما السطحية القاعدية الخلايا .



5-Fluorouracil (5-FU)

TARGET CELL

Carrier

5-FU

Uridine phosphorylase

Phosphoribosyl transferase

5-FUR → 5-FUMP

Uridine kinase

5-FUTP

5-FUDP

Ribonucleotide reductase

RNA

5-FdUMP

dUMP

dTMP

Thymidylate synthetase

N_5, N_{10} -methylene- FH_4

FH_2

Needed for DNA synthesis and cell growth

١. آليّة الفعل : يدخل الخلية بنظام نقل متواسط—ب حامل

ويتحول إلى 5-fluorodeoxyuridine

monophosphate [5-FdUMP]; (الشكل ٣٥

١١) ، الذي يتنافس مع الـ deoxyuridine

monophosphate(dUMP) على الـ

thymidylate synthase ، مثبطاً فعله بالتالي . إذ

ينقص تصنيع الدنا بسبب نقص الثيميدين ، مؤدياً

اختلال نمو الخلية و “موت بنقص—الثيميدين”

للخلايا السريعة الانقسام .

(ملاحظة : يعطى Leucovorin مع 5-FU ، لأنّ

تميم الإنزيم الفولات المختزل مطلوب في تثبيط

تصنيع الثيميديلات . مثال ، التدبير المعياري من أجل

سرطان القولون والمستقيم هو irinotecan مع -

(FU/leucovorin) . يُضمّن الـ 5-FU أيضاً في

الرنا ، وقد كشفت مستويات قليلة في الدنا . في الحالة

الأخيرة ، ثمة glycosylase يزيل/يقطع الـ 5-FU ،

مخرباً الدنا .

تأثير الـ 5-FU في الطور—س .

1. Mechanism of action: 5-FU itself is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; Figure 35.11), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and “thymidine-less death” of rapidly dividing cells. [Note: Leucovorin is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition. For example, a standard regimen for advanced colorectal cancer is irinotecan plus 5-FU/leucovorin.] 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S-phase of the cell cycle.

E. **Capecitabine** is a fluoropyrimidine carbamate. It is used in the treatment of colorectal and metastatic breast cancer. Capecitabine is well absorbed following oral administration. After being absorbed, capecitabine, which is itself nontoxic, **undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5-FU. This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors.** (Figure 35.12). Thus, the cytotoxic activity of capecitabine is the same as that of 5-FU and is **tumor specific**. The most important enzyme inhibited by 5-FU (and, thus, capecitabine) is thymidylate synthase.

٥. **Capecitabine** هو fluoropyrimidine carbamate . يمتص من جهاز الهضم . ثم يخضع لتفاعلات إنزيمية تنتهي بالحلمهة إلى 5-FU . هذه الخطوة تتحفز بالـ **thymidine phosphorylase** ، المتركّز في الأورام . بالتالي فعاليته السامة للخلايا مثل فعالية الـ 5-FU وهو نوعي للورم .

الإنزيم الأهم المتنبط بالـ 5-FU (وبالتالي بالـ capecitabine) هو **thymidylate synthase** .

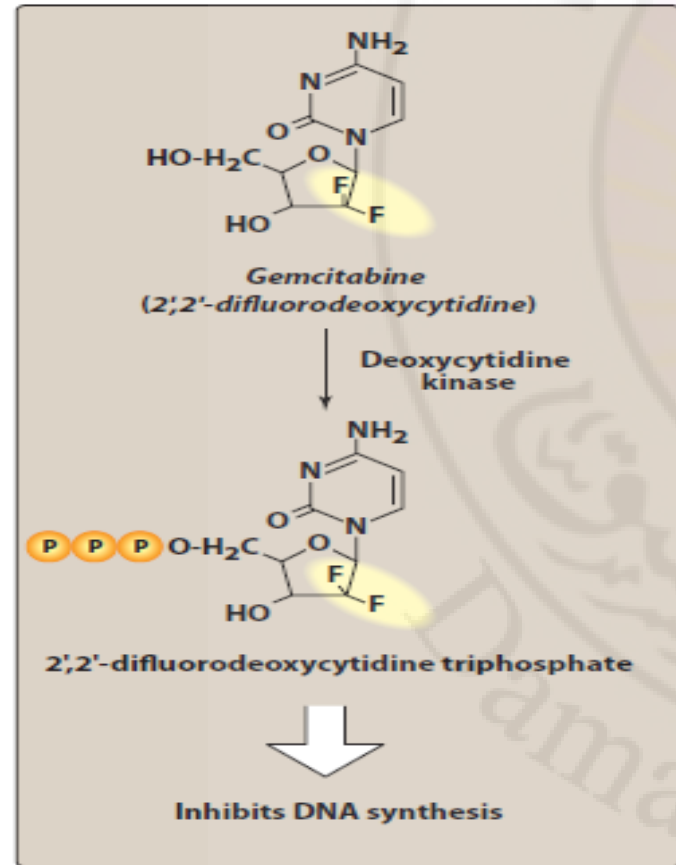
F. **Cytarabine** (cytidine analogs) . (*cytosine arabinoside* or *ara-C*) is an analog of 2'-deoxycytidine in which the natural ribose residue is replaced by d-arabinose. *Cytarabine acts as a pyrimidine antagonist*. The major clinical use of *cytarabine is in acute nonlymphocytic* (myelogenous) leukemia (AML). *Cytarabine enters the cell by a carrier-mediated process* and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate or ara-CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can terminate chain elongation. It is, therefore, S-phase (and, hence, cell cycle) specific.

و. الـ **Cytarabine** (مضاهي للسيتيدين) : *cytosine arabinoside* مضاهي للـ 2'-deoxycytidine يجري استبدال ثمالة الريبوز الطبيعي فيه بالـ d-arabinose . يعمل مناهضاً للبيريبيدين .

يستعمل في الابيضاض غير اللمفاوي (النقوي) الحادّ .

يدخل الخلية بواسطة ناقل ويجب أن يفسّر (مثل مناهضات البورين والبيريبيدين) بالديوكسي سيتيدين كيناز وغيرها من كيناز النوكليوتيد إلى شكل نوكلئوتيد (cytosine arabinoside triphosphate or ara-CTP) ليصير سام للخلية . الأخير مثبط فعّال للدنا وينهي إطالة السلسلة . لهذا ، هو نوعي للطور —س (نوعي دورة الخلية) .

G. **Azacitidine** is a pyrimidine nucleoside analog of cytidine. It is used for the treatment of myelodysplastic syndromes and AML. Azacitidine undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into RNA to inhibit RNA processing and function. It is S-phase cell cycle-specific. H. **Gemcitabine** is an analog of the nucleoside deoxycytidine. It is used most commonly for pancreatic cancer and non-small cell lung cancer. Gemcitabine is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2',2'-difluorodeoxycytidine triphosphate. (Figure 35.13). Gemcitabine is administered by IV infusion. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.



ز. الـ **Azacitidine**: نيكليوزيد بيريميديني مضاهي للسيتيدين . يستعمل لمعالجة متلازمات خَلَلُ التَّنَسُّجِ النُّخَاعِيِّ / خَلَلُ تَنْسُجِ النِّقْيِ .. يتنشط إلى المستقلب النوكليوتيدي **azacitidine triphosphate** ويجري تضمينه في الرنا ليثبط وظيفته .. نوعي للطور—س من الدورة الخلوية .

ح. الـ **Gemcitabine** **تسريب IV**: مضاهي للنوكليوزيد **ديوكسي سيتيدين** . لسرطان البنكرياس وسرطان الرئة غير صغير الخلايا . ركيزة لكيناز الديوكسي سيتيدين ، الذي يفسره إلى **2',2'-difluorodeoxycytidine triphosphate** (الشكل ٣٥ . ١٣)

Figure 35.13
Mechanism of action of gemcitabine.

Angiogenesis inhibitors

: Bevacitumab ,
Sunitinib .

Protease inhibitors :

Bortezomib

EGF-receptor

inhibitors : Cefitinib ,
cefuximab

Anarmed mono clonal

antibodies :

Rituximab ,
trastuzomab .

Drug	Mechanism of Action ¹
Bortezomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway
Carfilzomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway; maintains activity in bortezomib-resistant tumors
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery
Ziv-aflibercept	Inhibits binding of VEGF-A, VEGF-B, and PlGF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis
Sunitinib, pazopanib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR- α and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis

Notice that two of the listed antibodies for CD20 (a B-cell antigen) have a radioactive label. The antibody brings the radiation to the tumor cells to increase specificity of the radiation. **Ibritumomab tiuxetan** is a combination molecule. The antibody is the ibritumomab piece that is bonded to the chelator tiuxetan. The chelator provides the binding site for the radioactive ligand .

الأضداد **ANTIBODIES**: يجري تطوير أضداد تستهدف تعبير البروتين في خلايا الورم لتحسين النوعية في معالجة السرطان . القائمة في الأعلى التالية عينة موجودة—مع الهدف البروتيني للضد :

alemtuzumab—CD^{٥٢};

bevacizumab—vascular endothelial growth factor (VEGF) ;

cetuximab—epidermal growth factor receptor (EGFR);

gemtuzumab ozogamicin—CD33;

ibritumomab tiuxetan labeled with yttrium 90—CD20 ;

tositumomab labeled with I-131—CD20;

trastuzumab—HER2 (human epidermal growth factor receptor 2)

لاحظ أنّ اثنين من الأضداد للـ CD20 (a B-cell antigen) تمتلك وسم نشط إشعاعياً . الـ **ibritumomab tiuxetan** توليفي ، القطعة **ibritumomab** ترتبط بالخالب **tiuxetan** . يوفر الخالب مقر الارتباط للربطة النشطة إشعاعياً .

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
<i>Afatinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus	P-gp inhibitors and inducers	CBC, CMP	Administer on an empty stomach Reduce dose for significant diarrhea Use effective contraception for female patients
<i>Dabrafenib</i>	Inhibits mutated BRAF kinases	Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity	CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6	Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if warfarin)	Use effective contraception for female patients Administer on empty stomach May cause new primary malignancies
<i>Dasatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, diarrhea	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation
<i>Erlotinib</i>	Inhibits EGFR tyrosine kinase	Rash, ILD, hepatotoxicity	CYP3A4 substrates, acid-reducing agents, warfarin	CMP	Rash equated with increased response
<i>Ibrutinib</i>	Inhibits Bruton's tyrosine kinase	Neutropenia, thrombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia	CYP3A inhibitors and inducers	CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome	Avoid grapefruit juice and Seville oranges Can cause hepatitis B reactivation Use effective contraceptive
<i>Idelalisib</i>	Inhibits phosphatidylinositol 3-kinase	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection	CYP3A inducers and substrates	CBC, LFTs, pulmonary symptoms, infection	Use effective contraception for female patients
<i>Imatinib</i>	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, CHF	CYP3A4 substrates, warfarin	CBC, BCR-ABL	Monitor for development of heart failure
<i>Nilotinib</i>	Inhibits BCR-ABL kinase	Myelosuppression, QT prolongation, hepatotoxicity	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation Administer on empty stomach
<i>Osimertinib</i>	Inhibits EGFR tyrosine kinase	Diarrhea, rash, dry skin, nail toxicity, fatigue	Strong CYP3A inducers	CBC, ECG, electrolytes	Use effective contraceptive for female patients
<i>Pazopanib</i>	Multi-tyrosine kinase inhibitor	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting	CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; <i>simvastatin</i> ; drugs that reduce gastric pH	ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP	Use effective contraceptive for female patients
<i>Sorafenib</i>	Inhibits multiple intracellular and cell surface kinases	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue	CYP3A4 inducers, warfarin	BP, CMP	Wound healing complications, cardiac events
<i>Sunitinib</i>	Multi-tyrosine kinase inhibitor	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism	CYP3A4 substrates	BP, CMP, TSH	Monitor for development of heart failure
<i>Trametinib</i>	Reversible inhibitor of mitogen-activated extracellular kinases	Pyrexia, rash, diarrhea, vomiting, lymphedema	CYP2C8 substrates, P-gp	Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP	Used in combination with <i>dabrafenib</i> Administer on empty stomach
<i>Vemurafenib</i>	Inhibits mutated BRAF serine-threonine kinase	Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma	CYP3A4 inhibitors and inducers, CYP1A2 substrates	ECG, electrolytes, CMP, uveitis	May cause new primary cutaneous malignancies Use effective contraception in female patients

BMP = basic metabolic panel; BP = blood pressure; CBC = complete blood count; CHF = congestive heart failure; CMP = complete metabolic panel; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ILD = interstitial lung disease; INR = international normalized ratio; LFT = liver function test; LVEF = left ventricular ejection fraction; P-gp = P-glycoprotein; TSH = thyroid-stimulating hormone; UA = urinalysis.

Figure 35.32

Summary of tyrosine kinase inhibitors.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	MONITORING PARAMETERS	NOTES
<i>Bevacizumab</i>	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Cetuximab</i>	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea	Electrolytes, vital signs during infusion	Premedication with antihistamine required before infusion; rash equated with increased response
<i>Daratumumab</i>	Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis	Infusion reactions, diarrhea, fatigue, pyrexia	CBC with differential, vital signs during infusion	Can bind CD38 on red blood cells Type and screen patients before starting therapy Premedication with antihistamines, antipyretics, and corticosteroids required
<i>Ramucirumab</i>	Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands	Proteinuria, hypertension, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
<i>Rituximab</i>	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal infusion reaction, TLS, mucocutaneous reactions, PML	Vital signs during infusion, TLS labs	Fatal reactivation of hepatitis B Premedication required before infusion Increased risk of nephrotoxicity when given with <i>cisplatin</i>
<i>Trastuzumab</i>	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting	LVEF, CBC, pulmonary toxicity due to infusion reaction	Embryo-fetal toxicity Neutropenia in combination with chemotherapy Premedication with antihistamine and <i>acetaminophen</i> required

BP = blood pressure; CBC = complete blood count; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor protein 2; GI = gastrointestinal; LVEF = left ventricular ejection fraction; PML = progressive multifocal leukoencephalopathy; TLS = tumor lysis syndrome; VEGF = vascular endothelial growth factor.

Figure 35.31

Summary of monoclonal antibodies. (For drug dosages, refer to Appendix at the end of the book.)

Alkylating Agent	Mechanism of Action
Mechlorethamine	Forms DNA cross-links, resulting in inhibition of DNA synthesis and function
Chlorambucil	Same as above
Cyclophosphamide	Same as above
Bendamustine	Same as above
Melphalan	Same as above
Thiotepa	Same as above
Busulfan	Same as above
Carmustine	Same as above
Lomustine	Same as above
Altretamine	Same as above
Temozolomide	Methylates DNA and inhibits DNA synthesis and function
Procarbazine	Methylates DNA and inhibits DNA synthesis and function
Dacarbazine	Methylates DNA and inhibits DNA synthesis and function

Antimetabolites:

Drug	Mechanism of Action
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA
6-Thioguanine	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase.

TABLE 54-3 Antimetabolites: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Toxicity
Capecitabine	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Breast cancer, colorectal cancer, gastroesophageal cancer, hepatocellular cancer, pancreatic cancer	Diarrhea, hand-foot syndrome, myelosuppression, nausea and vomiting
5-Fluorouracil	Inhibits TS; incorporation of FUTP into RNA resulting in alteration in RNA processing; incorporation of FdUTP into DNA resulting in inhibition of DNA synthesis and function	Colorectal cancer, anal cancer, breast cancer, gastroesophageal cancer, head and neck cancer, hepatocellular cancer	Nausea, mucositis, diarrhea, bone marrow depression, neurotoxicity
Methotrexate	Inhibits DHFR; inhibits TS; inhibits de novo purine nucleotide synthesis	Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma	Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia
Pemetrexed	Inhibits TS, DHFR, and purine nucleotide synthesis	Mesothelioma, non-small cell lung cancer	Myelosuppression, skin rash, mucositis, diarrhea, fatigue, hand-foot syndrome
Cytarabine	Inhibits DNA chain elongation, DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of cytarabine triphosphate into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting, myelosuppression with neutropenia and thrombocytopenia, cerebellar ataxia
Gemcitabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase with reduced formation of dNTPs; incorporation of gemcitabine triphosphate into DNA resulting in inhibition of DNA synthesis and function	Pancreatic cancer, bladder cancer, breast cancer, non-small cell lung cancer, ovarian cancer, non-Hodgkin's lymphoma, soft tissue sarcoma	Nausea, vomiting, diarrhea, myelosuppression
Fludarabine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of fludarabine triphosphate into DNA; induction of apoptosis	Non-Hodgkin's lymphoma, CLL	Myelosuppression, immunosuppression, nausea and vomiting, fever, myalgias, arthralgias
Cladribine	Inhibits DNA synthesis and repair; inhibits ribonucleotide reductase; incorporation of cladribine triphosphate into DNA; induction of apoptosis	Hairy cell leukemia, CLL, non-Hodgkin's lymphoma	Myelosuppression, nausea and vomiting, and immunosuppression
6-Mercaptopurine (6-MP)	Inhibits de novo purine nucleotide synthesis; incorporation of triphosphate into RNA; incorporation of triphosphate into DNA	AML	Myelosuppression, immunosuppression, and hepatotoxicity
6-Thioguanine	Same as 6-MP	ALL, AML	Same as 6-MP

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DHFR, dihydrofolate reductase; dNTP, deoxyribonucleotide triphosphate; FdUTP, 5-fluorodeoxyuridine-5'-triphosphate; FUTP, 5-fluorouridine-5'-triphosphate; TS, thymidylate synthase.

TABLE 54-4 Natural product cancer chemotherapy drugs: Clinical activity and toxicities.

Drug	Mechanism of Action	Clinical Applications	Acute Toxicity	Delayed Toxicity
Bleomycin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, head and neck cancer	Allergic reactions, fever, hypotension	Skin toxicity, pulmonary fibrosis, mucositis, alopecia
Daunorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL	Nausea and vomiting, fever, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression
Docetaxel	Inhibits mitosis	Breast cancer, non-small cell lung cancer, prostate cancer, gastric cancer, head and neck cancer, ovarian cancer, bladder cancer	Hypersensitivity	Neurotoxicity, fluid retention, myelosuppression with neutropenia
Doxorubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma	Nausea, red urine (not hematuria)	Cardiotoxicity (see text), alopecia, myelosuppression, stomatitis
Etoposide	Inhibits topoisomerase II	Non-small cell and small cell lung cancer; non-Hodgkin's lymphoma, gastric cancer	Nausea, vomiting, hypotension	Alopecia, myelosuppression
Idarubicin	Oxygen free radicals bind to DNA causing single- and double-strand DNA breaks; inhibits topoisomerase II; intercalates into DNA	AML, ALL, CML in blast crisis	Nausea and vomiting	Myelosuppression, mucositis, cardiotoxicity
Irinotecan	Inhibits topoisomerase I	Colorectal cancer, gastroesophageal cancer, non-small cell and small cell lung cancer	Diarrhea, nausea, vomiting	Diarrhea, myelosuppression, nausea and vomiting
Mitomycin	Acts as an alkylating agent and forms cross-links with DNA; formation of oxygen free radicals, which target DNA	Superficial bladder cancer, gastric cancer, breast cancer, non-small cell lung cancer, head and neck cancer (in combination with radiotherapy)	Nausea and vomiting	Myelosuppression, mucositis, anorexia and fatigue, hemolytic-uremic syndrome
Paclitaxel	Inhibits mitosis	Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer	Nausea, vomiting, hypotension, arrhythmias, hypersensitivity	Myelosuppression, peripheral sensory neuropathy
Topotecan	Inhibits topoisomerase I	Small cell lung cancer, ovarian cancer	Nausea and vomiting	Myelosuppression
Vinblastine	Inhibits mitosis	Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma	Nausea and vomiting	Myelosuppression, mucositis, alopecia, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), vascular events
Vincristine	Inhibits mitosis	ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor	None	Neurotoxicity with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia, SIADH
Vinorelbine	Inhibits mitosis	Non-small cell lung cancer, breast cancer, ovarian cancer	Nausea and vomiting	Myelosuppression, constipation, SIADH

ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia.

Alkylating Agent :

(Nitrogen Mustards : Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, Bendamustine, Altretamine)

Alkyl sulfonates : Busulfan

Nitrosoureas : Carmustine, Lomustine....

Each one Forms DNA crosslinks, resulting in inhibition of DNA synthesis and function)

(Triazine : Dacarbazine , Temozolomide)

Methylhydrazine : Procarbazine

Each one Methylates DNA and inhibits DNA synthesis and function)

Cisplatin Forms intrastrand and interstrand DNA cross-links; binding to nuclear and cytoplasmic proteins

TABLE 54-5 Miscellaneous anti-cancer drugs: Clinical activity and toxicities.

Drug	Mechanism of Action ¹	Clinical Applications ¹	Acute Toxicity	Delayed Toxicity
Bortezomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway	Multiple myeloma, mantle cell lymphoma	Nausea and vomiting, fever	Peripheral sensory neuropathy, diarrhea, orthostatic hypotension, fever, pulmonary toxicity, reversible posterior leukoencephalopathy (RPLS), congestive heart failure (CHF), rare cases of QT prolongation
Carfilzomib	Inhibitor of the 26S proteasome; results in down-regulation of the NF- κ B signaling pathway; maintains activity in bortezomib-resistant tumors	Multiple myeloma	Fever	Fatigue, cardiac toxicity with CHF and myocardial infarction, myelosuppression, pulmonary toxicity, hepatotoxicity, orthostatic hypotension
Erlotinib	Inhibits EGFR tyrosine kinase leading to inhibition of EGFR signaling	Non-small cell lung cancer, pancreatic cancer	Diarrhea	Skin rash, diarrhea, anorexia, interstitial lung disease
Imatinib	Inhibits Bcr-Abl tyrosine kinase and other receptor tyrosine kinases, including PDGFR, and c-kit	CML, gastrointestinal stromal tumor (GIST), Philadelphia chromosome-positive ALL	Nausea and vomiting	Fluid retention with ankle and periorbital edema, diarrhea, myalgias, congestive heart failure
Bosutinib	Inhibits Bcr-Abl tyrosine kinase and retains activity in imatinib-resistant Bcr-Abl mutations except for the T315I and V299L mutations. Inhibits Src family tyrosine kinases.	CML	Nausea and vomiting	Diarrhea, fluid retention, myelosuppression, skin rash hepatotoxicity
Cetuximab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer, head and neck cancer (used in combination with radiotherapy), non-small cell lung cancer	Infusion reaction	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Panitumumab	Binds to EGFR and inhibits downstream EGFR signaling; enhances response to chemotherapy and radiotherapy	Colorectal cancer	Infusion reaction (rarely)	Skin rash, hypomagnesemia, fatigue, interstitial lung disease
Bevacizumab	Inhibits binding of VEGF-A to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer, breast cancer, non-small cell lung cancer, renal cell cancer, glioblastoma multiforme	Hypertension, infusion reaction	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, proteinuria
Ziv-aflibercept	Inhibits binding of VEGF-A, VEGF-B, and PlGF to VEGFR leading to inhibition of VEGF signaling; inhibits tumor vascular permeability; enhances tumor blood flow and drug delivery	Colorectal cancer	Hypertension	Arterial thromboembolic events, gastrointestinal perforations, wound healing complications, bleeding complications, diarrhea, mucositis, proteinuria
Sorafenib	Inhibits multiple RTKs, including raf kinase, VEGF-R2, VEGF-R3, and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, hepatocellular cancer	Nausea, hypertension	Skin rash, fatigue and asthenia, bleeding complications, hypophosphatemia
Sunitinib, pazopanib	Inhibits multiple RTKs, including VEGF-R1, VEGF-R2, VEGF-R3, PDGFR- α and PDGFR- β leading to inhibition of angiogenesis, invasion, and metastasis	Renal cell cancer, GIST	Hypertension	Skin rash, fatigue and asthenia, bleeding complications, cardiac toxicity leading to congestive heart failure in rare cases

¹See text for acronyms.

Anticancer Drugs

Kourtney LaPlant and Paige May

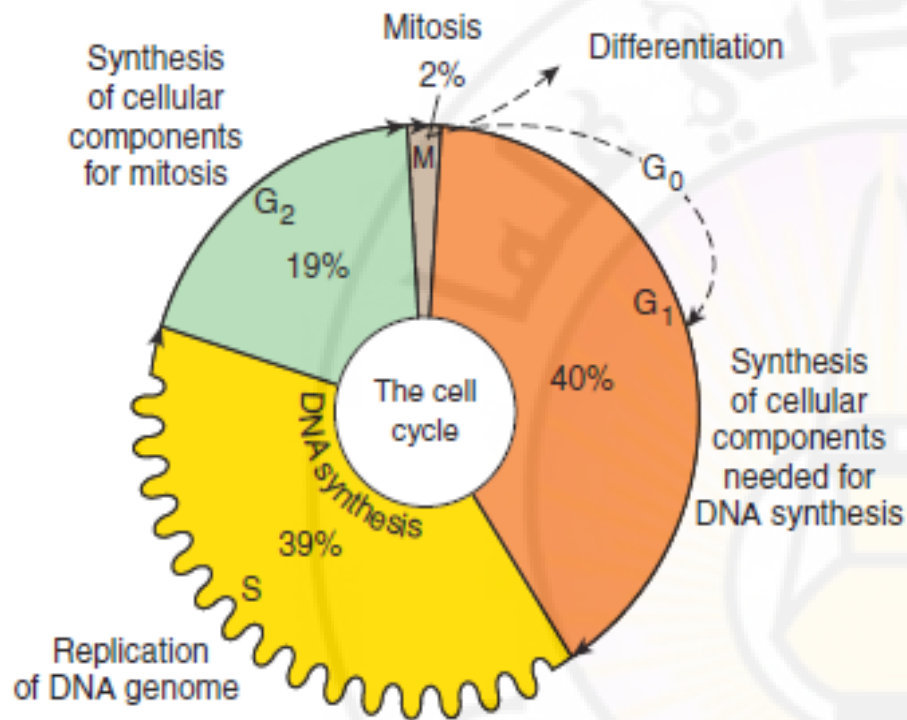
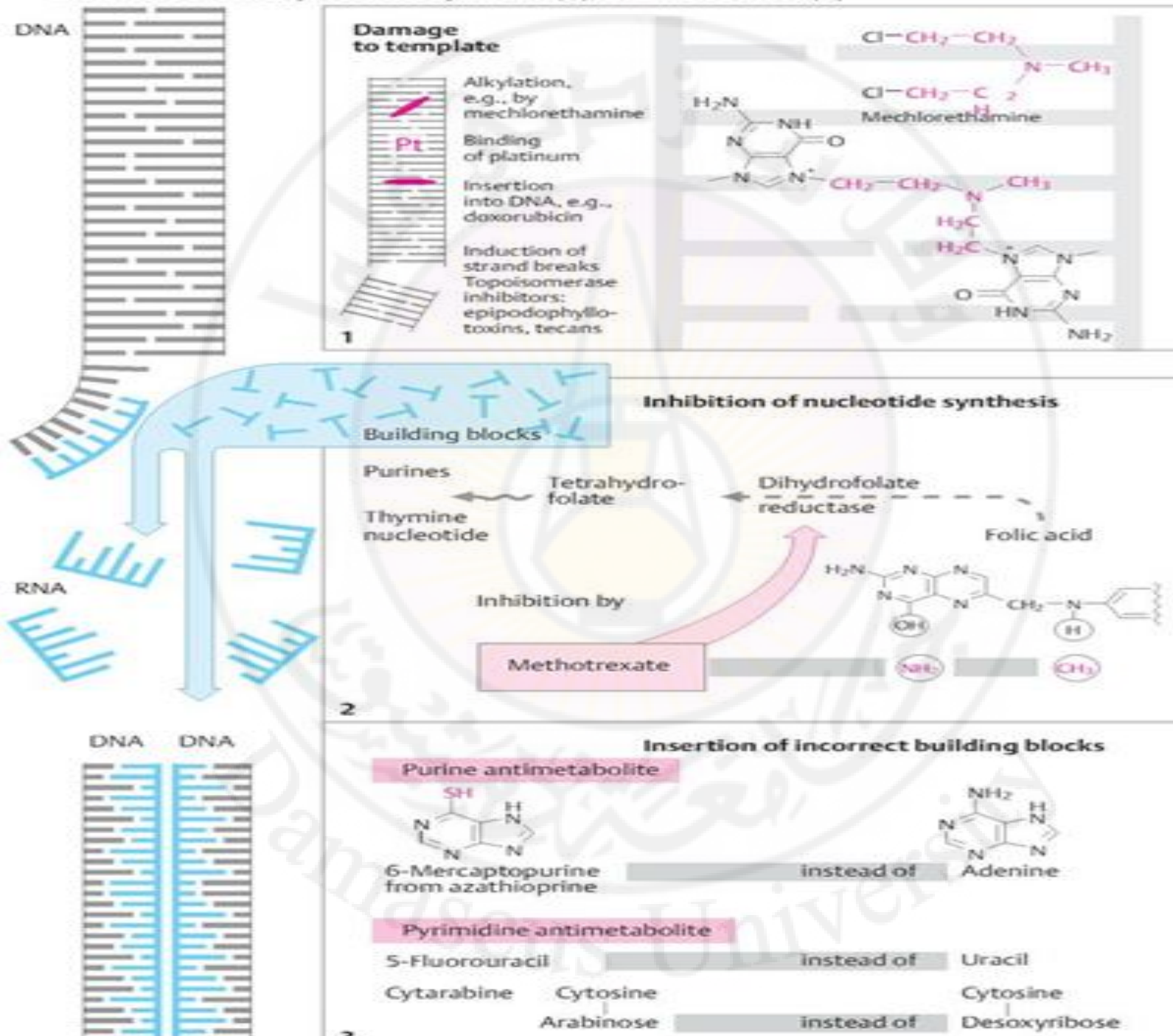


FIGURE 54-2 The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G₁, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle-specific (CCS) drugs (see Table 54-1). A second group of agents called cell cycle-nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G₀ compartment. CCNS drugs can kill both G₀ and cycling cells (although cycling cells are more sensitive).

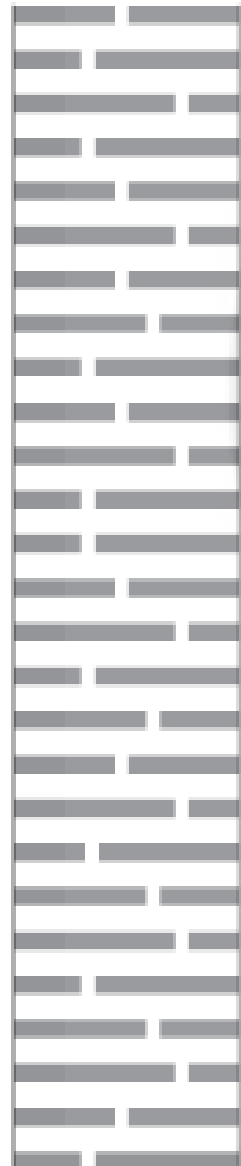
Cell Cycle-Specific (CCS) Agents	Cell Cycle-Nonspecific (CCNS) Agents
Antimetabolites (S phase)	Alkylating agents
Capecitabine	Altretamine
Cladribine	Bendamustine
Clofarabine	Busulfan
Cytarabine (ara-C)	Carmustine
Fludarabine	Chlorambucil
5-Fluorouracil (5-FU)	Cyclophosphamide
Gemcitabine	Dacarbazine
6-Mercaptopurine (6-MP)	Lomustine
Methotrexate (MTX)	Mechlorethamine
Nelarabine	Melphalan
Pralatrexate	Temozolomide
6-Thioguanine (6-TG)	Thiotepa
Topoisomerase II Inhibitor (G₁-S phase)	Antitumor antibiotics
Etoposide	Dactinomycin
Topoisomerase I Inhibitors (Camptothecins, G₂-M)	Mitomycin
Irinotecan	Platinum analogs
Topotecan	Carboplatin
Taxanes (M phase)	Cisplatin
Albumin-bound paclitaxel	Oxaliplatin
Cabazitaxel	Anthracyclines
Docetaxel	Daunorubicin
Paclitaxel	Doxorubicin
Vinca alkaloids (M phase)	Epirubicin
Vinblastine	Idarubicin
Vincristine	Mitoxantrone
Vinorelbine	
Antimicrotubule inhibitor (M phase)	
Ixabepilone	
Eribulin	
Antitumor antibiotics (G₂-M phase)	
Bleomycin	

A. Cytostatics: alkylating agents and cytostatic antitumorics (1), inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)

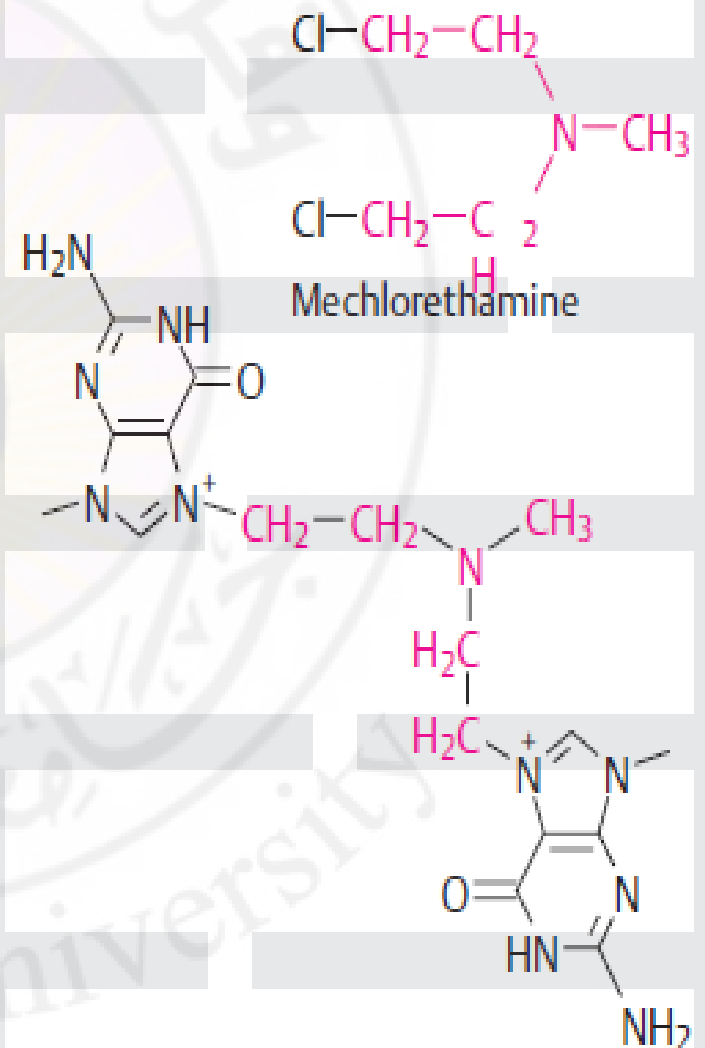
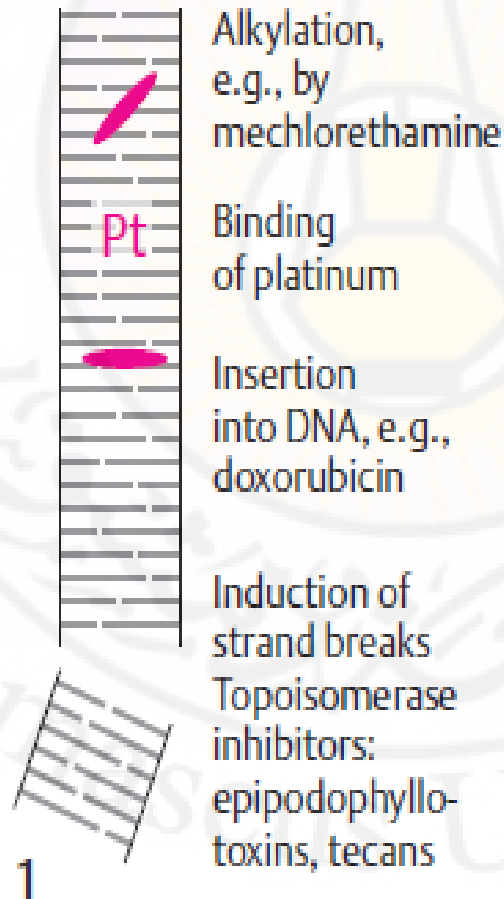


A. Cytostatics: alkylating agents and cytostatic antibiotics (1),
inhibitors of tetrahydrofolate synthesis (2), antimetabolites (3)

DNA



Damage
to template



HISTORY Alkylating Anticancer Drugs

The discovery and initial development of alkylating anticancer drugs are based on observations of the effects of chemical warfare in World War I (Chabner and Roberts, 2005). The pervasively **toxic sulfur mustard gas** that caused topical burns to skin, eyes, lungs, and mucosa also caused aplasia of the bone marrow and lymphoid tissue and ulceration of the GI tract (Krumbhaar, 1919). In 1942, **Louis Goodman and Alfred Gilman**, the originators of this text, demonstrated the activity of **nitrogen mustards against mouse lymphoma**. Their clinical studies of intravenous nitrogen mustards in patients with lymphoma launched the modern era of cancer chemotherapy (Gilman and Philips, 1946).

R. Lymphoma

Hodgkin lymphoma encompasses a distinctive group of neoplasms that are characterized by the presence of a *tumor giant عَمَلَق cell, the RS cell. Unlike most NHLs, Hodgkin lymphomas arise in a single lymph node or chain of lymph nodes* and typically spread in a stepwise fashion to anatomically contiguous مُجاوِر nodes. Although the Hodgkin lymphomas are now understood to be unusual tumors of B cell origin, they are distinguished from the NHLs by their unusual pathologic and clinical features.

يمكن تقسيم الأدوية إلى مجموعتين : الأدوية السامة للخلايا و الهرمونات . كل العوامل المؤلكة والصادات ومضادات الاستقلاب والأدوية المتنوعة هي سامة للخلايا .

Bleomycin :the cytotoxicity of bleomycin is due to **oxidative damage to DNA**. Bleomycin causes DNA fragmentation with predominantly single strand breakage, but also some double-strand breakage. Bleomycin causes scission of DNA by interacting with oxygen and ferrous ion . G2 and mitotic phases

Daunorubicin : Daunorubicin, an anthracycline antibiotic inhibits DNA topoisomerase II. Anthracyclines also intercalate into DNA and generate free radicals.

Doxorubicin : is an anthracycline antitumor antibiotic that **enhances formation of free oxygen radicals that alter cell membranes and induce Topoisomerase II (deoxyribonucleic acid) DNA damage**.

Epirubicin

Idarubicin : Idarubicin binds to DNA by intercalation and inhibits synthesis of nucleic acids, particularly DNA, and inhibits the activity of topoisomerase II, resulting in strand breaks. In addition, the quinone group of anthracyclines is reduced by cytochrome P450 reductase to generate semiquinone free radicals and oxygen radicals that attack DNA

Mitoxantrone : It interferes with DNA synthesis by intercalation with DNA or by inhibiting topoisomerase II.

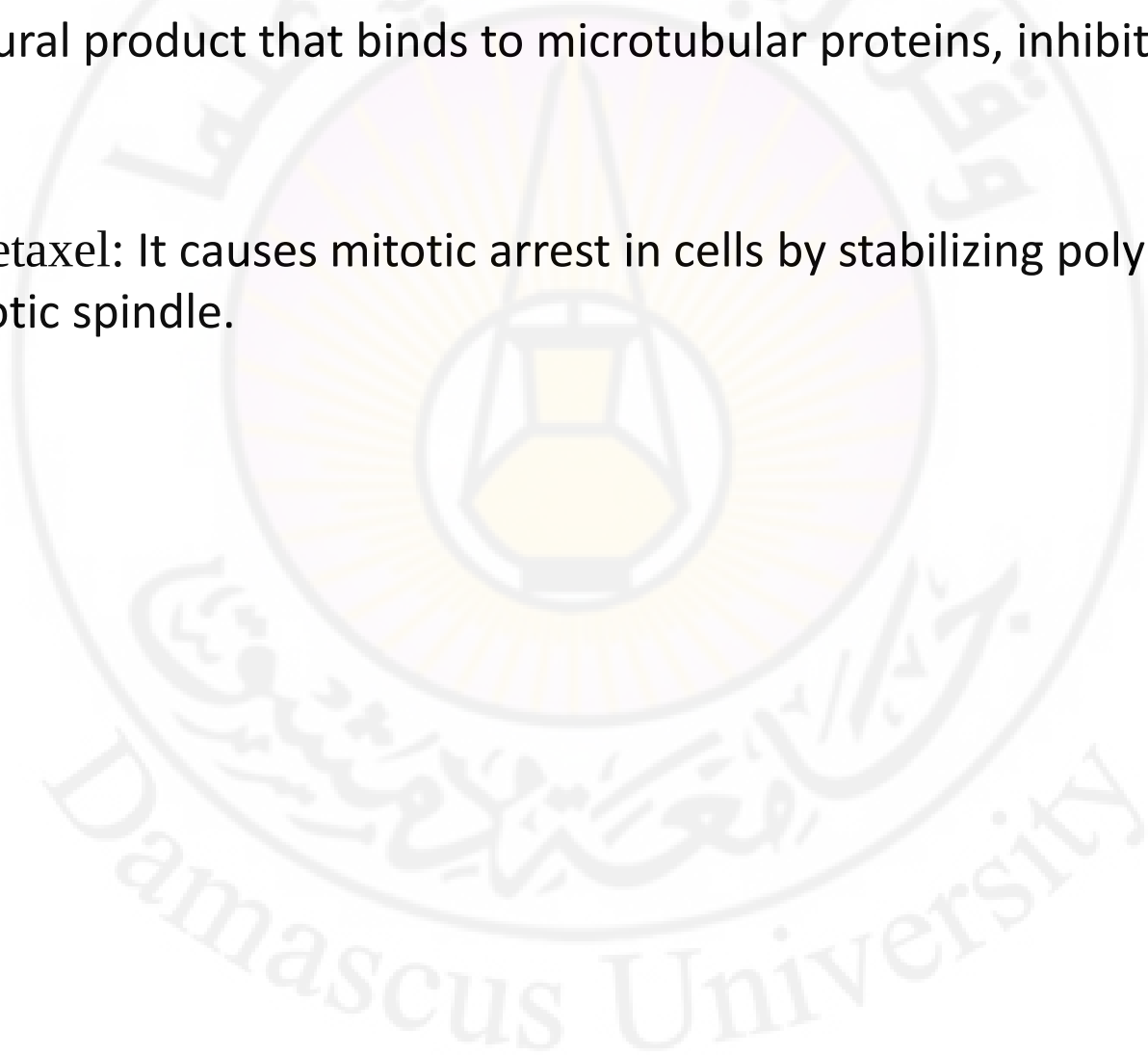
Actinomycin : Dactinomycin inhibits DNA-dependent RNA polymerase (choriocarcinoma)

Mitomycin

Vincristin : A vinca alkaloid, vincristine, acts by inhibiting mitosis . depolymerizes microtubules and causes mitotic arrest . A cytotoxic effect by binding to tubulin and preventing its polymerization. This action interferes with the formation of the mitotic spindle and mitosis.

Vinblastin : natural product that binds to microtubular proteins, inhibiting microtubule assembly.

Paclitaxel ; docetaxel: It causes mitotic arrest in cells by stabilizing polymerized tubulin and the mitotic spindle.



Topotecan : Topotecan cytotoxicity is due to inhibition of **topoisomerase I, an enzyme that relieves torsional strain إجهاد التَوَائِي during DNA replication.** Topotecan, like other camptothecin derivatives, inhibits topoisomerase I activity. The cleavable complex normally formed between DNA and topoisomerase I is stabilized by topotecan causing breaks in single-stranded DNA that cannot be religated. Because DNA synthesis is necessary for cytotoxicity, the action of topotecan may be S-phase-specific . A is a topoisomerase II inhibitor . An inhibitor of topoisomerase I which is involved in DNA replication. inhibitor of topoisomerase I.

Irinotecan : By inhibiting topoisomerase I, irinotecan relieves torsional strain in DNA, thereby causing reversible, single-strand breaks. **Irinotecan interferes with processes linked to DNA unwinding .. الفك /إرخاء /استرخاء**

Etoposide : causes DNA strand breaks in cells by binding to topoisomerase II and preventing re-joining of DNA strands. It binds to tubulin and causes mitotic arrest. Etoposide prevents cells from entering mitosis or destroys them in the premitotic phase. Cells in the S G2 phases of the cell cycle are more sensitive to etoposide. Etoposide induces double-strand breaks in DNA by forming a ternary complex with topoisomerase II and DN A. Resistance to etoposide develops because of enhanced expression of Pglycoprotein.

teniposide, forms ternary complexes with topoisomerase II and DNA, resulting in double-stranded DNA breaks and inhibition of repair . Teniposide prevents cells from entering mitosis or destroys them in the premitotic phase. Cells in the late S and early G2 phases of the cell cycle are more sensitive to teniposide. Teniposide, which forms a ternary complex with topoisomerase II and DNA, induces double-strand breaks in DNA. Although teniposide binds to tubulin at a site different from vinca alkaloids, it does not interfere with microtubular structure or function.

Mechlorethamine : immediately cyclizes, forming an ethylene immonium ion in a nonenzymatic reaction. The cyclic ring is highly reactive and reacts with the N-7 of guanine. While alkylation of any of the nucleophiles in the cell may occur, **the N-7 of guanine produces the only anti-cancer effect.** The second chloroethyl group then cyclizes and alkylates the DNA again. The internal cyclization of the bis-chloroethyl group is necessary for the pharmacological activity of nitrogen mustard and determines the ability to alkylate at the N-7 position of guanine. The two alkylations may occur on the same strand, or on two separate strands, leading to double or single strand breaks by the DNA repair enzymes Chabner et al (2001).

Chlorambucil : a derivative of nitrogen mustard, is an alkylating agent. Since it interacts with cellular DNA to produce chromosomal cross-linkages, it is cell cycle-phase nonspecific agent Chabner et al (2001).

Cyclophosphamide : Cyclophosphamide is activated in the liver by cytochrome P-450 enzymes to 4-hydroxy cyclophosphamide, which in turn isomerizes into aldophosphamide. Aldophosphamide is converted to phosphoramidate mustard, the alkylating agent, and acrolein, a cytotoxic moiety affecting the bladder Chabner et al (2001).

Bendamustine : ..

Melphalan : The mechanism of action of melphalan is similar to nitrogen mustard. Because of the amino acid in the molecule it is subject to carrier-mediated transport. Melphalan cyclizes in the cell, forming an ethylene immonium ion. The nitrogen becomes highly reactive and the ring opens and attaches to the N-7 of guanine. While alkylation of any of the nucleophiles in the cell may occur, alkylation of the N-7 of guanine is responsible for the anti-cancer effect. The second chloroethyl group then cyclizes and alkylates the DNA again. Because the internal cyclization of the bis-chloroethyl group determines the ability of the drug to alkylate at the N-7 position of guanine it is necessary for the biological activity of nitrogen mustards. The two alkylations may occur on the same strand or on separate strands, leading to double or single strand breaks by the DNA repair enzymes Chabner et al (2001)

Thiotepa : Thiotepa is activated in the liver and rapidly converted by mixed-function oxygenases to its major metabolite, triethylene phosphoramidate (TEPA). TEPA alkylates the N-7 position of guanine and induces DNA cross-links, leading to double or single stranded breaks, and, ultimately, inhibition of DNA replication Chabner et al (2001).

Busulfan : alkylates DNA at the N7 position of guanine causing interstrand cross-linkage Chabner et al (2001).

Carmustine : Carmustine alkylates the N-7 position of guanine to cause crosslinking of DN A. This results in intra دَاخِل - and inter بَيْن -strand breaks that inhibit DNA replication. Unlike the nitrogen mustards, nitrosoureas undergo spontaneous, nonenzymatic degradation resulting in the formation of highly electrophilic carbonium ions that alkylate DN A. The spontaneous degradation of carmustine may also inactivate certain DNA repair enzymes by generation of carbamoylating proteins Chabner et al (2001).

Lomustine : undergoes spontaneous nonenzymatic degradation that results in the formation of 2-chloroethyl carbonium ions that alkylate DN A. Like other alkylating agents, lomustine alkylates the N-7 of guanine to cause DNA cross-linking. This results in intraand inter-strand breaks that ultimately inhibit DNA replication. The spontaneous degradation of lomustine may also inactivate some DNA repair enzymes because of the formation of carbamoylating proteins Chabner et al (2001).
It crosses CNS

Altretamine : An alkylating agent, altretamine is a cancer chemotherapeutic agent. Its mechanism of action is alkylation of DNA leading to strand breaks Chabner et al (2001).

Dacarbazine : alkylates the N-7 of guanine to cause cross-linking of DNA, causing breaks in the DNA strands and, ultimately, inhibition of DNA replication Chabner et al (2001). Unlike the nitrogen mustards, dacarbazine methylates the N-7 of guanine by way of its methyl group Chabner et al (2001).

Procarbazine : Procarbazine appears to act by inhibiting DNA, RNA, and protein synthesis, possibly by blocking transmethylation of the methyl group of methionine into t-RN A. Procarbazine metabolism yields cytotoxic hydrogen peroxide. Azoxy metabolites of procarbazine liberate diazomethane, a potential methylating agent. These reactions can cause chromosomal damage, chromatid breaks, and translocations Chabner et al (2001). Repair of methylation of guanine via guanine-O6-alkyl transferase can lead to resistance.

Temozolomide : is an imidazotetrazine derivative of decarbazine and used via oral route.

Streptozotocin : like the other nitrosoureas, is an alkylating agent that acts by alkylating the N-7 of guanine to cause cross-linking of DN A. This results in intra- and inter-strand breaks that ultimately inhibit DNA replication. specifically for the treatment of pancreatic tumors . derived from *Streptomyces achromogenes* variety. It also displays antibacterial properties.

Antimetabolites :

5-Fluorouracil : A potent inhibitor of thymidylate synthase it interferes with DNA synthesis and with RNA function.

5-Fluorouracil is activated intracellularly to a 5'-monophosphate nucleotide (FUMP) either directly by 5-phosphoribosyl-1-pyrophosphate (PRPP) or in two steps by way of conversion to fluorouridine by uridine phosphorylase and then to FUMP by uridine kinase. FUMP is activated to FUDP and then reduced by the enzyme ribonucleotide reductase to F-dUDP, which leads to the formation of F-dUMP. 5-FU may also be directly converted into FdUR by thymidine phosphorylase and then to FdUMP by thymidine kinase. FdUMP forms a ternary complex with thymidylate synthetase and the folate cofactor, N⁵, N¹⁰-methylene tetrahydrofolate. Thus, 5-FU inhibits the conversion of dUMP to thymidylate (TMP). Addition of 5-formyl-tetrahydrofolate (leucovorin) increases the formation of the ternary complex and enhances responses to 5-FU.

Capacitabine : ..

Methotrexate : Methotrexate (MTX) induces an effect similar to 5-fluorouracil (5-FU) by interrupting the formation of thymine within the cell, which leads to the inability to replicate DNA. Unlike 5-FU, which inhibits the action of thymidylate synthetase, MTX binds tightly to dihydrofolate reductase (DHFR) and blocks the formation of tetrahydrofolate, leading to the depletion of associated folate co-factors. However, the same effect-arrestment of DNA, RNA, and protein synthesis as is induced by 5-FU results.

Pemetrexed : Pemetrexed, thymidylate synthase and transferase inhibitor, is used in a treatment for several solid tumors. This compound is not only a thymidylate synthase inhibitor but also a potent inhibitor of human dihydrofolate reductase. Pemetrexed probably acts upon multiple intracellular targets and the antitumor effect may be derived from its simultaneous inhibition of multiple folate-requiring enzymes. Thus, this compound has been designated as a multitargeted antifolate. The drug also causes concentration- and time-dependent apoptosis Norman (2001).

Cytarabine : A pyrimidine antimetabolite, cytarabine, inhibits DNA polymerase and causes chain termination.

Cytarabine diffuses into cells and is activated by deoxycytidine kinase to the monophosphate. It is converted to the di- and tri-phosphates by non-specific cellular enzymes. Cytosine triphosphate inhibits DNA polymerase by competition of Ara-CTP for dCTP. It is also a weak inhibitor of ribonucleotide reductase. Cytarabine is a cell cycle S-phase specific drug Chabner et al (2001).

Gemcitabine : After diffusing into cells, gemcitabine is activated by nucleoside kinases to di- and triphosphate forms. Gemcitabine diphosphate inhibits ribonucleotide reductase, leading to a reduction in the concentration of deoxynucleotides and inhibition of DNA synthesis. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. Because dCTP concentrations are already reduced by the diphosphate, the incorporation of the triphosphate is increased causing further inhibition of DNA synthesis. Unlike cytarabine, a closely related antimetabolite, gemcitabine is not cell cycle S-phase specific Chabner et al (2001).

Fludarabine : After diffusing into the cell it is activated by deoxycytidine kinase to the monophosphate, which is then converted to the di- and tri-phosphates by non-specific cellular enzymes. Fludarabine triphosphate is incorporated into DNA and inhibits the enzymes responsible for DNA synthesis. Since apoptosis is a major effect of fludarabine, it does not require cell division to be cytotoxic Chabner et al (2001).

Cladribine : A purine nucleoside analog .

6-Thioguanine : A purine derivative

6-Mercaptopurine : purine analog, 6-mercaptopurine, inhibits nucleic acid synthesis by multiple mechanisms, including incorporation into DNA.

Cisplatin : Cisplatin causes a cross-linking of DNA strands via alkyl groups. Cisplatin, which causes intra-strand DNA cross-linking
Once activated cisplatin reacts with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bifunctional covalent links, very similar to alkylating reactions. The intrastrand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis. Only the cis-dichloro structure is active as an antitumor agent. Cisplatin has immunosuppressive and mutagenic properties. It is classified as an alkylating agent with cell cycle nonspecific characteristics.

Carboplatin : Carboplatin causes crosslinks within DNA, inhibiting its synthesis

Oxaliplatin : Oxaliplatin has selectivity for tumor cells with high rates of DNA synthesis.

The DNA topoisomerases are nuclear enzymes that **reduce torsional stress** الإجهاد الإلتوائي in supercoiled مُفْرِطُ الِئْتِاف DNA, allowing selected regions of DNA to become sufficiently untangled to permit replication, repair, and transcription. Two classes of topoisomerase (I and II) mediate DNA strand breakage and resealing.

Camptothecin analogues inhibit the function of topoisomerase I; other drugs, such as anthracyclines, epipodophyllotoxins, and acridines, inhibit topoisomerase II.

The camptothecins bind to and stabilize the normally transient DNA–topoisomerase I cleavable complex. Although the initial cleavage action of topoisomerase I is not affected, the religation step is inhibited, leading to the accumulation of single-stranded breaks in DNA. These lesions are reversible and not by themselves toxic to the cell. However, the collision تَصَادُم of a DNA replication fork with this cleaved strand of DNA causes an irreversible double-strand DNA break, ultimately leading to cell death.

Tangle = حُبَيْكَة [ج: حَبَائِك] (تشابك أو عقدة عصبية) .

Pharma. The **alkylating agents** are a diverse group of anticancer drugs that covalently bind an alkyl group or a substituted alkyl group to cellular constituents. Their common property is the capacity to become strong **electrophiles** through the formation of carbonium ion intermediates or to form transition complexes with the target molecules. These reactions yield covalent linkages by alkylation with various nucleophilic groups such as **sulfhydryl** or **carboxyl**.

Clinically, the most important actions of the alkylating agents are those that **effect DNA synthesis and cell division**. Although they interact with cells in all phases of the cell cycle, their therapeutic effects and toxicity are due primarily to interference with rapidly proliferating cells.

Pharma. The **antimetabolites** represent a relatively large group of anticancer agents that **structurally resemble natural substrates, but differ enough to interfere with their metabolism.**

___Included are

folic acid antagonists, such as methotrexate;

purine antimetabolites, such as 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatin, and cladribine; and the

pyrimidine antimetabolites such as 5-fluorouracil, 5-fluorodeoxyuridine, cytarabine, and gemcitabine.

Antimetabolites disrupt nucleic acid synthesis by interfering with production of a major nucleotide metabolite or by substituting for the natural metabolite.

Like most cytotoxic anticancer agents, antimetabolites are toxic to normal cells, especially those in the bone marrow and gastrointestinal tract.

Notably important immuno-oncology targets are the **programmed death ligand 1 (PD-L1)** and its cognate receptor, PD-1, which is found on activated T cells, B cells, and myeloid cells. PD-L1 up regulation allows melanoma, lung, renal, and gastric cancers to evade the host immune system. PD-1 checkpoint inhibitors, such as **nivolumab** and **pembrolizumab**, have been approved. Another example of effective immuno-oncology therapy is the blocking antibody against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), which down regulates cytotoxic T-lymphocytes and is used for the treatment of melanoma.

من أهداف الـ immuno-oncology لجين-1 الموت المبرمج (PD-L1) ومستقبلته القريبة PD-1 الموجودة على الخلايا التائية المنشّطة وخلايا النقي . يسمح التنظيم صعوداً للـ PD-L1 للملانوما وسرطانات الرئة والكلية والمعدة بتجنب جهاز مناعة المضيف . مثبطات نقاط ضبط الـ PD-1 مثل nivolumab و pembrolizumab مثبتة .

Normally, only immunosuppressive cells such as Tregs and MDSCs express the protein PD-L1, which binds to its receptor PD-1 on cytotoxic T cells. This interaction suppresses T cells so they are “exhausted,” or unable to carry out their cytolytic function, and prevents unchecked immune cell destruction of tissues. Tumor cells mimic the role of the normal immunosuppressive components of the immune system, placing the T cells into the “exhaustion” state by expressing PD-L1 on their cell surfaces. The discovery of the PD-L1 and PD-1 interaction helps explain why tumors are often not rejected by the host, even though ample cytotoxic T cells are present. Two antibodies are currently approved that inhibit this pathway; one is a humanized monoclonal antibody that neutralizes PD-L1 (**nivolumab**), and the other is a humanized monoclonal antibody that neutralizes PD-1 (**pembrolizumab**).

فقط خلايا مثبطة للمناعة تعبر البروتين PD-L1 ، الذي يرتبط بال PD-1 على التائية السامة للخلية . هذا التأثير يثبط التائية فلا تقدر على حلّ الخلايا ويمنع تخريب النسيج بخلايا المناعة غير المضبطة . خلايا الورم تحاكي دور المكونات الطبيعية الكابتة للمناعة في الجهاز المناعي ، واضعة التائية في حالة الإنهاك بواسطة تعبير PD-L1 على سطوح خلاياها . اكتشاف تأثير الـ PD-L1 والـ PD-1 يساعد شرح لماذا لا يجري رفض الأورام عادةً من قبل المضيف ، رغم وجود خلايا تائية سامة للخلية كافية . ضدّان يثبطان هذا الطريق ؛ nivolumab يستعدل الـ PD-L1 ، و pembrolizumab يستعدل الـ PD-1

Difficulty level: Easy

26. A 10-year-old boy suffering from acute lymphoblastic leukemia started maintenance therapy that included high dose methotrexate. Two weeks later, a blood test with differential showed a white blood cell count of $1800/\text{mm}^3$ (normal $4500\text{--}11,000/\text{mm}^3$). The oncologist believed the result was related to an excessive dose of methotrexate and ordered an antidote agent. Which of the following drugs would be appropriate for the patient at this time?

A. Vitamin B12 B. Pyridoxine C. Folic acid D. Vitamin B3 E. Leucovorin

Learning objective: Identify the drug to be used as a methotrexate antidote.

26. **E** Leucovorin can be given to counteract the adverse effects that methotrexate has on normal cells. Leucovorin (formyl tetrahydrofolate, also called folinic acid) is accumulated more readily by normal cells than by neoplastic cells. The administration of this drug results in rescue of the normal cells, because the drug bypasses the step in the purine synthesis that is blocked by methotrexate (i.e., dihydrofolate to tetrahydrofolate).

ANTIRHEUMATIC DRUGS

OVERVIEW : inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA).. In RA, white blood cells (WBCs) view the synovium as non-self and initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)- α and interleukin (IL)-1, into the synovial cavity, ultimately leading to joint destruction and other systemic abnormalities characteristic of RA.. B lymphocytes produce rheumatoid factor and other autoantibodies to maintain inflammation. These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, pain, and reduced quality of life. Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, and halting or slowing disease progression..

النظرة العامة : يؤدي التنشيط غير الملائم لجهاز المناعة إلى التهاب وأمراض متواسطة بالمناعة مثل الـ **RA** .. في هذا المرض ترى الـ **WBCs** الغشاء الزليلي أجنبياً وتبدأ هجوماً التهابياً . تنشيط الـ WBC يؤدي إلى تنبيه اللمفاويات التائية التي تُجَنِّد وتنشط الوحيدات والبلاعم . تُفَرِّز هذه الخلايا سيتوكينات مؤيدة للالتهاب ، متضمنة **TNF- α** و **IL-1** إلى الجوف الزليلي ، تؤدي في النهاية إلى تخريب المفصل وغيرها .. تنتج الخلايا البائية العامل الرثياني وأضداد ذاتية إضافية لاستدامة الالتهاب . تسبب تفاعلات الدفاع هذه أذى نسيجي متقدم ، مسبباً ضرر المفصل و تآكلات وعجز وظيفي وألم ونقص جودة الحياة . تتضمن المعالجة الدوائية أدوية مضادة للالتهاب و/أو كابحات المناعة ..

V. TRADITIONAL DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs)

Traditional DMARDs (*methotrexate, hydroxychloroquine, leflunomide, or sulfasalazine*) are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease. Monotherapy may be initiated with any of the traditional DMARDs, although *methotrexate* is generally preferred. For patients with inadequate response to monotherapy, a combination of traditional DMARDs, or use of a TNF inhibitor or non-TNF biologic agent may be needed. NSAIDs or glucocorticoids can also be used for their anti-inflammatory actions.

الأدوية المضادة للروماتيزم (الرثية) المحوّرة/المعدلة — للمرض (DMARDs) : الـ methotrexate والـ hydroxychloroquine والـ leflunomide والـ sulfasalazine أدوية شائعة تستعمل في معالجة التهاب المفاصل الروماتويدي (RA) وتبطّء مسار المرض وتحرّض الهدأة وتمنع التخرّب الإضافي للمفاصل والنسج المكتنفة .. ينبغي البدء بها حالاً لتأجيل التدهور .

تحبذ المعالجة الأحادية ويفضل البدء بالميثوتريكسات .

إذا لم تكف المعالجة الأحادية قد يُحتاج توليف من الـ DMARDs ، أو استعمال مثبّط للـ TNF أو غيره . يمكن استعمال الـ NSAIDs أو الـ GCs لتأثيراتها المضادة للالتهاب .

A. **Methotrexate** is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. It has become a mainstay of treatment in patients with rheumatoid arthritis. Response to *methotrexate* usually occurs within 3 to 6 weeks of starting treatment. Other traditional DMARDs, TNF inhibitors, or non-TNF biologic agents can be added to *methotrexate* if there is inadequate response to monotherapy with this agent. Doses of *methotrexate* required for RA treatment are much lower than those needed in cancer chemotherapy and generally administered once weekly, thereby minimizing adverse effects. Common adverse effects of *methotrexate* when used for RA are mucosal ulceration and nausea. Cytopenias (particularly leukopenia), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Supplementation with *folic acid* may improve tolerability of *methotrexate* and reduce gastrointestinal and hepatic adverse effects.] Periodic liver function tests, complete blood counts, and monitoring for signs of infection are recommended. *Methotrexate* is contraindicated in pregnancy.

أ. الـ **Methotrexate** : مناهض لحامض الفوليك يثبط إنتاج السيتوكين والتصنيع الحيوي لنوكليوتيد البورين ، مؤدياً إلى تأثيرات كابطة للمناعة ومضادة للالتهاب . صار ركن أساسي في معالجة الـ RA .

الاستجابة خلال ٣—٦ أسابيع عادةً ..

جرعته هنا أقل بكثير من جرعته في السرطان ، مرة أسبوعياً ..
قد يحدث تقرح المخاطية و غثيان . قد يسبب قلة الكريات (خصوصاً قلة الكريات البيض) و تشمع الكبد ومتلازمة شبيهة-التهاب الرئة الحاد مع طول الاستعمال .
(ملاحظة : الدعم بحامض الفوليك قد يحسن تحمل الميثوتريكسيت ويقلل ضرر الهضم والكبد) . ممنوع استعماله أثناء الحمل .
يوصى باختبارات دورية لوظيفة الكبد وتعداد الدم الشامل ورصد علامات عدوى .

B. Hydroxychloroquine

Hydroxychloroquine [hye-drox-ee-KLOR-oh-kwin] is used for early, mild RA and may be combined with methotrexate. Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. Hydroxychloroquine has less adverse effects on the liver and immune system than other DMARDs. However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

ب. الـ **Hydroxychloroquine** : للحالات الخفيفة من الـ RA وقد يولف مع الميثوتريكسيت
آلية فعله في اضطرابات المناعة الذاتية مجهولة ،
يلزم ٦ أسابيع — ٦ شهور لتبدأ تأثيراته .

أقل ضرراً على الكبد وجهاز المناعة من باقي الـ DMARDs . لكن ، قد يسبب تسمم العين ،
متضمناً ضرر شبكية متعذر العكس ورواسب قرنية واضطرابات مركزية وانزعاجات
هضمية وتصبغ وطفح الجلد .

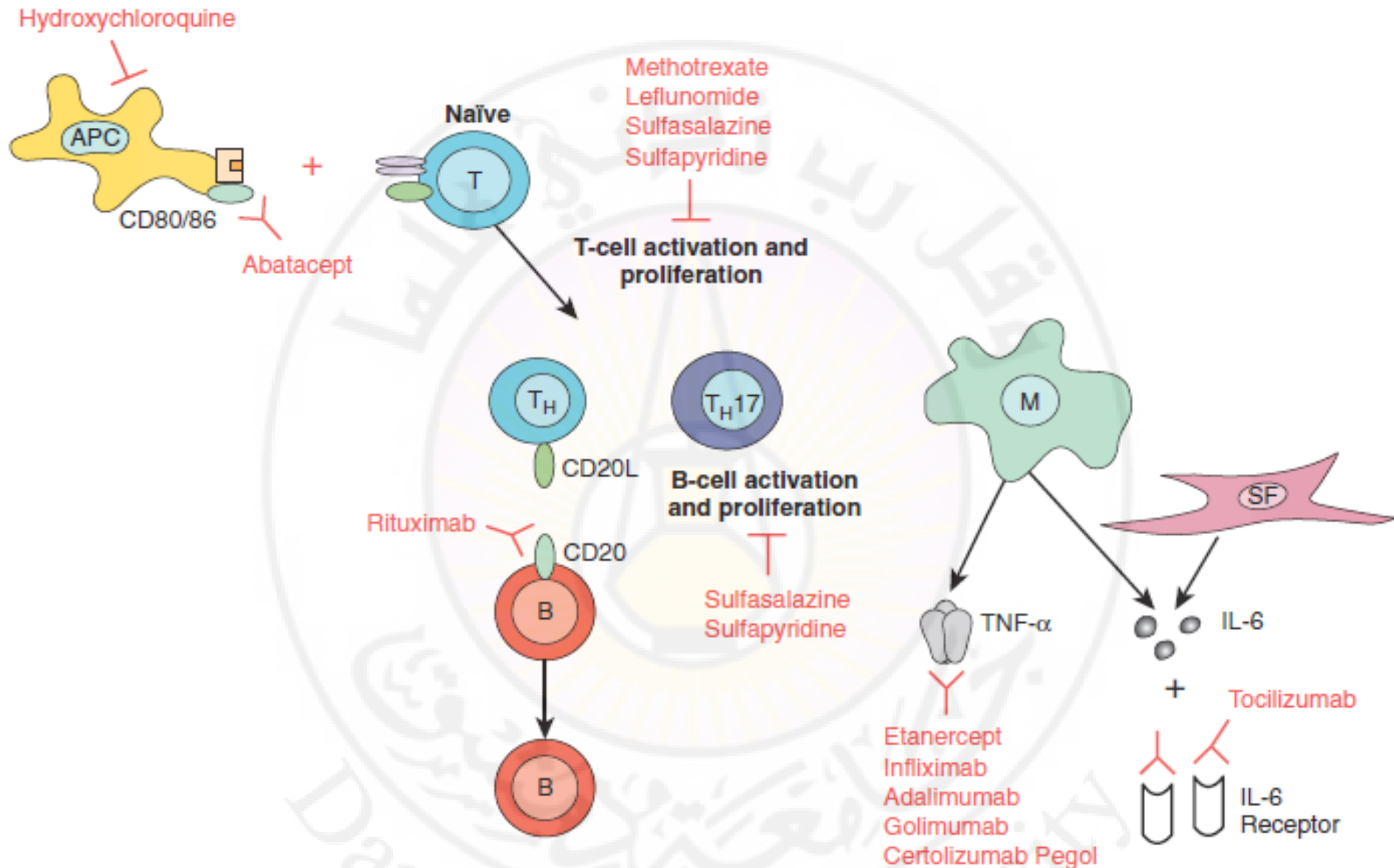
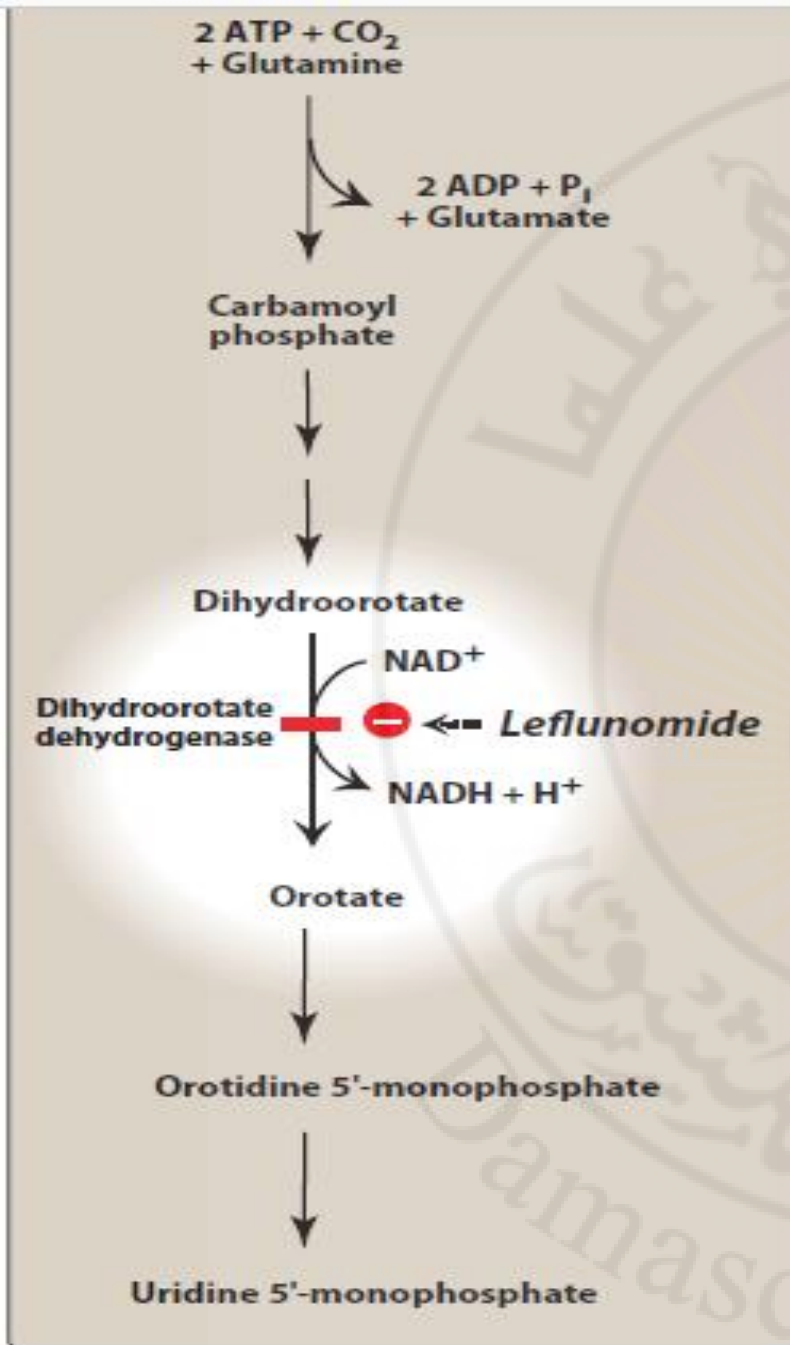


FIG. 35.2 Disruption of the Inflammatory Pathway by DMARDs. The nonspecific conventional DMARDs (methotrexate, leflunomide, sulfasalazine, and sulfapyridine) inhibit the proliferation and activation of T and B cells, whereas hydroxychloroquine affects the activation of antigen-presenting cells (APCs). The biological and targeted DMARDs interact with specific cytokines such as tumor necrosis factor- α (TNF- α), cytokine targets such as the interleukin-6 (IL-6) receptor, or cell surface proteins such as CD20 expressed by B-lymphocytes to potentially inhibit inflammation.



C. **Leflunomide** [le-FLOO-no-mide] is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH, an enzyme necessary for pyrimidine synthesis (Figure 40.18).

ج. الـ **Leflunomide** : دواء مُخَوِّر للمناعة يسبب توقف خلايا لمفاويات المناعة الذاتية عبر فعله على الـ dihydroorotate dehydrogenase (DHODH). إذ أنه يستقلب إلى مثبط عكوس للـ DHODH ، الإنزيم الضروري لتصنيع البيريميدين (الشكل ٤٠ ، ١٨) .

Figure 40.18

Leflunomide may be used as monotherapy in patients who have intolerance or contraindications to use of methotrexate in RA, or it may be used in combination with methotrexate for patients with suboptimal response to methotrexate alone. Common adverse effects include headache, diarrhea, and nausea. Other effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia. The drug is not recommended in patients with liver disease as it can be hepatotoxic. Leflunomide is contraindicated in pregnancy. Monitoring parameters include signs of infection, complete blood count, electrolytes, and liver enzymes.

يمكن استعمال الـ Leflunomide معالجة أحادية للـ RA عند عدم تحمل الميثوتريكسيت ، أو بالتوليف معه عند غير متحملي الميثوتريكسيت وحيداً .

تتضمن تأثيراته الضائرة الشائعة صداع وإسهال و غثيان . إضافةً إلى نقص الوزن وتفاعلات أرجية ، متضمنة متلازمة شبيهة-النزلة وطفح الجلد و ثعلبة/حاصة (فقد الشعر الموضّع) ونقص بوتاسيوم الدم .

لا يوصى به لمرضى الكبد لأنه يمكن أن يسمم الكبد .

ممنوع الاستعمال في الحمل .

تتضمن مُتَّابِئات المراقبة علامات عدوى وتعداد الدم الشامل والكهرليات وإنزيمات الكبد

- D. **Sulfasalazine**. Sulfasalazine [sul-fa-SAH-la-zeen] has recommendations for use similar to leflunomide in the treatment of RA. Its mechanism of action in treating RA is unclear. The onset of activity is 1 to 3 months, and it is associated with GI adverse effects (nausea, vomiting, anorexia) and leukopenia.
- E. **Glucocorticoids**. Glucocorticoids (see Chapter 26) are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until other DMARDs become effective. Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

د. الـ **Sulfasalazine** : له نفس دواعي الاستعمال في الـ RA مثل الـ leflunomide .
آلية فعله في معالجة الـ RA غير واضحة .

سرعة بدء الفعالية تحتاج ١—٣ شهور ،

يتربط مع تأثيرات ضائرة هضمية (غثيان وقياء وقهم) ، وقلة الكريات البيض .

هـ. **القشرانيّات السكرية** : شائعة الاستعمال في الـ RA لتوفير تفريج أعراض ريثما تصير باقي الـ DMARDs فعالة .

ينبغي دائماً استخدامها بأقل جرعة وأقصر فترة ممكنة لتجنب التأثيرات الضائرة المترابطة مع الاستعمال الطويل-الأمد .

VI. BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

IL-1 and TNF- α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF- α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF- α inhibitors (*adalimumab*, *certolizumab*, *etanercept*, *golimumab*, and *infliximab*) are biologic DMARDs which have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy.

الأدوية البيولوجية المضادة للروماتيزم المَحَوْرَة (المعدلة) للمرض :

الإنترلوكين-1 (IL-1) وعاملُ نَحْرِ الوَرَمِ—الألفا (TNF- α) سيتوكينين مؤيدين
للالتهاب مُكتَتَفان في إِمْرَاضِ الـ RA . إذ أَنهما عَندَما يُفَرَزَانِ مِنَ البَلَاعِمِ الزَّلِيلِيَّةِ يَنبَهِانِ
الخلايا الزَّلِيلِيَّةَ لِكَي تَتَكَثَّرَ وَتَصْنَعَ كَوَلاَجِينَازَ ، بِالتَّالِي تَدْرُكُ الغُضُرُوفَ وَتَنبَهِ ارْتِشَافَ
العَظْمِ وَتَتَبَطُّ تَصْنِيعَ بروتيوغليكان .

مُثَبِّطَاتِ الـ TNF- α (*adalimumab* و *certolizumab* و *etanercept* و *golimumab* و *infliximab*) أدوية بيولوجية مضادة للروماتيزم محورة للمرض
تنقص علامات وأعراض الـ RA ، وتقلل ترقّي الضَّرَرِ البَنِيَوِيِّ ، وَتَحْسِنُ الوَظِيفَةَ
الفيزيائية .

تلاحظ الاستجابة السريرية خلال ٢ أسبوع .

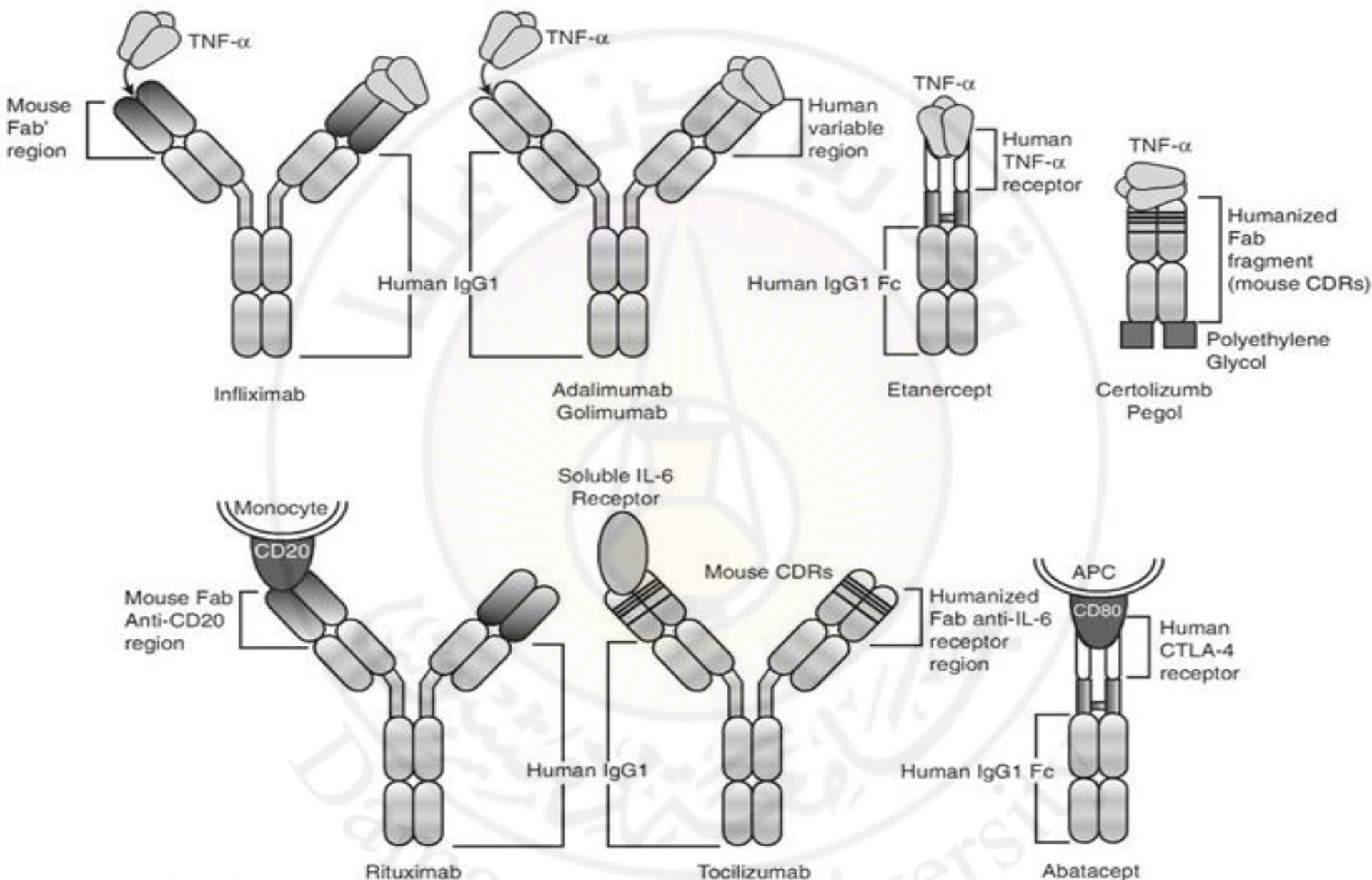


FIG. 35.3 Structures of the Biological and Targeted DMARDs. The light striped gray denotes the Fab and Fc portions of human antibodies (IgG1), while the darker striped gray indicates mouse Fab regions. The black stripes within the human Fab regions indicate mouse amino acids that form the complementary determining regions (CDR) in the humanized antibodies. The dark gray squares indicate polyethylene glycol moieties. *TNF- α* , Tumor necrosis factor- α ; APC, antigen-presenting cell; *IL-6*, interleukin-6.

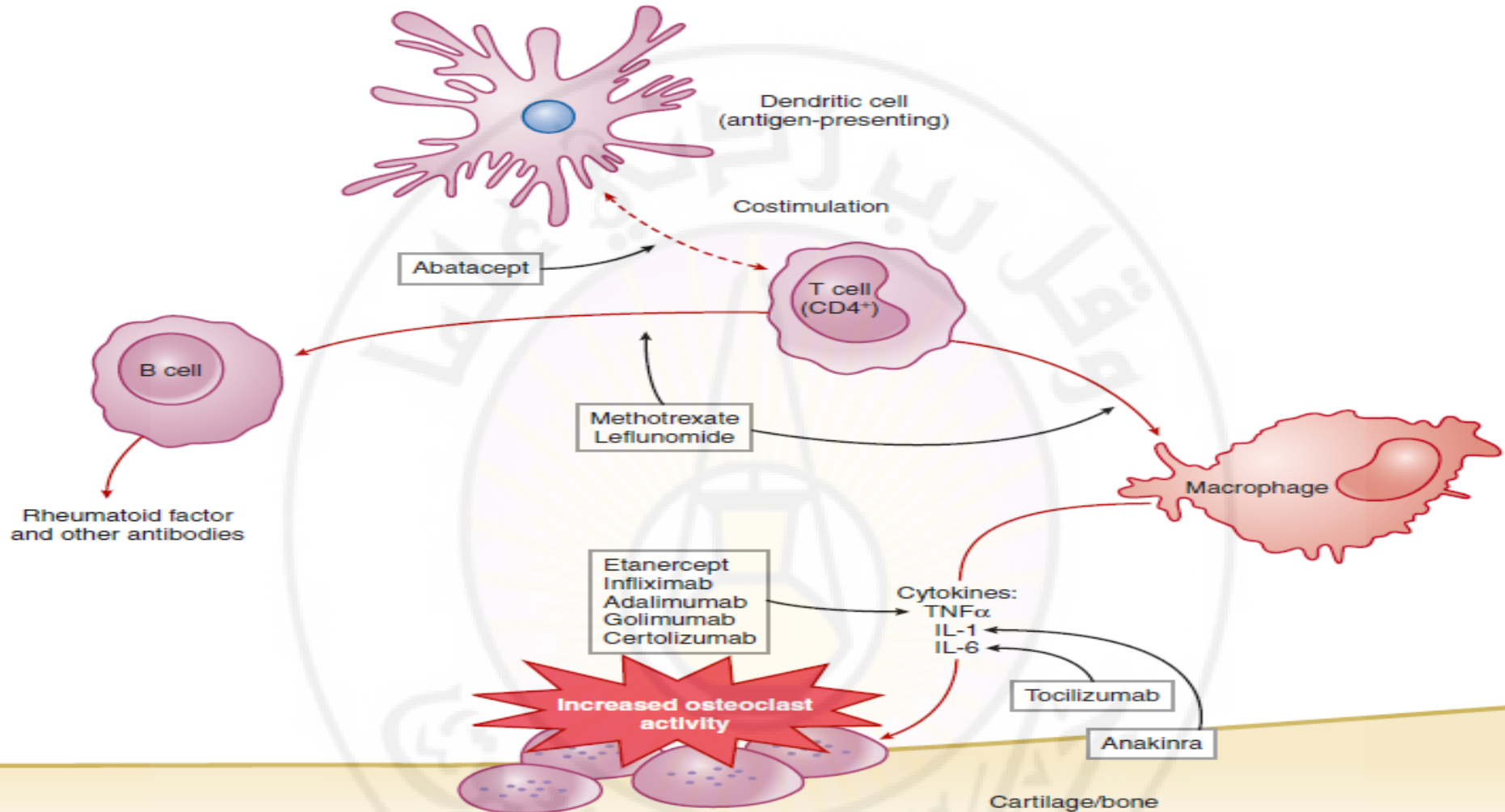


Fig. 30.1 Pathogenesis of rheumatoid arthritis and sites of action of selected antirheumatic drugs. In this simplified view of the immune system, dendritic (antigen-presenting) cells phagocytose antigens and present them to T cells, thereby activating the T cells. Activated T cells stimulate the production of B and T cells. B cells produce plasma cells that form rheumatoid antibodies. Helper T cells activate macrophages and cytotoxic T cells. Together, T cells, macrophages, and cytotoxic T cells produce cytotoxic cytokines (tumor necrosis factor- α [TNF α], interleukin [IL]-1, IL-6, and others) and prostaglandins that cause joint inflammation, synovial proliferation, and bone and cartilage destruction. Abatacept blocks the costimulation of T cells. Methotrexate and leflunomide inhibit the proliferation and activity of T cells and B cells. Etanercept, infliximab, adalimumab, golimumab, and certolizumab inactivate TNF α . Anakinra blocks the action of IL-1, and tocilizumab and sarilumab inactivate IL-6. Not shown are the **GC** that inhibit T-cell activation and IL-2 production by regulation of gene transcription. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) also inhibit the formation of prostaglandins. Immunoglobulin G–rheumatoid factor (IgG-RF) complexes are detected in the blood of patients with rheumatoid arthritis.

TNF- α inhibitors are usually employed in RA after a patient has an inadequate response to traditional DMARDs. These agents may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one TNF- α inhibitor, a traditional DMARD may be added, or therapy with a non-TNF biologic agent or a different TNF- α inhibitor may be tried. TNF- α inhibitors should be used cautiously in those with heart failure, as they can cause and/or worsen pre-existing heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF- α inhibitors.

تطبق مثبطات الـ TNF- α في الـ RA عادةً بعد ما تكون استجابة المريض للأدوية السابقة غير كافية ..

إذا فشلت المعالجة الأحادية بمثبط واحد يمكن إضافة الـ DMARD السابقة ، أو معالجة بيولوجية مغايرة أو مثبط آخر للـ TNF- α .

ينبغي الحذر عند استعمال مثبطات الـ TNF- α عند **مرضى فشل القلب** ، لأنها تسبب للحالة المسبقة أو تسببها .

لوحظ اختطار زائد للمفوما وغيرها من السرطانات مع استعمال مثبطات الـ TNF- α .

Biologic DMARDs include the TNF- α inhibitors as well as the non-TNF biologic agents (*abatacept*, *rituximab*, *tocilizumab*). Like TNF- α inhibitors, non-TNF biologics are generally used in RA after a patient has an inadequate response to traditional DMARDs, and they may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one non-TNF biologic, a trial of another non-TNF biologic with or without *methotrexate* is warranted.

تتضمن الـ Biologic DMARDs الأدوية البيولوجية المثبطة للـ TNF- α والأدوية البيولوجية غير المثبطة للـ TNF- α (*abatacept* و *rituximab* و *tocilizumab*) . الأخيرة مثل السابقة تستعمل في الـ RA بعد عدم كفاية استجابة المريض للأدوية الأقدم ، ويمكن استعمالها وحيدة أو بالتوليف مع القديمة . إذا فشلت المعالجة الأحادية يكون تجريب دواء آخر من نفس هذا الصنف البيولوجي مع ميثوتريكسات أو بدونه مبرراً .

Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis. [Note: TNF- α inhibitors and non-TNF biologic agents should not be used together due to the risk of severe infections.] Reactivation of hepatitis B may occur with use of these agents. Live vaccinations should not be administered to patients taking any of the biologic DMARDs. Characteristics of the TNF- α inhibitors and non-TNF biologic therapies for the treatment of RA are outlined below. [Note: TNF- α inhibitors find use in a number of disorders, such as ulcerative colitis and Crohn's disease (see Chapter 42), psoriasis, and ankylosing spondylitis.]

يكون المرضى المتناولين الـ biologic DMARDs في خطر زائد للعدوى ، مثل السلّ و عدوى الفطريات الانتهازية والإنتان .

(ملاحظة : لا ينبغي استعمال الأدوية البيولوجية المثبطة وغير المثبطة للـ TNF- α معاً بسبب خطر عدوى شديدة) . قد يحدث استنشاق التهاب الكبد—ب مع هذه الأدوية .

لا ينبغي إعطاء اللقاحات الحية لمرضى يتناولون أيّ من هذه الأدوية البيولوجية ..

ملاحظة : مثبطات الـ TNF- α تستعمل في التهاب القولون التقرحي وداء كرون والصدفية و التهابُ الفقارِ المُقسِّط (التهابُ الفقارِ الرُّوماتويديّ) ankylosing spondylitis (rheumatoid spondylitis) .

A. **Adalimumab**. Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF- α and interferes with its activity by blocking interaction of TNF- α with cell surface receptors. Adalimumab is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, and increased risk of infections.

B. **Certolizumab pegol**. Certolizumab [ser-toe-LIZ-oo-mab] is a humanized antibody that neutralizes biological actions of TNF- α . It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. Its adverse effects are similar to other TNF- α inhibitors.

أ. **Adalimumab** : ضد وحيد النسيلة يرتبط بالـ TNF- α ويتداخل (يعترض) مع نشاطه عبر إحصاره تأثير الـ TNF- α مع مستقبلات سطح الخلية .

يعطى تحت الجلد أسبوعياً أو كل أسبوعين .

قد يسبب صداع و غثيان و نَدْرَة المُحَبَّبات و طفح و تفاعل في مقر الحقن و زيادة اختطار العدوى .

ب. **Certolizumab pegol** : ضد مؤنسَن يستعِدِل الأفعال البيولوجية للـ TNF- α .

يُؤَلَّف مع غليكول بولي إيثيلين (pegylated) و يعطى كل ٢ أسبوع تحت الجلد .

تأثيراته الضائرة مثل تلك لباقي مثبطات الـ TNF- α .

C. **Etanercept**. [ee-TAN-er-cept] is a genetically engineered fusion protein that binds to TNF- α , thereby blocking its interaction with cell surface TNF- α receptors. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in hindering the RA disease process, improving function, and achieving remission (Figure 40.19). *Etanercept* is given subcutaneously once weekly and is generally well tolerated.

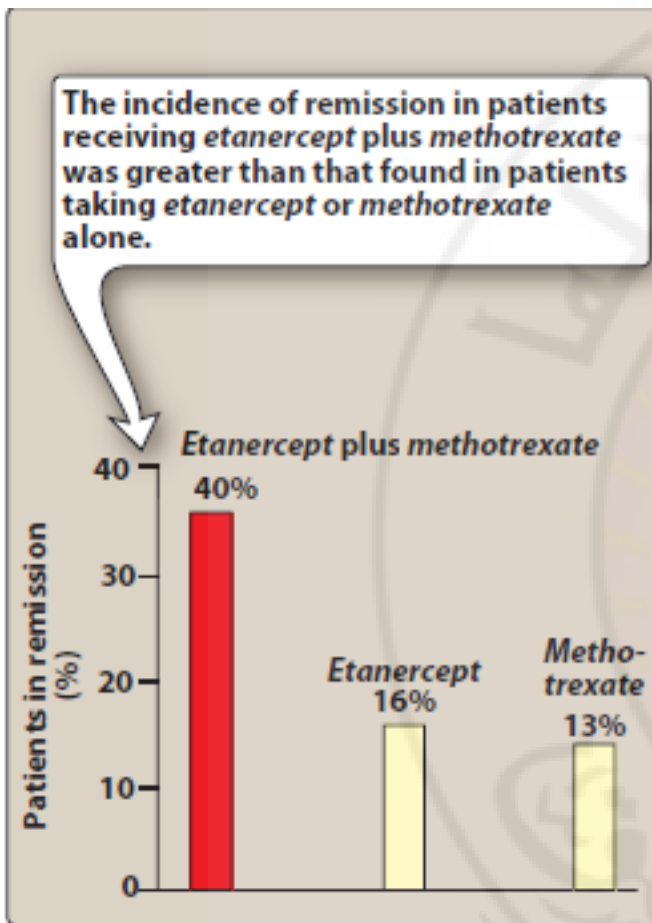


Figure 40.19

Incidence of remission from the symptoms of RA after 1 year of therapy.

ج. **Etanercept** : بروتين اندماجي مُهندَس وراثيًا .

توليفه مع الميثوتريكسات فعّال أكثر من أيّ منهما وحيداً في عرقلة عمليّة مرض الـ RA ، محسّناً الوظيفة ومنجزاً الهدأة (الشكل ٤٠ . ١٩) .

يعطى تحت الجلد مرة أسبوعياً وهو جيد التحمّل .

- D. **Golimumab**. [goe-LIM-ue-mab] neutralizes the biological activity of TNF- α by binding to it and blocking its interaction with cell surface receptors. It is administered subcutaneously once a month in combination with methotrexate. Golimumab may increase hepatic enzymes.
- E. **Infliximab**. [in-FLIX-i-mab] is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF- α and inhibits binding with its receptors. This agent is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies and reduced efficacy. *Infliximab* should be administered with *methotrexate*. *Infliximab* is administered as an IV infusion every 8 weeks. Infusion-related reactions, such as fever, chills, pruritus, and urticarial, may occur.

د. **Golimumab** :

يستعمل النشاط البيولوجي لـ TNF- α بارتباطه به وإحصار تأثيره بمستقبلاته على سطح الخلية .

يعطى تحت الجلد مرة شهرياً بالتوليف مع ميثوتريكسات . قد يزيد إنزيمات الكبد .

هـ. **Infliximab** :

ضد وحيد النسيلة خيمري مركب من جزئين بشري وفأري . يرتبط نوعياً بالـ TNF- α البشري ويثبط ارتباطه بمستقبلاته .

استعماله وحيداً يسبب تكون أضداد له تنقص نجاعته . ينبغي إعطاؤه مع ميثوتريكسات . يسرّب وردياً كل ٨ أسابيع .

تحدث تفاعلات متعلقة-بالتسريب مثل حمى وحمى مترافقة مع رعدة وحكة وشرى .

F. **Abatacept**. T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (macrophages or B cells) must interact with the receptor on the T cell and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. *Abatacept [a-BAT-ah-cept]* is a recombinant fusion protein and costimulation modulator that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation and reducing the inflammatory response. *Abatacept is administered as an IV infusion every 4 weeks.* Common adverse effects include infusion-related reactions, headache, upper respiratory infections, and nausea.

و **Abatacept** : تتطلب المفاوضات التائية تأثيرين لتنشيط :

(١) يجب أن تتأثر الخلية المقدّمة للمستضد مع المستقبل على الخلية التائية و

(٢) يجب أن يتأثر البروتين CD80/CD86 الموجود على الخلية المقدّمة للمستضد مع البروتين CD28 على الخلية التائية .

الـ **Abatacept** بروتين اندماجي مأشوب ومُحوّر للتنشيط المشترك ، يتنافس مع الـ **CD28** على الارتباط بالبروتين **CD80/CD86** ، فيمنع بالتالي التنشيط الكامل للخلية التائية وينقص الاستجابة الالتهابية .

يعطى تسريباً وريدياً كل ٤ أسابيع .

تتضمن التأثيرات الضائرة تفاعلات متعلقة-بالتسريب وصداع وعداوى تنفسية علوية وغثيان

G. **Rituximab**. In RA, B lymphocytes can perpetuate the inflammatory process in the synovium by 1) activating T lymphocytes, 2) producing autoantibodies and rheumatoid factor, and 3) producing proinflammatory cytokines, such as TNF- α and IL-1. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Administration of rituximab results in B-cell depletion. Rituximab is administered as an intravenous infusion every 16 to 24 weeks. To reduce the severity of infusion reactions, methylprednisolone is administered 30 minutes prior to each infusion. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

ز. الـ **Rituximab** :

في الـ RA ، تُديم اللِّمفاويات البائية العملية الالتهابية في الغِشاء الزَّلِيلِيّ عبرَ إنتاج أضداد ذاتية والعاملُ الرُّوماتويديّ

الـ **Rituximab** ضدَّ وحيد النسيلة خيمري مهندَس وراثيّاً مُوجَّه ضدَّ المستضد CD20
الموجود على سطح اللِّمفاويات البائية الطبيعية والخبيثة . يستنفذ الخلايا البائية .

يسرَّب ويريداً كل ١٦-٢٤ أسبوع .

يعطى methylprednisolone قبيل التسريب بـ ٣٠ د لإنقاص شدة تفاعلات التسريب (شرى ونقص ضغط ووذمة وعائية تحدث خلال التسريب الأول) .

TABLE 35.1 Disease-Modifying Antirheumatic Drugs (DMARDs)

Classification	Mechanism/Target	Generic Name	Consequences
Conventional	Antimetabolite	Methotrexate	Depletes T and B cells and macrophages
		Leflunomide	
	APC directed	Sulfasalazine	Prevents APC maturation; inhibits proliferation of T and B cells
		Hydroxychloroquine	Inhibits APC function; inhibits proliferation of T and B cells
Biological	TNF- α	Chloroquine	Binds TNF- α , preventing it from activating its receptor; protects bone from destruction
		Infliximab	
		Adalimumab	
		Golimumab	
		Certolizumab pegol	
	APC directed	Etanercept	Binds CD80 on APC; prevents activation of T cells; antiinflammatory
		Abatacept	
Targeted synthetic	B cells	Rituximab	Binds to CD20 on B cells, preventing their proliferation and differentiation
	IL-6 receptor (IL-6R)	Tocilizumab	Binds IL-6R, preventing activation of macrophages and osteoclasts
	IL-1 (IL-1R)	Anakinra	Antagonist at IL-1R, preventing immune activation
	Janus kinase (JAK)	Tofacitinib	Inhibits JAK blocking JAK-mediated intracellular signaling

H. **Tocilizumab** and **sarilumab**

Tocilizumab [toe-si-LIZ-ue-mab] and sarilumab [sar-IL-ue-mab] are recombinant monoclonal antibodies that bind to IL-6 receptors and inhibit activity of the proinflammatory cytokine IL-6. Both tocilizumab and sarilumab are administered as a subcutaneous injection every 2 weeks. Tocilizumab may also be administered as an intravenous infusion every 4 weeks. Adverse reactions to tocilizumab include elevated liver function tests, hyperlipidemia, neutropenia, hypertension, and infusion-related and injection site reactions. Adverse reactions for sarilumab are similar.

ح. الـ **Tocilizumab** والـ **sarilumab** : أضداد وحيدة نسيطة ترتبط بمستقبلات الـ IL-6 وتنشط نشاط السيتوكين IL-6 المؤيد للالتهاب.

يعطيان تحت الجلد كل ٢ أسبوع .

يسبب التوسيليزوماب زيادة في اختبارات وظيفة الكبد وفرط شحوم الدم وقلة العدلات وفرط الضغط وتفاعلات متعلقة بمقر الحقن .. التأثيرات الضائرة للساريلوماب مشابهة .

VII. OTHER DRUGS FOR RHEUMATOID ARTHRITIS

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane. *Tofacitinib* [toe-fa-SYE-ti-nib] is a synthetic small molecule that is an oral inhibitor of Janus kinases. It is indicated for the treatment of moderate-to-severe established RA in patients who have had an inadequate response or intolerance to *methotrexate*. *Metabolism of tofacitinib* is mediated primarily by CYP3A4, and dosage adjustments may be required if the drug is taken with potent inhibitors or inducers of this isoenzyme.

الأدوية الإضافية في التهاب المفاصل الروماتويدي :

الـ Janus kinases إنزيمات داخل الخلية تُحوّر/تنظم نشاط الخلية المناعية استجابةً لارتباط وسائط التهابية بالغشاء الخلوي .

التوفاسيتينيب **Tofacitinib** جزيء صناعي صغير مثبط للـ Janus kinases يعطى بالفم . يوصى به لمعالجة الـ RA المتوسطة—الشديدة لغير المستجيبين للميثوتريكسات .

يستقلب بالـ CYP3A4 ، وقد يتطلب ضبط مقدار الجرعة إذا أُعطي مع مثبطات قوية أو محرضات هذا النَظير الإنزيمي .

VIII. DRUGS USED FOR THE TREATMENT OF GOUT.

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 40.20).

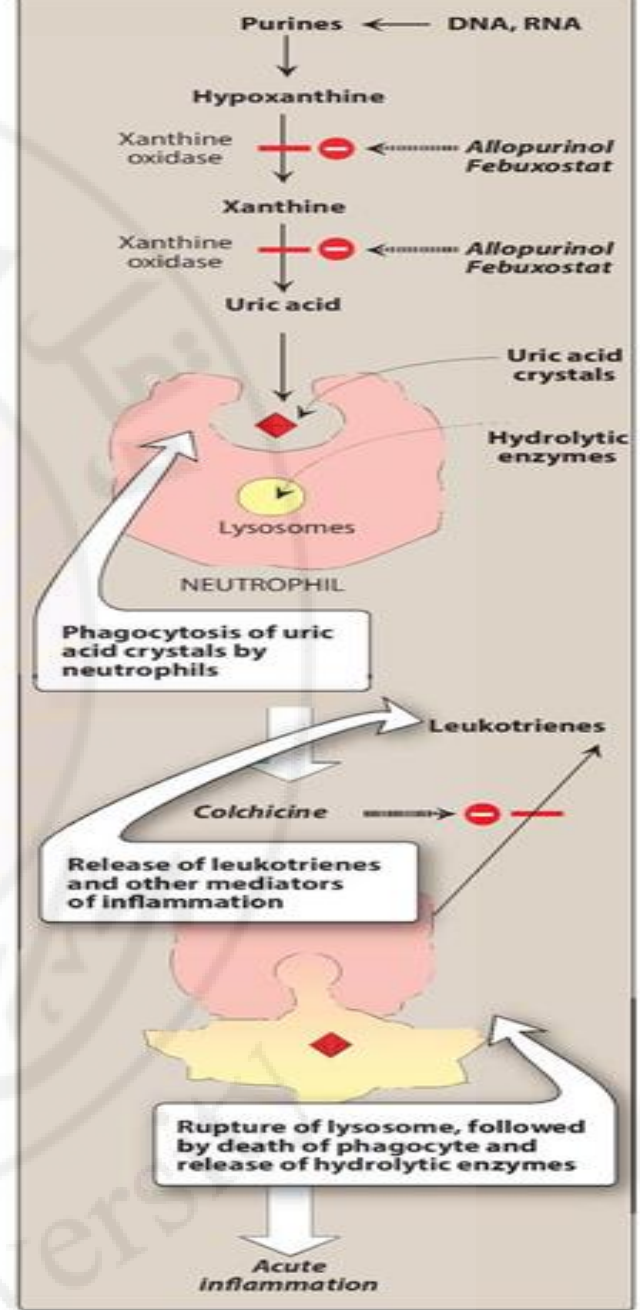


Figure 40.20

Role of uric acid in the inflammation of gout.

الأدوية المستعملة لمعالجة التقرس : النقرس

اضطراب استقلابي مميز بمستويات كبيرة من حامض اليوريك في الدم (فرط يوريك الدم). يؤدي فرط يوريك الدم إلى ترسب يورات الصوديوم في النسيج، خصوصاً المفاصل والكلية. يُبدء ترسب بلورات الصوديوم عملية التهابية تكتنف ارتشاح المحببات التي تبلع بلورات الصوديوم (الشكل ٤٠.٢٠).

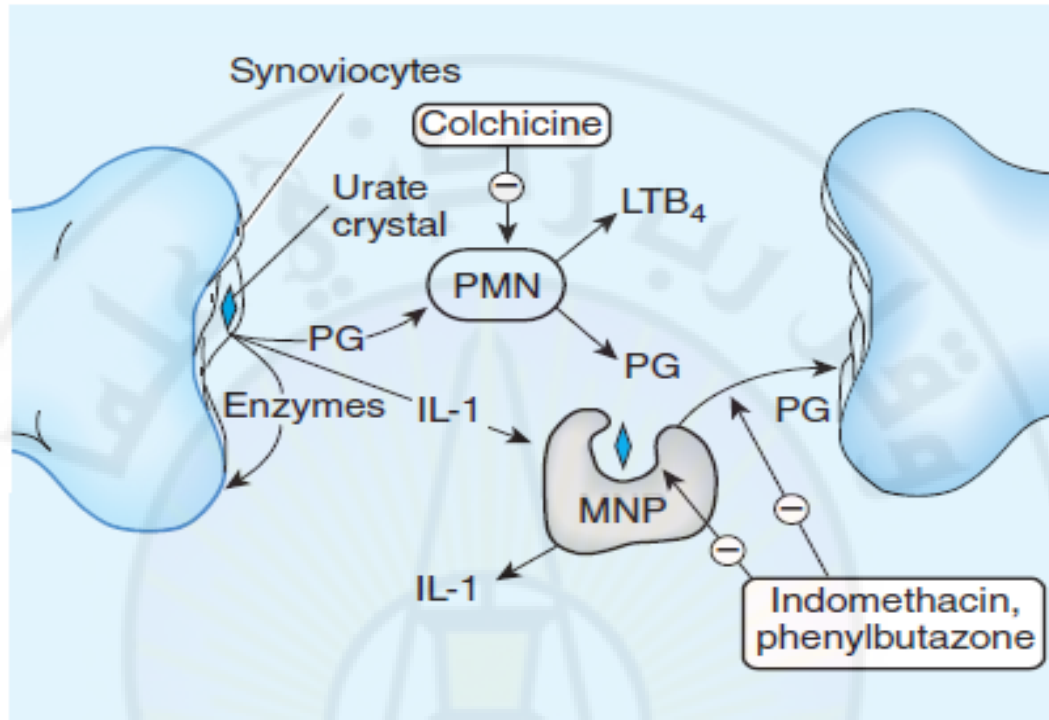


FIGURE 36-5 Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG, prostaglandin; IL-1, interleukin-1; LTB₄, leukotriene B₄.

الشكل ٣٦-٥ : الأحداث الفيزيولوجية المرضية في مفصل نقرسي . الخلايا الزليلية تبتلع بلورات اليورات ثم تفرز وسائط التهابية تجذب وتنشط الكريات البيض المتعددة الشكل النووي PMN والخلايا البالعة الوحيدة النواة (البلاعم) MNP . الأدوية الفعالة في النقرس تثبط بلعمة البلورات والكريات البيض المتعددة النوى وإطلاق البلاعم للوسائط الالتهابية ..

Acute flares of gout usually present as pain, swelling, **tenderness**, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

تتجلى الهجمات الحادة للنقرس بألم وتورم ووهن/وجع عند المسّ ، واحمرار في المفاصل المصابة (مثل إصبع القدم الكبير والركب والكواحل (رسغ القدم) والأرساغ / المِعَصَم أو المرافق/الأكواع) .

سبب فرط يوريك الدم في النقرس خلل توازن بين إنتاج زائد لحمض اليوريك و/أو عدم قابلية طرح حامض اليوريك كلياً .

تكتنّف معظم الاستراتيجيّات العلاجية للنقرس تتقيص مستوى حامض اليوريك أقل من نقطة التشبّع (٦ ميلي غرام/ديسي لتر) ، فيمنع ترسب بلورات اليورات . يمكن إنجاز هذا باعتراض تصنيع حامض اليوريك أو بزيادة طرحه .

A. Treatment of acute gout. Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, and *colchicine* are effective agents for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or **tophi** (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

أ. معالجة النقرس الحاد : ينجم النقرس الحاد عن استهلاك زائد للكحول والنظام الغذائي الغني بالبورينات ومرض الكلية .. الـ NSAIDs (الدواء المُختار **Indomethacin**) والقشرانيات الستيرويدية والكولشيسين فعّالة في التهاب المفاصل النقرسي الحاد . إعطاء الكورتيكوستيرويدات داخل-المفصل (عند إصابة مفصل أو اثنين) ملائم للنقرس الحاد ، أو كورتيكوستيرويدات مجموعية عند إصابة مفاصل أكثر . يكون المرضى مرشحين للمعالجة الوقائية الخافضة-اليورات إن كان لديهم أكثر من هجمتين في العام أو صار لديهم مرض كلية مزمن وحصيات في الكلية أو **ثُوف** (ترسب بلورات يورات في المفاصل والعظام والغضاريف وغيرها من بنى الجسم) .

B. Treatment of chronic gout. Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, *NSAIDs*, or *corticosteroids*) should be initiated with urate-lowering therapy and continued for at least 6 months.]

ب. معالجة النقرس المزمن : غاية المعالجة الخافضة-اليورات في النقرس المزمن تنقيص تواتر الهجمات ومضاعفات النقرس .

تتضمن استراتيجيات المعالجة استعمال مثبطات أكسيداز الزانثين لإنقاص تصنيع حامض اليوريك أو استعمال ادوية طارحة لليوريك لزيادة طرحه .

مثبطات أكسيداز الزانثين (**allopurinol** و **febuxostat**) أدوية خافضة-اليورات خط أول . قد تستعمل طارحات اليورات (**probenecid**) للمرضى غير المتحملين مثبطات أكسيداز الزانثين أو فشل الخط الأول في إنجاز استجابة كافية . { ملاحظة : البدء بالمعالجة الخافضة-اليورات يؤهب لهجمة نقرس حادة بسبب التبدلات السريعة في تراكيز يورات المصل .

ينبغي بدء أدوية الوقاية من هجمة نقرس حادة (جرعة كولشيسين صغيرة ، NSAIDs ، أو كورتيكوستيرويدات) مع معالجة خافضة-اليورات واستمرارها ٦ شهور على الأقل } .

C. Colchicine. *Colchicine [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.*

1. Mechanism of action: *Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint. Furthermore, colchicine blocks cell division by binding to mitotic spindles.*

2. Therapeutic uses: *The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: Colchicine must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons. Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.*

ج. الـ **Colchicine** : قلواني نباتي مستعمل لمعالجة هجمات النقرس الحاد . غير طارح لليوريك ولا مسكّن ، رغم تفريجه الألم في هجمات النقرس الحادة .

١. آليّة الفعل : يرتبط بالتوبولين ، البروتين النببي المجهرى ، مسبباً نزع بلمرته . هذا يُخلّ بوظائف خلويّة ، مثل حركة العدلات ، فينقص هجرتها إلى المفصل الملتهب . إضافةً أنّه يحصر انقسام الخلية بارتباطه بمغازل الانقسام الفتيلي (الخيطي) .

٢. الاستعمالات العلاجية : فعاليته المضادة للالتهاب نوعية للنقرس ، يفرج الألم عادةً أثناء ١٢ ساعة . (ملاحظة : يجب إعطاؤه خلال ٣٦ ساعة من بدء الهجمة ليكون فعال) . حلت الـ NSAIDs محله في معالجة الهجمات النقرسية الحادة للسلامة . يستعمل الكولشيسين أيضاً للوقاية لمنع هجمات النقرس الحادة عند المرضى البادئين معالجة خافضة-لليورات .

3. Pharmacokinetics: Colchicine is administered orally and is rapidly absorbed from the GI tract. Colchicine is metabolized by hepatic CYP450 3A4 and other tissues. It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life. A portion of the drug is excreted unchanged in the urine.

4. Adverse effects: Colchicine may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 40.21). Chronic administration may lead to myopathy, **neutropenia, aplastic anemia**, and alopecia. The drug **should not be used in pregnancy** and should be used with caution in patients with hepatic, renal, or cardiovascular disease. Adequate **drug holiday** must be given between dosages to avoid cumulative toxicity. Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, clarithromycin and itraconazole) or P-gp inhibitors (for example, amiodarone and verapamil) and those with severe renal impairment.



Figure 40.21

Some adverse effects of *colchicine*.
GI = gastrointestinal.

D. Allopurinol. Allopurinol [al-oh-PURE-i-nole], a **xanthine oxidase inhibitor**, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (**Figure 40.20**).

1. Therapeutic uses: Allopurinol is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

د. الـ **Allopurinol** : مثبط لأوكسيداز الزانثين ، مضاهئ للبورين . يُنقص إنتاج حامض اليوريك بتنشيطه تنافسياً الخطوتين الأخيرتين في التصنيع الحيوي لحامض اليوريك المُخَفَّز بأوكسيداز الزانثين (الشكل ٤٠ . ٢٠) .

١ . **الاستعمالات العلاجية :** معالجة خافضة-اليورات فعّالة في معالجة التقرس وفرط يوريك الدم الثانوي لحالات إضافية ، مثل تلك المترافقة مع خباثات مُعَيَّنة (الخباثات التي ينتج فيها كميات ضخمة من البورينات ، خصوصاً بعد المعالجة الكيميائية) .

2. Pharmacokinetics: *Allopurinol is completely absorbed after oral administration.* The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing. The drug and its active metabolite are excreted in the urine. Dose adjustment is needed if the estimated glomerular filtration rate is less than 30 mL/min/1.73 m².

3. Adverse effects: *Allopurinol is well tolerated by most patients.* Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, *colchicine*, NSAIDs, or corticosteroids can be administered concurrently.

٢. الحرائك الدوائية : يمتص من الهضم . مستقلبه الأولي الألوزانثين (أكسي بورينول) أيضاً مثبت لأكسيداز الزانثين ذو عمر نصف ١٥ إلى ١٨ ساعة . لهذا ، يدوم تثبيط فعّال لأكسيداز الزانثين بجرعة-يومية . يطرح الدواء ومستقلبه الفعّال في البول . ثمة حاجة لضبط الجرعة إذا كان الترشيح الكبيبي أقل من ٣٠ ميلي لتر/دقيقة/١.٧٣ متر مربع .

التأثيرات الضائرة : تفاعلات فرط تحسس ، خصوصاً طفح الجلد . يزداد هذا الاختطار عند منقوصي وظيفة الكلية . يمكن إعطاء الكولشيسين والـ NSAIDs أو الكورتيكوستيرويدات معه لأنّ هجمات النقرس الحادة قد تحدث أكثر أثناء الشهور الأولى للمعالجة به .

E. Febuxostat. is an oral xanthine oxidase inhibitor structurally unrelated to allopurinol. Febuxostat is rapidly absorbed after oral administration with the time to reach peak concentration (t_{max}) being of approximately 1 hour. The drug is highly bound to albumin in blood (~99%) and appears to have a low-to-medium apparent volume of distribution of approximately 0.7 l/kg. Febuxostat is indicated for the long-term management of hyperuricemia in patients with gout at a dose of 10 to 120 mg once daily. Febuxostat is well tolerated. Its adverse effect profile is similar to that of allopurinol, although the risk for rash and hypersensitivity reactions may be reduced. Febuxostat does not have the same degree of renal elimination as allopurinol and thus requires less adjustment in those with reduced renal function. The most common adverse events include abnormal liver function test results, abdominal pain, diarrhea, headache, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms. Febuxostat should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to allopurinol.

Febuxostat. [feb-UX-oh-stat] : **مثبط لأوكسيداز الزانثين** فموي غير متعلق بنيوياً بالألوبيورينول . يمتص سريعاً ($t_{max} = 1h$) ، يرتبط جداً بالبروتين الدم ٩٩% ($V_d = 0.7 \text{ l/kg}$) . **للمعالجة طويلة الأمد لفرط حمض يوريك الدم** لمرضى النقرس بجرعة ١٠ إلى ١٢٠ ملغ يومياً . تأثيراته الضائرة مثل الألوبيورينول ربما مع نقص الطفح وتفاعلات فرط التحسس . **أقل حاجة لضبط الجرعة لمرضى الكلية** . يسبب ألم بطن وإسهال وصداع وشذوذ اختبارات الكبد .. ينبغي الحذر عند استعماله لمرضى القلب والسكتة لأنه أكثر خطراً هنا من الألوبيورينول .

F. Probenecid. *Probenecid [proe-BEN-a-sid] is an oral uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate–anion exchanger in the proximal tubule. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. Probenecid should be avoided if the creatinine clearance is less than 50 mL/min. Adverse effects include nausea, vomiting, and dermatologic reactions, and, rarely, anemia or anaphylactic reactions. It is used at a dose of 0.25 to 0.5 g twice daily. However, intermittent colchicine therapy is indicated to avoid acute precipitation of gout.*

الـ **Probenecid** : مُحَقِّزُ بِيْلَةِ حَمَضِ اليوريك فموي . حامض عضوي ضعيف يعزز
التصفية الكلوية لحمض اليوريك بتنشيط مبادل أنيون—اليورات في النبيب القريب .
بالجرعات العلاجية يحصر عودة امتصاص حمض اليوريك من الأنبوب القريب . ينبغي
تجنبه إذا كانت تصفية الكرياتينين أقل من ٥٠ ميلي لتر/الدقيقة . تتضمن تأثيراته الضائرة
غثيان وقياء وتفاعلات جلدية ، ونادراً فقر دم أو تفاعلات تأقية . يستعمل بجرعة ٠,٢٥ ،
إلى ٠,٥ غرام مرتين يومياً . عال أية حال ، يوصى بمعالجة متقطعة بالكولشيسين لتجنب
التعجيل الحاد للنقرس .

G. Pegloticase. Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with pegloticase, and patients should be premedicated with antihistamines and corticosteroids. F

الـ **Pegloticase** : شكل مأشوب من إنزيم أكسيداز اليورات أو اليوريكاز . يعمل بتحويل حمض اليوريك إلى الأنتوين ، المستقلب الذوّاب في الماء غير السام الذي يطرح بالكلية . يوصى به لمرضى النقرس بعد فشل المعالجة المعيارية مثل مثبطات أكسيداز الزانثين . يعطى تسريب IV كل أسبوعين . قد تحدث تفاعلات متعلقة—بالتسريب وتاق فينبغي معالجة المرضى مسبقاً بمضادات الهيستامين والكورتيكوستيرويدات .

للاطلاع

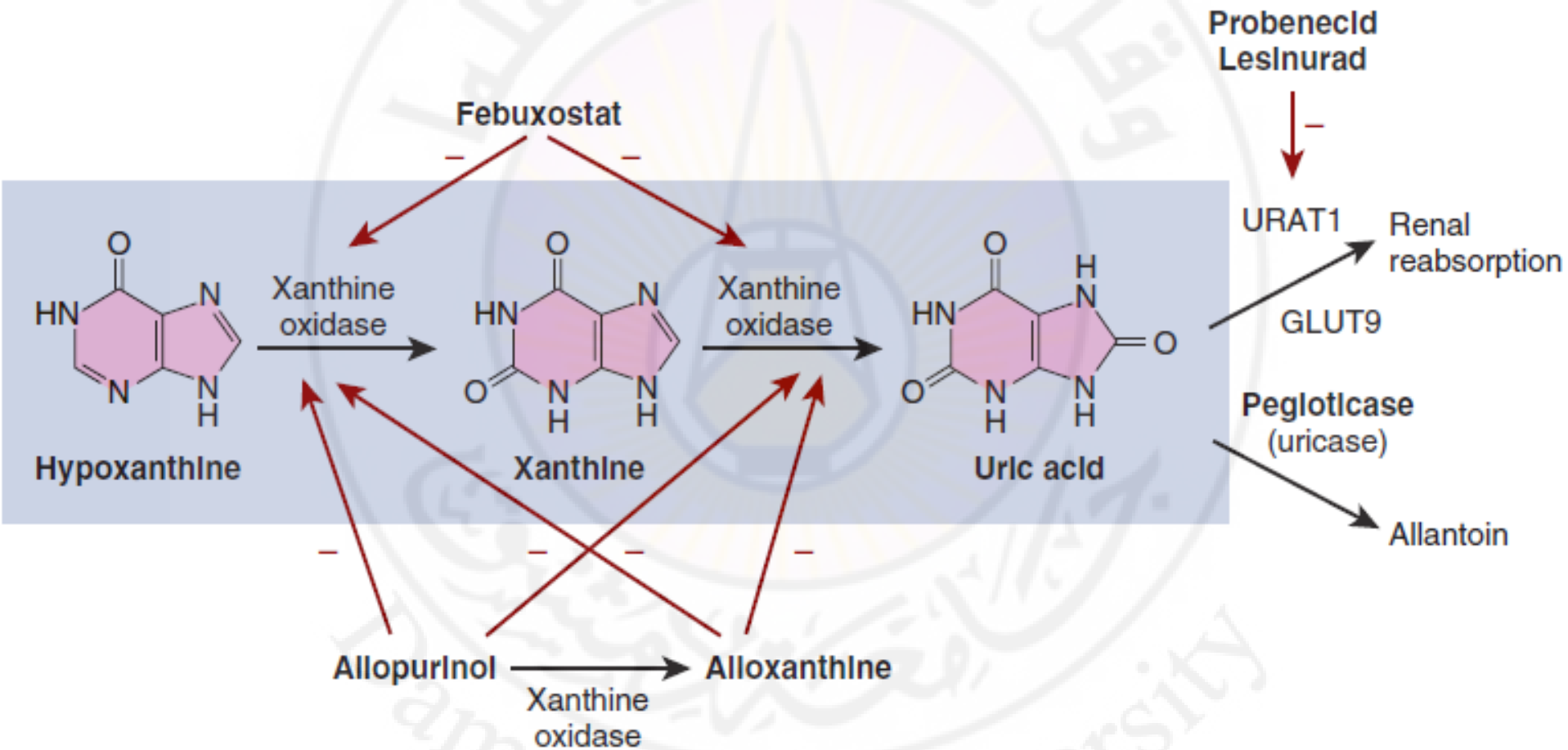


FIG. 32.1 Uric Acid Synthesis and Metabolism and the Sites of Action of Drugs Used for the Prophylactic Treatment of Gout. URAT1 and GLUT9 are the primary transporters in the renal proximal

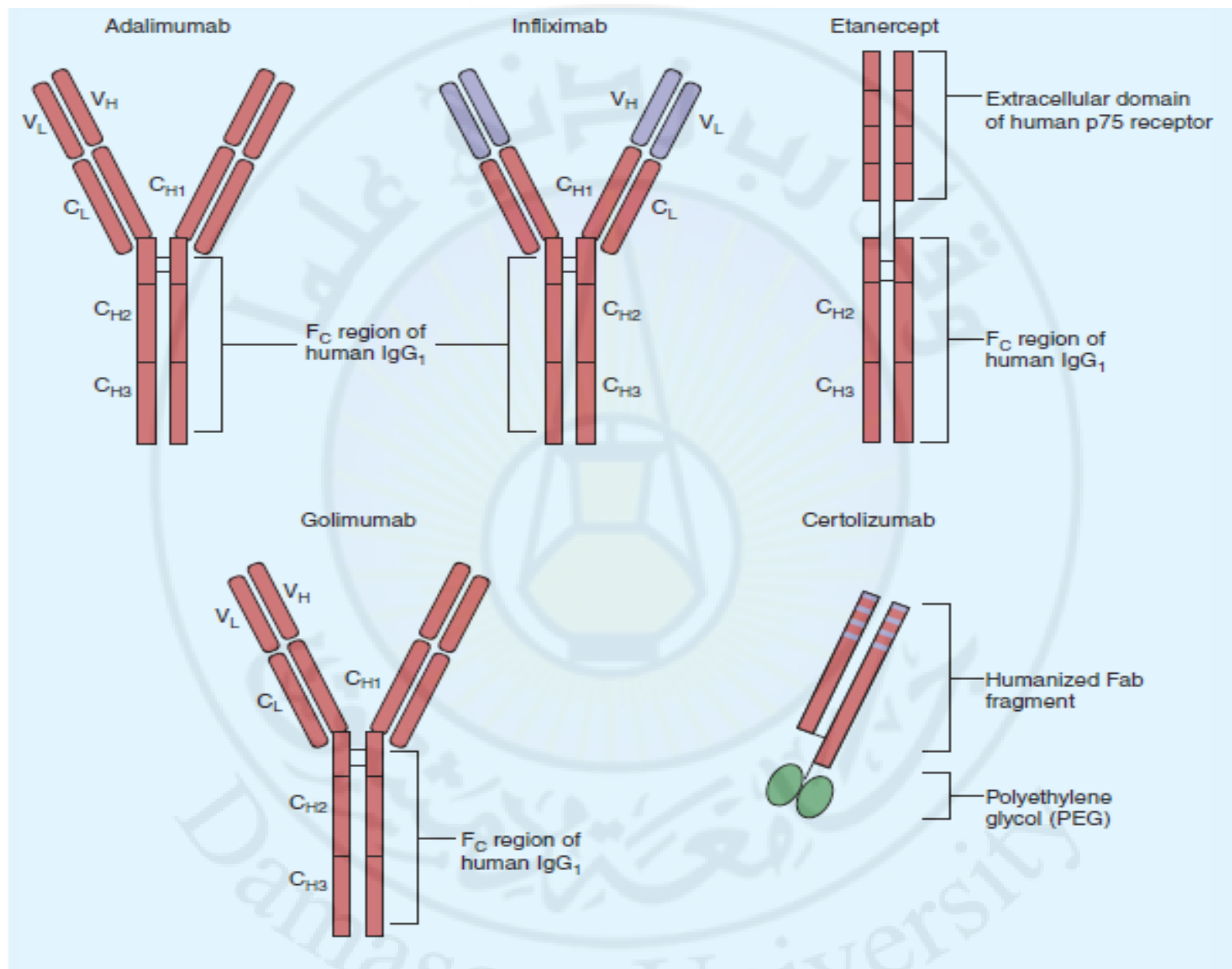


FIGURE 36–4 Structures of TNF- α antagonists used in rheumatoid arthritis. C_H, constant heavy chain; C_L, constant light chain; F_C, complex immunoglobulin region; V_H, variable heavy chain; V_L, variable light chain. Red regions, human derived; blue regions, mouse derived; green regions, polyethylene glycol (PEG).

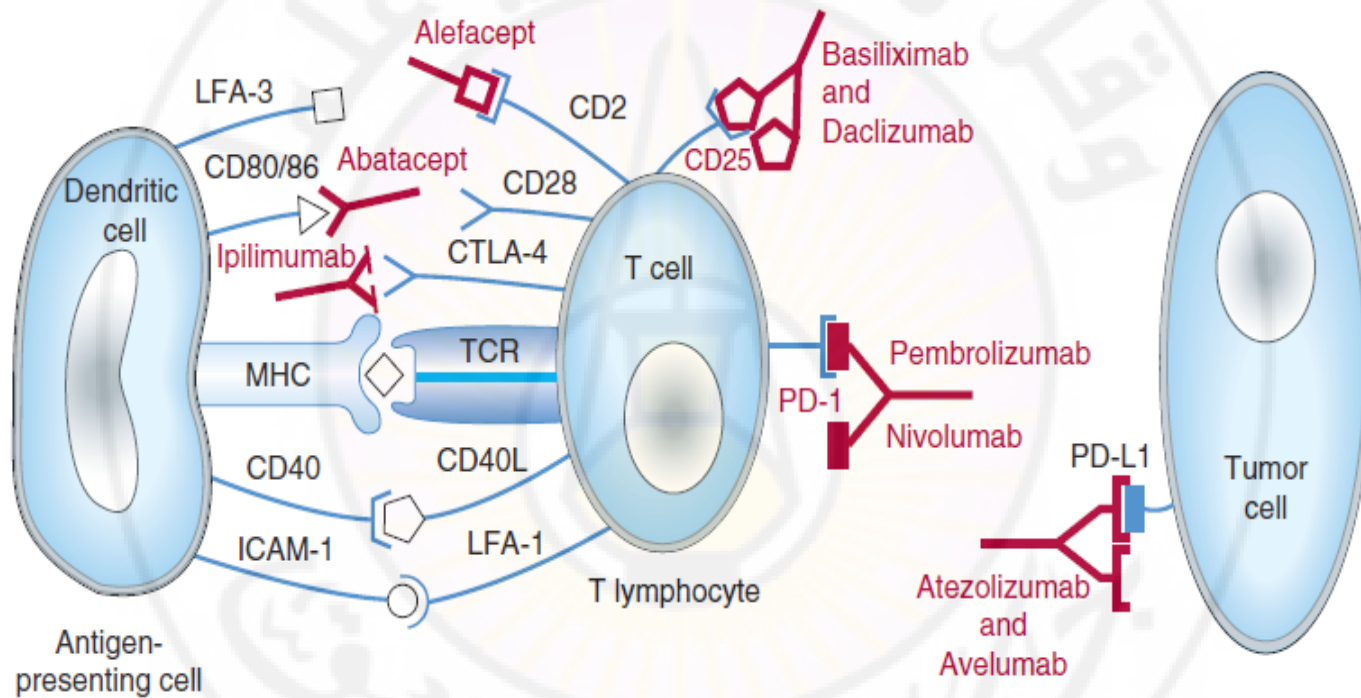


FIGURE 55-7 Actions of some monoclonal antibodies (shown in red). CTLA-4-IgF_c fusion protein (CTLA-4-Ig, abatacept) binds to CD80/86 on DC and inhibits T-cell costimulation. Alefacept inhibits activation of T cells by blocking the interaction of LFA-3 and CD2. Basiliximab and daclizumab block IL-2 from binding to the IL-2 receptor (CD25) on T cells, preventing activation; CD25 is also important for the survival of T regulatory cells. T-cell activation can be maintained or restored if CTLA-4 interaction with CD80/86 is blocked using an anti-CTLA-4 antibody (ipilimumab); ipilimumab inhibits CTLA-4 signaling and prolongs activation. Pembrolizumab and nivolumab bind to PD-1, while atezolizumab binds to PD-L1. Each of these three Mabs inhibits the negative signal delivery by PD-1, also prolonging T cell activation.

Hemoglobin concentrations must be greater than 9 g/dL to start *tofacitinib* and must be monitored during therapy due to the risk for anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. *Tofacitinib* treatment may also increase the risk for new primary malignancy and opportunistic infections. Due to long-term safety concerns, *tofacitinib* is usually reserved for patients who have inadequate response or intolerance to other agents. [Note: *Anakinra*, *azathioprine*, *cyclosporine*, *gold*, and *minocycline* are other agents used infrequently in the treatment of RA due to their adverse effect profile or the availability of other agents with more proven efficacy.] f

يجب أن تكون تراكيز الخضاب أكثر من (9 g/dL) لبدء إعطاء هذا الدواء وأن يراقب أثناء المعالجة بسبب اختطار فقر الدم . بطريقة مماثلة ، ينبغي تفقد اللمفاويات والعدلات قبيل بدء المعالجة ومراقبتها أثناء المعالجة .

قد تزيد المعالجة بالتوفاسيتينيب أيضاً اختطار الخبائث الأولية الجديدة والعداوى الانتهازية . لهذا يدّخر عادةً للمرضى غير المستجيبين أو غير المتحملين لباقي الأدوية .

(ملاحظة : الـ *Anakinra* والـ *azathioprine* والـ *cyclosporine* والـ *الذهب* والـ *minocycline* أدوية إضافية في معالجة الـ RA ، لكنها نادرة الاستعمال بسبب تأثيراتها الضائرة أو توافر أدوية أكثر نجاعة) . f

VIII. DRUGS USED FOR THE TREATMENT OF GOUT.

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 40.20).

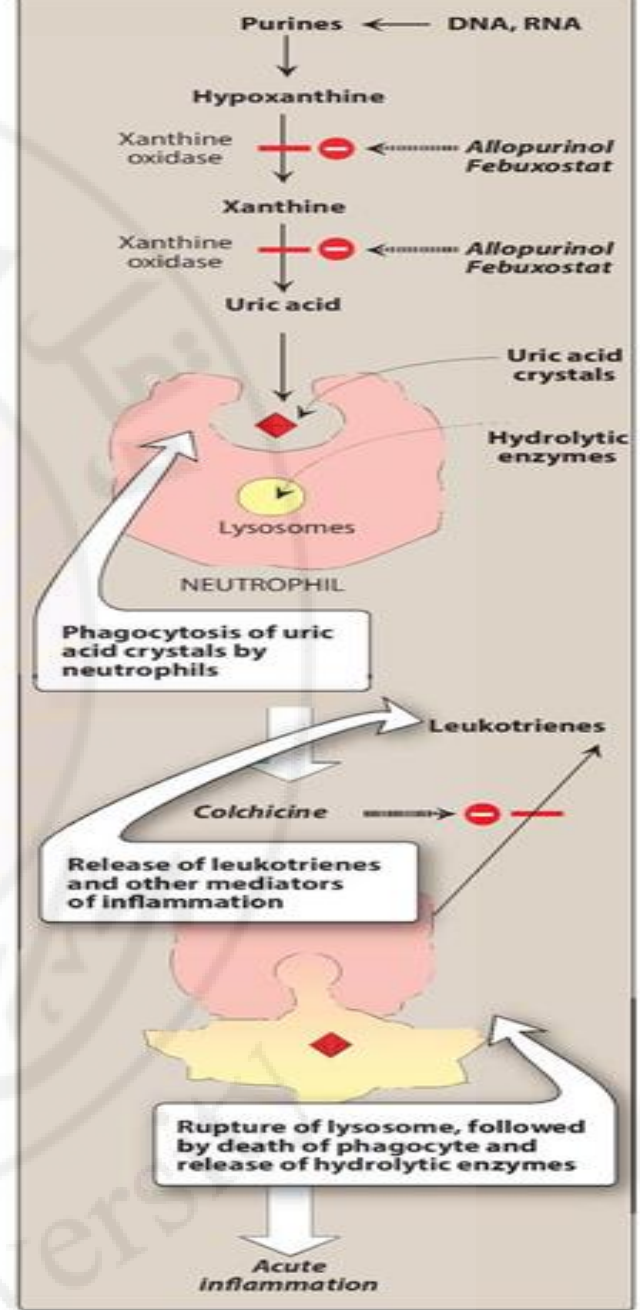


Figure 40.20

Role of uric acid in the inflammation of gout.

الأدوية المستعملة لمعالجة التقرس : النقرس

اضطراب استقلابي مميز بمستويات كبيرة من حامض اليوريك في الدم (فرط يوريك الدم). يؤدي فرط يوريك الدم إلى ترسب يورات الصوديوم في النسيج، خصوصاً المفاصل والكلية. يُبدء ترسب بلورات الصوديوم عملية التهابية تكتنف ارتشاح المحببات التي تبلع بلورات الصوديوم (الشكل ٤٠.٢٠).

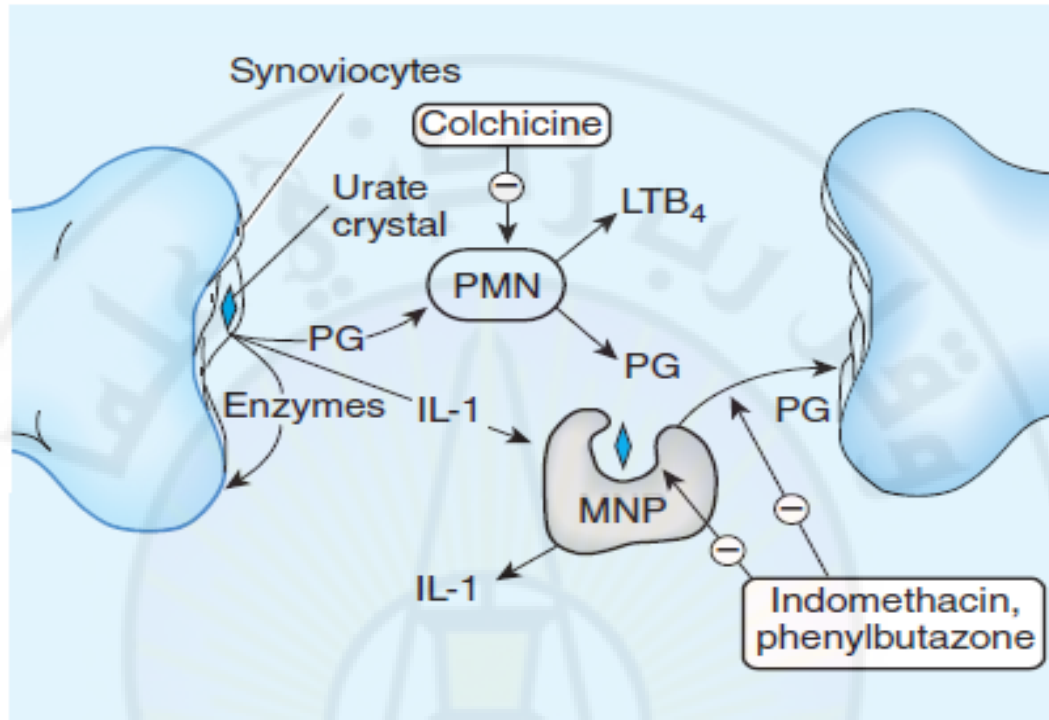


FIGURE 36-5 Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG, prostaglandin; IL-1, interleukin-1; LTB₄, leukotriene B₄.

الشكل ٣٦-٥ : الأحداث الفيزيولوجية المرضية في مفصل نقرسي . الخلايا الزليلية تبتلع بلورات اليورات ثم تفرز وسائط التهابية تجذب وتنشط الكريات البيض المتعددة الشكل النووي PMN والخلايا البالعة الوحيدة النواة (البلاعم) MNP . الأدوية الفعالة في النقرس تثبط بلعمة البلورات والكريات البيض المتعددة النوى وإطلاق البلاعم للوسائط الالتهابية ..

Acute flares of gout usually present as pain, swelling, **tenderness**, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

تتجلى الهجمات الحادة للنقرس بألم وتورم ووهن/وجع عند المسّ ، واحمرار في المفاصل المصابة (مثل إصبع القدم الكبير والركب والكواحل (رسغ القدم) والأرساغ / المِعَصَم أو المرافق/الأكواع) .

سبب فرط يوريك الدم في النقرس خلل توازن بين إنتاج زائد لحمض اليوريك و/أو عدم قابلية طرح حامض اليوريك كلياً .

تكتنّف معظم الاستراتيجيّات العلاجية للنقرس تتقيص مستوى حامض اليوريك أقل من نقطة التشبّع (٦ ميلي غرام/ديسي لتر) ، فيمنع ترسب بلورات اليورات . يمكن إنجاز هذا باعتراض تصنيع حامض اليوريك أو بزيادة طرحه .

A. Treatment of acute gout. Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. NSAIDs, corticosteroids, and *colchicine* are effective agents for the management of acute gouty arthritis. *Indomethacin* is considered the classic NSAID of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or **tophi** (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

أ. معالجة النقرس الحاد : ينجم النقرس الحاد عن استهلاك زائد للكحول والنظام الغذائي الغني بالبورينات ومرض الكلية .. الـ NSAIDs (الدواء المُختار **Indomethacin**) والقشرانيات الستيرويدية والكولشيسين فعّالة في التهاب المفاصل النقرسي الحاد . إعطاء الكورتيكوستيرويدات داخل-المفصل (عند إصابة مفصل أو اثنين) ملائم للنقرس الحاد ، أو كورتيكوستيرويدات مجموعية عند إصابة مفاصل أكثر . يكون المرضى مرشحين للمعالجة الوقائية الخافضة-اليورات إن كان لديهم أكثر من هجمتين في العام أو صار لديهم مرض كلية مزمن وحصيات في الكلية أو **ثُوف** (ترسب بلورات يورات في المفاصل والعظام والغضاريف وغيرها من بنى الجسم) .

B. Treatment of chronic gout. Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout. Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion. Xanthine oxidase inhibitors (*allopurinol*, *febuxostat*) are first-line urate-lowering agents. Uricosuric agents (*probenecid*) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents. [Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose *colchicine*, *NSAIDs*, or *corticosteroids*) should be initiated with urate-lowering therapy and continued for at least 6 months.]

ب. معالجة النقرس المزمن : غاية المعالجة الخافضة-اليورات في النقرس المزمن تنقيص تواتر الهجمات ومضاعفات النقرس .

تتضمن استراتيجيات المعالجة استعمال مثبطات أكسيداز الزانثين لإنقاص تصنيع حامض اليوريك أو استعمال أدوية طارحة لليوريك لزيادة طرحه .

مثبطات أكسيداز الزانثين (**allopurinol** و **febuxostat**) أدوية خافضة-اليورات خط أول . قد تستعمل طارحات اليورات (**probenecid**) للمرضى غير المتحملين مثبطات أكسيداز الزانثين أو فشل الخط الأول في إنجاز استجابة كافية . { ملاحظة : البدء بالمعالجة الخافضة-اليورات يؤهب لهجمة نقرس حادة بسبب التبدلات السريعة في تراكيز يورات المصل .

ينبغي بدء أدوية الوقاية من هجمة نقرس حادة (جرعة كولشيسين صغيرة ، NSAIDs ، أو كورتيكوستيرويدات) مع معالجة خافضة-اليورات واستمرارها ٦ شهور على الأقل } .

C. Colchicine. *Colchicine [KOL-chi-seen], a plant alkaloid, is used for the treatment of acute gouty attacks. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.*

1. Mechanism of action: *Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint. Furthermore, colchicine blocks cell division by binding to mitotic spindles.*

2. Therapeutic uses: *The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: Colchicine must be administered within 36 hours of onset of attack to be effective.] NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons. Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.*

ج. الـ **Colchicine** : قلواني نباتي مستعمل لمعالجة هجمات النقرس الحاد . غير طارح لليوريك ولا مسكّن ، رغم تفريجه الألم في هجمات النقرس الحادة .

١. آليّة الفعل : يرتبط بالتوبولين ، البروتين النببي المجهرى ، مسبباً نزع بلمرته . هذا يُخلّ بوظائف خلويّة ، مثل حركة العدلات ، فينقص هجرتها إلى المفصل الملتهب . إضافةً أنّه يحصر انقسام الخلية بارتباطه بمغازل الانقسام الفتيلي (الخيطي) .

٢. الاستعمالات العلاجية : فعاليته المضادة للالتهاب نوعية للنقرس ، يفرج الألم عادةً أثناء ١٢ ساعة . (ملاحظة : يجب إعطاؤه خلال ٣٦ ساعة من بدء الهجمة ليكون فعال) . حلت الـ NSAIDs محله في معالجة الهجمات النقرسية الحادة للسلامة . يستعمل الكولشيسين أيضاً للوقاية لمنع هجمات النقرس الحادة عند المرضى البادئين معالجة خافضة-اليورات .

3. Pharmacokinetics: Colchicine is administered orally and is rapidly absorbed from the GI tract. Colchicine is metabolized by hepatic CYP450 3A4 and other tissues. It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life. A portion of the drug is excreted unchanged in the urine.

4. Adverse effects: Colchicine may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 40.21). Chronic administration may lead to myopathy, **neutropenia, aplastic anemia**, and alopecia. The drug **should not be used in pregnancy** and should be used with caution in patients with hepatic, renal, or cardiovascular disease. Adequate **drug holiday** must be given between dosages to avoid cumulative toxicity. Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, clarithromycin and itraconazole) or P-gp inhibitors (for example, amiodarone and verapamil) and those with severe renal impairment.



Figure 40.21

Some adverse effects of *colchicine*.
GI = gastrointestinal.

D. Allopurinol. Allopurinol [al-oh-PURE-i-nole], a **xanthine oxidase inhibitor**, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (**Figure 40.20**).

1. Therapeutic uses: Allopurinol is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

د. الـ **Allopurinol** : مثبط لأوكسيداز الزانثين ، مضاهئ للبورين . يُنقص إنتاج حامض اليوريك بتنشيطه تنافسياً الخطوتين الأخيرتين في التصنيع الحيوي لحامض اليوريك المُخَفَّز بأوكسيداز الزانثين (الشكل ٤٠ . ٢٠) .

١. **الاستعمالات العلاجية :** معالجة خافضة-اليورات فعّالة في معالجة التقرس وفرط يوريك الدم الثانوي لحالات إضافية ، مثل تلك المترافقة مع خباثات مُعَيَّنة (الخباثات التي ينتج فيها كميات ضخمة من البورينات ، خصوصاً بعد المعالجة الكيميائية) .

2. Pharmacokinetics: *Allopurinol is completely absorbed after oral administration. The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing. The drug and its active metabolite are excreted in the urine. Dose adjustment is needed if the estimated glomerular filtration rate is less than 30 mL/min/1.73 m².*

3. Adverse effects: *Allopurinol is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function. Because acute attacks of gout may occur more frequently during the first several months of therapy, colchicine, NSAIDs, or corticosteroids can be administered concurrently.*

٢. الحرائك الدوائية : يمتص من الهضم . مستقلبه الأولي الألوزانثين (أكسي بورينول) أيضاً مثبت لأكسيداز الزانثين ذو عمر نصف ١٥ إلى ١٨ ساعة . لهذا ، يدوم تثبيط فعّال لأكسيداز الزانثين بجرعة-يومية . يطرح الدواء ومستقلبه الفعّال في البول . ثمة حاجة لضبط الجرعة إذا كان الترشيح الكبيبي أقل من ٣٠ ميلي لتر/دقيقة/١.٧٣ متر مربع .

التأثيرات الضائرة : تفاعلات فرط تحسس ، خصوصاً طفح الجلد . يزداد هذا الاختطار عند منقوصي وظيفة الكلية . يمكن إعطاء الكولشيسين والـ NSAIDs أو الكورتيكوستيرويدات معه لأنّ هجمات النقرس الحادة قد تحدث أكثر أثناء الشهور الأولى للمعالجة به .

E. Febuxostat. is an oral xanthine oxidase inhibitor structurally unrelated to allopurinol. Febuxostat is rapidly absorbed after oral administration with the time to reach peak concentration (t_{max}) being of approximately 1 hour. The drug is highly bound to albumin in blood (~99%) and appears to have a low-to-medium apparent volume of distribution of approximately 0.7 l/kg. Febuxostat is indicated for the long-term management of hyperuricemia in patients with gout at a dose of 10 to 120 mg once daily. Febuxostat is well tolerated. Its adverse effect profile is similar to that of allopurinol, although the risk for rash and hypersensitivity reactions may be reduced. Febuxostat does not have the same degree of renal elimination as allopurinol and thus requires less adjustment in those with reduced renal function. The most common adverse events include abnormal liver function test results, abdominal pain, diarrhea, headache, joint-related signs and symptoms, and musculoskeletal and connective tissue signs and symptoms. Febuxostat should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to allopurinol.

Febuxostat. [feb-UX-oh-stat] : **مثبط لأوكسيداز الزانثين** فموي غير متعلق بنيوياً بالألوبيورينول . يمتص سريعاً ($t_{max} = 1h$) ، يرتبط جداً بالبروتين الدم ٩٩% ($V_d = 0.7 \text{ l/kg}$) . **للمعالجة طويلة الأمد لفرط حمض يوريك الدم** لمرضى النقرس بجرعة ١٠ إلى ١٢٠ ملغ يومياً . تأثيراته الضائرة مثل الألوبيورينول ربما مع نقص الطفح وتفاعلات فرط التحسس . **أقل حاجة لضبط الجرعة لمرضى الكلية** . يسبب ألم بطن وإسهال وصداع وشذوذ اختبارات الكبد .. ينبغي الحذر عند استعماله لمرضى القلب والسكتة لأنه أكثر خطراً هنا من الألوبيورينول .

F. Probenecid. *Probenecid [proe-BEN-a-sid] is an oral uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate–anion exchanger in the proximal tubule. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid. Probenecid should be avoided if the creatinine clearance is less than 50 mL/min. Adverse effects include nausea, vomiting, and dermatologic reactions, and, rarely, anemia or anaphylactic reactions. It is used at a dose of 0.25 to 0.5 g twice daily. However, intermittent colchicine therapy is indicated to avoid acute precipitation of gout.*

الـ **Probenecid** : مُحَقِّزُ بِيْلَةِ حَمَضِ اليوريك فموي . حامض عضوي ضعيف يعزز
التصفية الكلوية لحمض اليوريك بتنشيط مبادل أنيون—اليورات في النبيب القريب .
بالجرعات العلاجية يحصر عودة امتصاص حمض اليوريك من الأنبوب القريب . ينبغي
تجنبه إذا كانت تصفية الكرياتينين أقل من ٥٠ ميلي لتر/الدقيقة . تتضمن تأثيراته الضائرة
غثيان وقيء وتفاعلات جلدية ، ونادراً فقر دم أو تفاعلات تأقية . يستعمل بجرعة ٠,٢٥ ،
إلى ٠,٥ غرام مرتين يومياً . عال أية حال ، يوصى بمعالجة متقطعة بالكولشيسين لتجنب
التعجيل الحاد للنقرس .

G. Pegloticase. Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with pegloticase, and patients should be premedicated with antihistamines and corticosteroids. F

الـ **Pegloticase** : شكل مأشوب من إنزيم أكسيداز اليورات أو اليوريكاز . يعمل بتحويل حمض اليوريك إلى الأنتوين ، المستقلب الذوّاب في الماء غير السام الذي يطرح بالكلية . يوصى به لمرضى النقرس بعد فشل المعالجة المعيارية مثل مثبطات أكسيداز الزانثين . يعطى تسريب IV كل أسبوعين . قد تحدث تفاعلات متعلقة—بالتسريب وتاق فينبغي معالجة المرضى مسبقاً بمضادات الهيستامين والكورتيكوستيرويدات .

للاطلاع

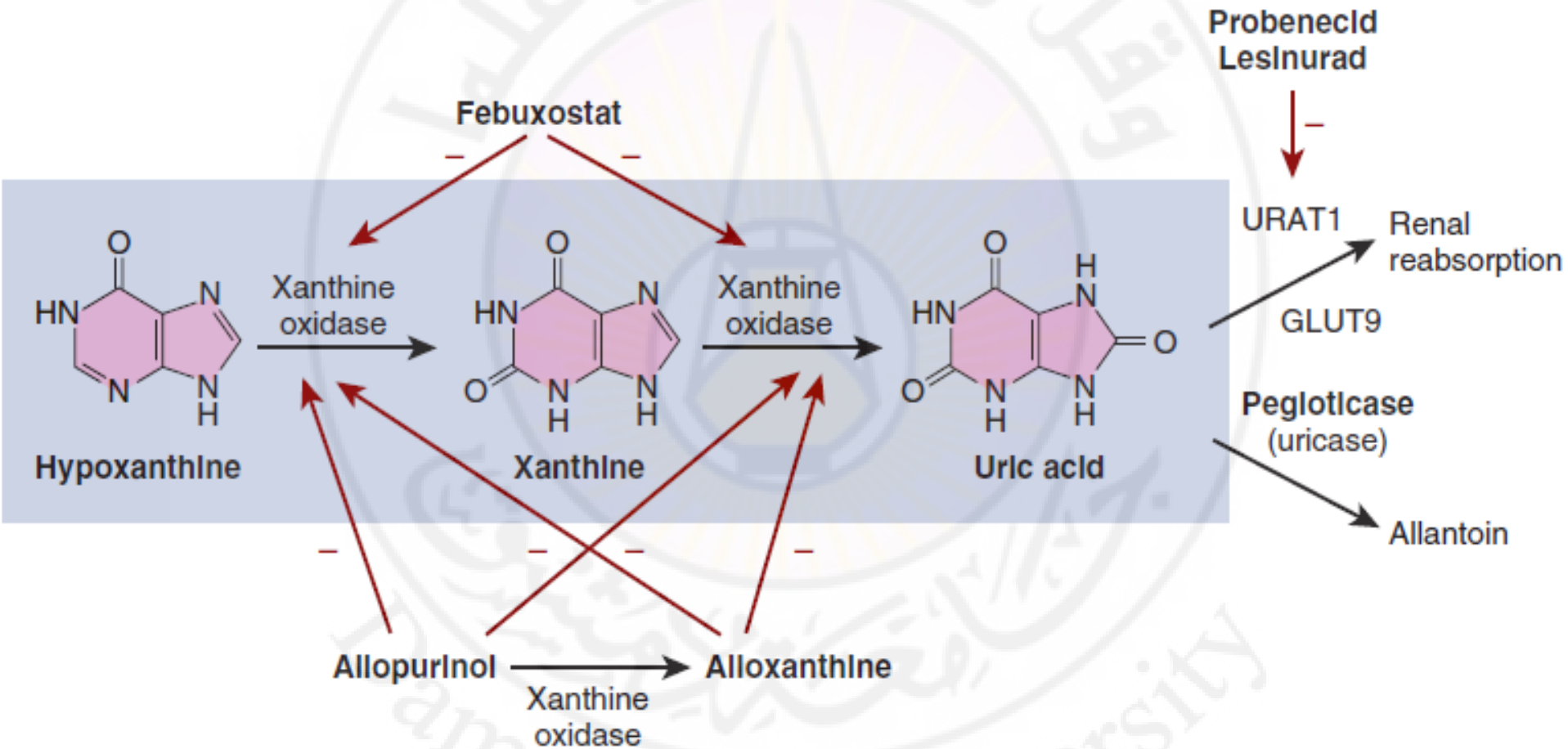


FIG. 32.1 Uric Acid Synthesis and Metabolism and the Sites of Action of Drugs Used for the Prophylactic Treatment of Gout. URAT1 and GLUT9 are the primary transporters in the renal proximal

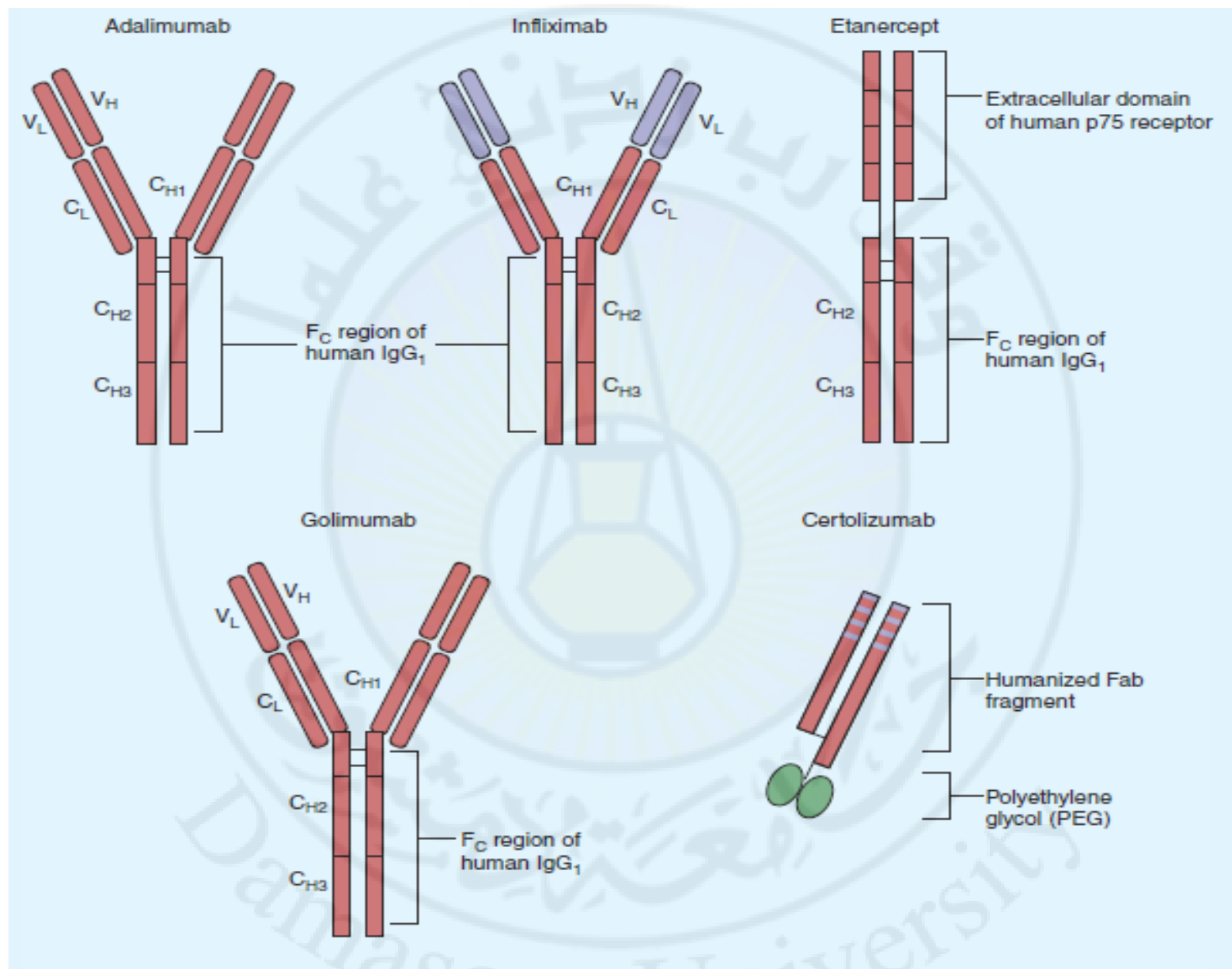


FIGURE 36–4 Structures of TNF- α antagonists used in rheumatoid arthritis. C_H, constant heavy chain; C_L, constant light chain; F_C, complex immunoglobulin region; V_H, variable heavy chain; V_L, variable light chain. Red regions, human derived; blue regions, mouse derived; green regions, polyethylene glycol (PEG).

The background of the slide features a large, faint watermark of the Damascus University logo. The logo is circular, with Arabic calligraphy at the top and bottom, and a central emblem depicting a sun or starburst. The text "Damascus University" is written in English at the bottom of the circle.

Drugs Used to Treat Headache Disorders and Obesity

VI. DRUGS USED TO TREAT HEADACHE DISORDERS

The most common types of headaches are migraine, tension-type, and cluster headaches. Migraines can usually be distinguished from cluster headaches and tension-type headaches by the characteristics as shown in **Figure 39.8**. Patients with severe migraine headaches report one to five attacks per month of moderate-to-severe pain which is usually unilateral. Headache disorders significantly affect quality of life and result in considerable healthcare costs. Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines (**Figure 39.9**). Serotonin agonists (triptans and ergot alkaloids) are effective as abortive agents in the treatment of migraines.

الأدوية المستعملة في معالجة اضطرابات الصداع : تُمثّل الشَّقِيقَةُ وَصُدَاغُ التَّوَثُّرِ وَالصُّدَاغُ الْعُنُقُودِيّ أَشْبَعَ أَنْمَاطِ الصَّدَاعِ . يُمْكِنُ تَمْيِيزُ الشَّقِيقَةِ عَادَةً عَنْ الصُّدَاغِ الْعُنُقُودِيّ وَصُدَاغِ التَّوَثُّرِ بِالْمُمِيزَاتِ الْمَوْجُودَةِ فِي **الشَّكْلِ ٣٩ . ٨** .

يَبْلُغُ مَرْضَى الشَّقِيقَةِ الشَّدِيدَةِ عَنْ نَوْبَةٍ إِلَى خَمْسَةِ نَوْبَاتٍ مُتَوَسِّطَةٍ إِلَى شَدِيدَةٍ الْأَلَمِ شَهْرِيًّا وَوَحِيدَةٍ الْجَانِبِ عَادَةً . تَوْثَّرُ هَذِهِ الْاضْطِرَابَاتُ عَلَى جُودَةِ الْحَيَاةِ وَكُلْفَتِهَا كَبِيرَةٌ .

تَكْتَنِفُ الْمَعَالِجَةُ تَجَنُّبُ مَثِيرَاتِ الصَّدَاعِ (مِثْلُ الْكَحُولِ وَالشُّوْكُولَا وَالْكَرْبِ) وَاسْتِعْمَالِ عِلَاجَاتٍ مَجْهُضَةٍ لِلصَّدَاعِ الْحَادِ ، وَمَعَالِجَةٍ وَقَائِيَةٍ لِلصَّدَاعَاتِ الْمُتَوَاتِرَةِ أَوْ الشَّدِيدَةِ (**الشَّكْلِ ٣٩ . ٩**) . نَاهِضَاتُ السِيرُوتُونِينِ (التَّرِيْبِتَانَاتُ وَقُلُوبَانِيَّاتُ الْأَرْغُوتِ "الْمِهْمَازُ") فَعَالَةٌ كَأَدْوِيَةٍ مَجْهُضَةٍ لِلشَّقِيقَةِ .

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

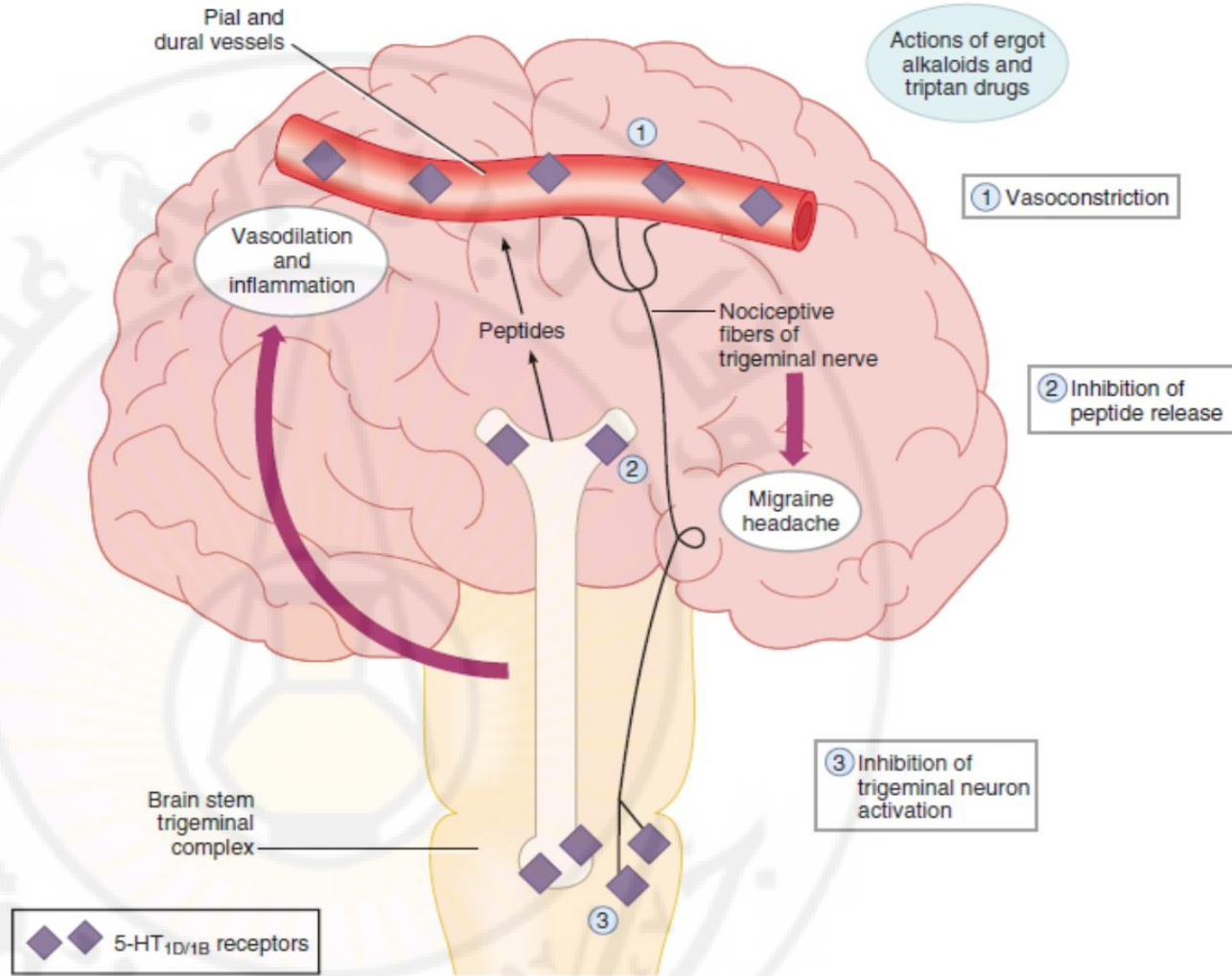
Figure 39.8
 Characteristics of migraine, cluster, and tension-type headaches.

	ROUTE	DOSE
Triptans:		
<i>Almotriptan</i>	Oral	6.25–25 mg/day, once or twice a day
<i>Eletriptan</i>	Oral	20–80 mg/day, twice a day
<i>Frovatriptan</i>	Oral	2.5–7.5 mg/day, up to thrice a day
<i>Naratriptan</i>	Oral	1–5 mg/day, once in 4-hour interval
<i>Rizatriptan</i>	Oral	5–30 mg/day, once in 2-hour interval
<i>Sumatriptan</i>	Oral/intranasal/subcutaneous	Oral = 25–200 mg/day, once in 2 hours if required Intranasal = 5–40 mg/day, once in 2 hours if required Subcutaneous = 6–12 mg/day, twice a day with 1 hour interval
<i>Zolmitriptan</i>	Oral/intranasal	Oral: 1–10 mg/day (once in 2 hr) Intranasal = 5–10 mg/day, once in 2 hours if required
Ergots:		
<i>Dihydroergotamine</i>	Sublingual/IM/subcutaneous/IV/intranasal	Sublingual = 2–6 mg/day, 30 minutes of interval Subcutaneous/IM = 1–3 mg/day, once in 1-hour interval IV = 1–2 mg/day, once in 1-hour interval Intranasal = 1–3 mg/day, once in 15 minutes on both nostrils
<i>Ergotamine</i>	Oral/sublingual/suppository	Oral: Adult = 1–6 mg/day or 1–10 mg/week, with 30 minutes of interval Children = 1–3 mg/day or 1–5 mg/week, with 30 minutes of interval Sublingual = 2–6 mg/day, with 30 minutes of interval Suppository = 2–10 mg/week, once in 1 hour interval
Other agents:		
NSAIDs (refer to Chapter 40): <i>Aspirin, Ibuprofen, Indomethacin, ketorolac</i> <i>Naproxen</i>		
Prophylactic medications: Anticonvulsants (refer to Chapter 12) β -Blockers (refer to Chapter 7) Calcium channel blockers (refer to Chapter 16) Tricyclic antidepressants (refer to Chapter 10)		

Figure 39.9

Summary of drugs used to treat migraine headache and their dosages. Modified from D. D. Dubose, A. C. Cutlip, and W. D. Cutlip. Migraines and other headaches: an approach to diagnosis and classification. *Am. Fam. Physician* 51: 1498 (1995).

Fig. 29.1 Mechanisms of ergot alkaloids and triptan drugs used in the treatment of migraine headache disorder. Migraine attacks are thought to result from trigeminal neurovascular dysfunction. When neurons in the trigeminal complex release peptides such as substance P and calcitonin gene-related peptide (CGRP), this causes vasodilation and inflammation of pial and dural vessels. These events activate nociceptive trigeminal fibers and cause moderate to severe pain that is characteristic of migraine headaches. Ergot alkaloids and triptan drugs terminate the pain by activating serotonin 5-HT_{1B/1D} receptors at several sites: (1) They activate receptors on pial and dural vessels and thereby cause vasoconstriction. (2) They activate presynaptic receptors to inhibit the release of peptides and other mediators from trigeminal neurons. (3) They activate receptors in the brainstem, which is believed to inhibit the activation of trigeminal neurons responsible for migraine attacks. CGRP antagonists (not shown) are also effective in the treatment of migraine.



شكل ٢٩. ١. آليات قلوانيات الإرغوت والتريبتانات المستعملة في معالجة اضطراب صداع الشقيقة. تنجم هجمات الشقيقة عن خلل وعائي عصبي لمثلث التوائم. عندما تُطلق عصبونات مثلث التوائم بببتيدات مثل المادة P والببتيد المتعلق—بمورثة الكالسيتونين CGRP، يسبب هذا توسيع أوعية والتهاب الأوعية الحنونة والجافية. تُنشِط هذه الأحداث ألياف مثلث التوائم المستقبلية للأذية وتسبب ألم متوسط إلى شديد مُميّز لصداع الشقيقة. تُنهي قلوانيات الإرغوت والتريبتانات الألم بتنشيطها المستقبلات 5-HT_{1B/1D} عند مقرّات: (١) تُنشِط مستقبلات على الأوعية الحنونة والجافية فتضيق الأوعية. (٢) تُنشِط مستقبلات قبل المشبك لتنشط إطلاق بببتيدات من عصبونات مثلث التوائم. (٣) تُنشِط مستقبلات في جذع الدماغ، ممّا يثبط تنشيط عصبونات مثلث التوائم المسؤولة عن هجمات الشقيقة. مناهضات الـ CGRP (غير مرئية هنا) فعّالة أيضاً في معالجة الشقيقة.

A. Types of migraine. There are two main types of migraine headaches. The first, migraine without aura, is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). The majority of patients with migraine do not have aura. In the second type, migraine with aura, the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual (flashes, zigzag lines, and glare) and occur approximately 20 to 40 minutes before headache pain begins. In the 20%–30% of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache in migraines with or without auras is similar. Women are threefold more likely than men to experience either type of migraine.

أ. أنماط الشقيقة : ثمة نمطان مهمّان للشقيقة .

النمط الأول شقيقة بدون أورة (بَادِرَة) ، صداع شديد أحادي الجانب نابض يستمر ٢—٧٢ ساعة نموذجياً . تتفاقم بالنشاط الجسدي وتترافق مع غثيان وقيء ورهاب الضوء والصوت .. معظم مرضى الشقيقة بدون أوره .

النمط الثاني مع أوره ، يُستَهَلّ الصداع بأعراض عصبية تدعى نسمات ، بصرية أو حسية ، أو تسبب اضطرابات كلامية أو حركية . تكون هذه الأعراض البَادِرَة غالباً بصرية (ومضات وخطوط متعرجة وإبهار البصر) وتحدث تقريبا ٢٠—٤٠ دقيقة قبل بدء ألم الصداع . تمثل ٢٠—٣٠% من حالات الشقيقة .. الصداع متماثل في النمطين . تمثل الشقيقة بشقيها عند النساء ثلاث أضعاف مقارنة مع الرجال .

B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. The hypoperfusion persists throughout the aura and well into the headache phase. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial vasodilation, which leads to release of neuroactive molecules, such as substance P, neurokinin A, and calcitonin gene-related peptide.

ب. الأسس البيولوجية لصداع الشقيقة : يُعَدّ انتشار تثبيط النشاط العصبي المترافق مع نقص جريان الدم في معظم الجزء الخلفي من كرة المخ أوّل مَظْهَر للشقيقة ذات النسمة (الاستهلال). ينتشر نقص التروية هذا تدريجياً نحو الأمام فوق سطح قشرة المخ والمناطق المجاورة من الدماغ. يدوم نقص التروية أثناء استهلال الشقيقة ويتحسن في طور الصداع.

لا يبدي مرضى الشقيقة الخالية من النسمة نقص تروية .

سبب الألم في النمطين توسيع الأوعية الشريانية خارج القحف وداخله ، الذي يؤدي إلى إطلاق جزيئات نشطة عصبياً ، مثل المادة—P والكينين العصبي—أ و الببتيد المتعلق—بمورثة الكالسيتونين .

C. Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and antiemetics (for example, *prochlorperazine*) to control vomiting. Opioids are reserved as rescue medication when other treatments for a severe migraine are not successful. Migraine-specific therapy includes triptans and ergot alkaloids, which are 5-HT_{1B/1D} receptor and 5-HT_{1D} receptor agonists, respectively. It has been proposed that activation of 5-HT₁ receptors by these agents leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels.

ج. **المعالجة الأعراضية للشقيقة الحادة** : يمكن تصنيف المعالجة الحادة إلى غير نوعية للشقيقة ونوعية .

تتضمن **المعالجة غير النوعية** المسكنات مثل الـ **NSAIDs** ومضادات القيء (مثل **prochlorperazine**) لضبط القيء . تُدخَّر أفيونيات المفعول كمداواة إنقاذية عند إخفاق باقي المعالجات للشقيقة الشديدة .

تتضمن **المعالجة النوعية-لشقيقة** التريبتانات وقلوانيات الأرغوت (المهماز) ، **الناهضة** للمستقبلات 5-HT_{1B/1D} والمستقبلات 5-HT_{1D} على التوالي .

تنشيط المستقبلات 5-HT₁ بهذه الأدوية يؤدي إلى تضيق الأوعية وتنشيط إطلاق ببتيدات عصبية مؤيدة للالتهاب على العصب الثلاثي التوائم المُعَصَّب للأوعية الدموية القحفية .

Through activation of presynaptic 5-HT_{1D} and 5-HT_{1F} receptors, the triptans inhibit the release of CGRP and other peptides implicated in the dilation of intracranial blood vessels, thereby preventing this effect and contributing to vasoconstriction.

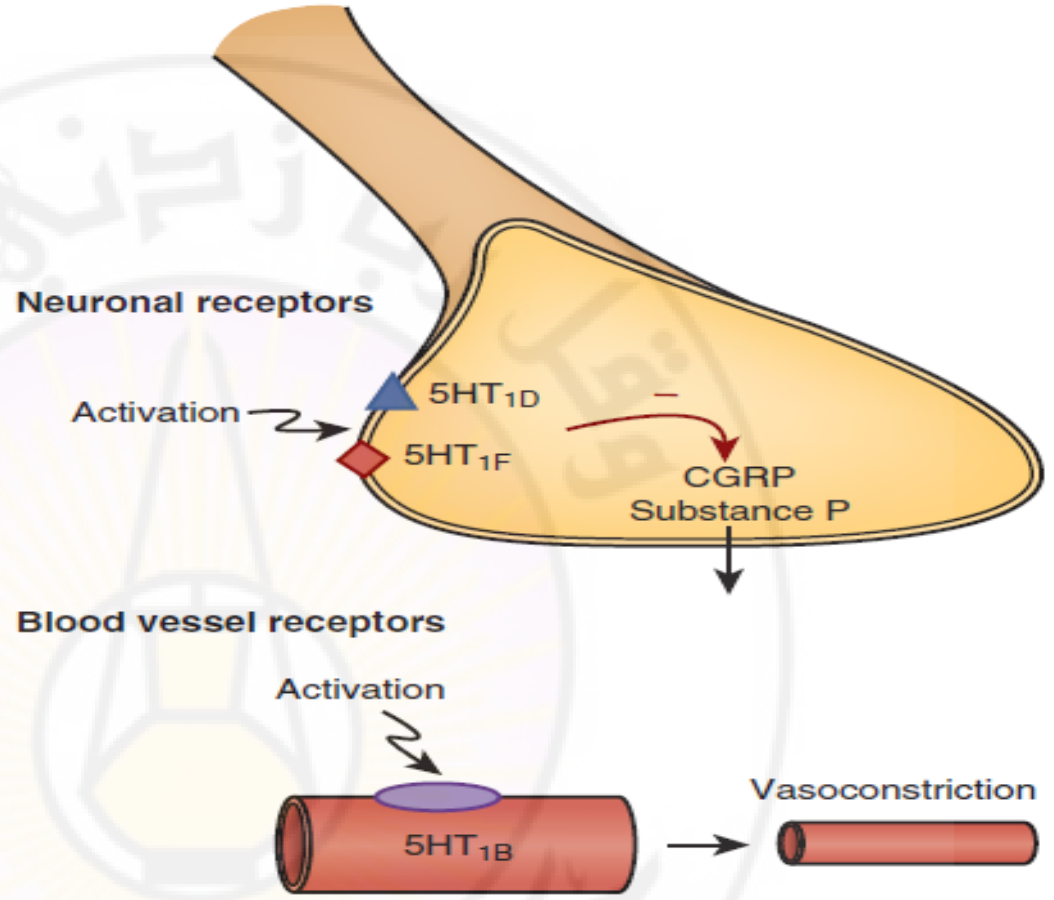


FIG. 31.1 Effects of Serotonin 1 (5-HT₁) Receptor Activation on Neurons and Blood Vessels. The 5-HT_{1D} and 5-HT_{1F} receptors are located presynaptically where they function to inhibit the release of calcitonin gene-related peptide (CGRP) and substance P. 5-HT_{1B} receptors are located on blood vessels where activation leads to vasoconstriction.

التريبتانات بتنشيطها المستقبلات 5-HT_{1D} و 5-HT_{1F} تثبط إطلاق الـ CGRP وبتثبيدات إضافية متورطة في توسيع أوعية دموية داخل القحف ، وبالتالي تمنع هذا التأثير وتساهم في تضيق الأوعية .

الشكل ٣١. ١ . تأثيرات تنشيط مستقبلات السيروتونين ١ (5-HT₁) على العصبونات والأوعية الدموية . المستقبلات 5-HT_{1D} و 5-HT_{1F} متوضعة قبل المشبك حيث تعمل على تثبيط إطلاق الـ CGRP و المادة-P . الـ 5-HT_{1B} متوضعة على الأوعية الدموية حيث يؤدي تنشيطها إلى تضيق الأوعية .

1. **Triptans:** This class of drugs includes *almotriptan* [al-moe-TRIPtan], *eletriptan* [el-e-TRIP-tan], *frovatriptan* [fro-e-va-TRIP-tan], *naratriptan* [nar-a-TRIP-tan], *rizatriptan* [rye-za-TRIP-tan], *sumatriptan* [soo-ma-TRIP-tan], and *zolmitriptan* [zole-ma-TRIPtan]. Sumatriptan was the first available triptan and is the prototype of this class. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70% of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with dihydroergotamine and the vasoconstriction caused by ergotamine (see below) are much less pronounced with the triptans.

١. التريبتانات : يتضمن هذا الصنف من الأدوية *almotriptan* و *eletriptan* و *frovatriptan* و *naratriptan* و *rizatriptan* و *sumatriptan* و *zolmitriptan*. تُجهض هذه الأدوية سريعاً وبفاعلية صداع الشقيقة وتقلص شدته عند حوالي ٧٠% من المرضى.

التريبتانات ناهضات للسيروتونين تعمل على مجموعة فرعية من مستقبلات السيروتونين موجودة على الأعصاب المحيطية الصغيرة التي تعصب الوعائية داخل القحف.

الغثيان الذي يحدث مع الـ dihydroergotamine وتضيق الأوعية الحاد مع الـ ergotamine أقل بكثير مع التريبتانات.

Sumatriptan is given subcutaneously, intranasally, or orally

(sumatriptan is also available in a combination product with naproxen).

Zolmitriptan is available orally and by nasal spray. All other agents are taken orally. The onset of the parenteral drug sumatriptan is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. **Frovatriptan** is the longest acting triptan, with a half-life of more than 24 hours. Individual response to triptans varies, and a trial of more than one triptan may be necessary before treatment is successful.

يُعطى الـ **Sumatriptan** تحت الجلد وداخل الأنف أو في الفم (يتوافر أيضاً في مُنتج توليفي مع naproxen). يتوافر الـ **Zolmitriptan** فموياً و بَخاخ للأنف . باقي الأدوية تُؤخذ في فموياً . سرعة بدء تأثير الـ sumatriptan الحقني حوالي ٢٠ دقيقة ، مقارنة مع ١ إلى ٢ ساعة عندما يُعطى في الفم . لهذا الدواء مُدة تأثير قصيرة ، وعمر نصف إخراج ٢ ساعة . يرجع (ينكس) الصداع عادةً خلال ٢٤ إلى ٤٨ ساعة بعد جرعة مفردة من الدواء ، لكن الجرعة الثانية فعّالة في إجهاض الصداع عند معظم المرضى .

يُعدّ الـ **Frovatriptan** التريبتان الأطول أمداً ، مع عمر-النصف أكثر من ٢٤ ساعة . تتغاير الاستجابة الإفرادية للتريبتانات وقد يكون تجريب أكثر من تريبتان ضرورياً مسبقاً لتكون المعالجة ناجحة .

Elevation of blood pressure and other cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. Dizziness and malaise have also been seen with the use of triptans.

ثمة تقارير عن زيادة ضغط الدم وغيره من الأحداث القلبية مع استعمال التريبتان . لهذا ،
ينبغي عدم إعطاء التريبتانات للمرضى ذوي عوامل الاختطار من أجل مرض الشريان
التاجي بدون إنجاز تقييم القلب قبيل الإعطاء . تتضمن الأحداث الضائرة الإضافية مع
استعمال التريبتانات إحساسات الألم والضغط في الصدر والرقبة والحلق والفك . تلاحظ
الدوخة والوعكة (الفتور) أيضاً مع استعمال التريبتانات .

2. Ergot alkaloids: Ergot is the dried sclerotium of the fungus *Claviceps purpurea* which grows on rye plant. Ergot alkaloids such as **ergotamine** and **ergonovine** are potent bioactive compounds. *Ergotamine* and **dihydroergotamine** [dye-hye-droe-er-GOT-a-meen], a semisynthetic derivative of *ergotamine*, are *ergot alkaloids approved for the treatment of migraine headaches*. The action of the ergot alkaloids is complex, with the ability to bind to 5-HT₁ receptors, α receptors, and dopamine receptors. 5-HT₁ receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents. *Ergotamine is currently available sublingually* and is mostly effective when used in the early stages of the migraine. It is also available as an oral tablet or suppository containing both *ergotamine and caffeine*. *Ergotamine is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches*.

٢. قلوانيات الأرغوت : الأرغوت هو الأصلوبة المجففة لفطر الدبوسية الفُرُفُريّة النامي على نبات الشَّيْلَم . **الأرغوتامين** و **الإرغونوفين** مركّبين مُنَشِّطَيْن حَيَوِيَّيْن قَوِيَّيْن . **الأرغوتامين** و **ثنائي هيدروأرغوتامين** ، المشتقّ نصف التصنيعي للأرغوتامين ، قلوانيات إرغوت مبرهنة لمعالجة صداع الشقيقة ..

ترتبط بالمستقبلات 5-HT₁ والـ α ومستقبلات الدوبامين .

تُعَدّ المستقبلات 5-HT₁ على الأوعية الدموية داخل القحف أهداف تسبب تضيق الأوعية مع استعمال هذه الأدوية .

يتوافر الأرغوتامين تحت اللسان الفعّال إن استعمل في المراحل المبكرة من الشقيقة . يتوافر أقراص فموية أيضاً وتحاميل تحتوي أرغوتامين مع كافئين . يستعمل الأرغوتامين يومياً وأسبوعياً بقيود تجريبية حازمة بسبب قابليته إحداث اعتماد وصداع ارتداديّ .

Secale cornutum
(ergot)

Fungus:
Claviceps purpurea

Secale alkaloids

Effect on
vasomotor tone

Tonic contraction of uterus

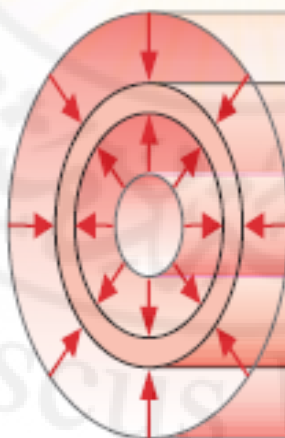
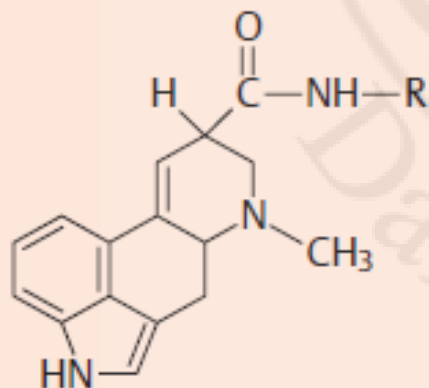
e.g., ergometrine

Oxygen supply
diminished

Contraindication
before delivery

Indication:
postpartum
uterine atonia

e.g., ergotamine



Fixation of lumen at intermediate caliber

Dihydroergotamine is administered intravenously or intranasally and has an efficacy similar to that of *sumatriptan*. The use of *dihydroergotamine* is limited to severe cases of migraines. Nausea is a common adverse effect. *Ergotamine and dihydroergotamine* are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors. Apart from migraine, ergot alkaloids such as *ergonovine* and *methylergonovine* are used as uterotonic in postpartum women. After intravenous administration, the effect can be observed within 10 minutes. The plasma half-life of *methylergonovine* is between 0.5 and 2 hours. Considering this action of ergot alkaloids on the uterus, it is contraindicated in patients who have migraine during pregnancy or who are likely to become pregnant. Ergot alkaloids are known to cause fetal distress and miscarriage in pregnant women.

يعطى الـ IV Dihydroergotamine أو داخل الأنف ونجاعته تماثل نجاعة السوماتريبتان ، لكن استعماله مقتصر على الشقيقة الشديدة ويسبب الغثيان .

ممنوع استعمال الـ Ergotamine والـ dihydroergotamine لمرضى الذبحة والداء الوعائي المحيطي لأنهما مضيّقان للأوعية ..

يستعمل الـ **ergonovine** والـ **methylergonovine** مُقَوِّيان لتَوَثُّر الرَّجَم عند النساء بعد الولادة . إذ يلاحظ التأثير بعد الحقن الوريدي بـ ١٠ دقائق (عمر النصف للـ **methylergonovine** ٠,٥ — ٢ ساعة) . لهذا تُمنع قلوانيات الأروغوت أثناء الحمل أو المتوقع حملهن . تسبب قلوانيات الأروغوت ضائقة جنينية و إجهاض عند الحوامل .

3. Nonspecific therapies: Other therapies for acute migraine attacks include analgesics, antiemetics, nonsteroidal anti-inflammatory drugs, and corticosteroids.

D. Prophylaxis for migraine headache

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. β -Blockers are the drugs of choice for migraine prophylaxis; however, calcium channel blockers, anticonvulsants, and tricyclic antidepressants have also shown effectiveness in migraine prevention (**Figure 39.10**). Flunarizine

٣. المعالجات غير النوعية : تتضمن المعالجات الإضافية لهجمات الشقيقة الحادة المسكنات ومضادات القيء والـ NSAIDs والكورتيكوستيرويدات .

د. الوقاية من صداع الشقيقة : يوصى بالمعالجة التي تمنع حدوث الشقيقة عندما تحدث الهجمات مرتين أو أكثر في الشهر وتكون آلام الرأس شديدة أو مصحوبة بمضاعفات بعلامات عصبية خطيرة .

تُعدّ محصرات البيتا الأدوية المُختارة للوقاية من الشقيقة ؛ على كل حال تُبدي محصرات قنوات الكالسيوم ومضادات الاختلاج ومضادات الاكتئاب الثلاثية الحلقة فعالية في منع الشقيقة (**الشكل ٣٩ . ١٠**) .

Recently

The cosmetic agent **botulinum toxin** A (Botox) was recently approved for the prevention of migraines. **Its exact mechanism is unknown**; however, Botox disrupts the neurotransmission of acetylcholine by preventing vesicle fusion with the membrane of the presynaptic terminal.

CGRP-Targeted Monoclonal Antibodies for prevention .

Galcanezumab (Emgality) (SC) ; **Galcanezumab binds CGRP and thereby blocks the binding of CGRP to the CGRP receptor.**

fremanezumab (Ajovy), SC on a quarterly (3 months) schedule, and **eptinezumab** (Vypepti) IV infusion on a quarterly basis.

Erenumab (Aimovig) which **targets the CGRP receptor and not the CGRP peptide.**

CGRP Receptor Antagonists

1. **Ubrogepant** was the first **small molecule CGRP receptor antagonist** to be approved and marketed. It is an oral medication indicated for the **acute treatment of migraine** with or without aura in adults. Ubrogepant should be taken at a dose of 50 or 100 mg and may be repeated in 2 hours if the migraine does not subside. The most common **adverse reactions** from clinical trials (at least 2% and greater than placebo) were **nausea** and **somnolence**. Although clinical trials showed that ubrogepant relieved migraine pain in a greater percentage of treated patients than those in the placebo group, the results were not particularly strong, and there was no comparator group such as sumatriptan. A second CGRP receptor antagonist,
2. **Rimegepant**, was very recently approved and is formulated as an **orally disintegrating tablet** for sublingual or oral use. The most common adverse effect of rimegepant was nausea.

Agents used to treat an acute attack

TRIPTANS

- Triptans rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 80% of patients.
- Triptans are serotonin agonists, acting at 5-HT_{1D} receptors.

DIHYDRO-ERGOTAMINE

- Dihydroergotamine is a vasoconstrictor.
- Most effective when given during the prodromal phase.
- Contraindicated in pregnancy and in patients with peripheral vascular disease or coronary artery disease.

ANALGESICS

- Anti-inflammatory drugs such as *aspirin*, *naproxen*, and *ibuprofen* are useful in relieving migraine attacks.
- Severe pain may require administration of opioids such as *codeine sulfate* or *meperidine*.

Agents used in prophylaxis

Several classes of drugs are effective in reducing the frequency and severity of migraine attacks:

- β -Blockers: *Propranolol* and *nadolol*
- Tricyclic antidepressant: *Amitriptyline*
- Anticonvulsant: *Divalproex*
- Calcium channel blocker: *Verapamil*

Time

Start of attack

Asymptomatic phase

- Between attacks, no symptoms or pathologic features are evident.

Prodromal phase

- Visual disturbances that precede the actual headache.
- Associated with arterial vasoconstriction and release of serotonin.

Headache phase

- Pain, nausea, and vomiting.
- Associated with cerebral vasodilation and lower-than-normal levels of serotonin.

Figure 39.10

Drugs useful in the treatment and prophylaxis of migraine headaches.

E. Drugs for tension and cluster headache

Analgesics (NSAIDs, *acetaminophen*, *aspirin*) are used for symptom relief of tension headaches, and *caffeine* and *butalbital* are often combined with *acetaminophen* or *aspirin*. Triptans, along with inhalation of 100% oxygen, are used as first-line abortive strategies for cluster headache.

ه. الأدوية المستعملة في معالجة صداع التوتر والصداع العنقودي :

تستعمل المُسكِّنات (الـ NSAIDs والأسييتامينوفين والأسبرين) لتفريج أعراض صداع التوتر ، ويؤلف الكافئين والـ butalbital عادةً مع الأسييتامينوفين أو الأسبرين .
تُستعمل التريبتانات متواكبةً مع إنشاق ١٠٠% أكسجين كإستراتيجيات الخط—الأول المُجهضة للصداع العنقودي .

VII. DRUGS FOR OBESITY

The term “obesity” is given to individuals with a body mass index (BMI) 30 kg/m² or greater. Obesity is due in part to an energy imbalance; however, it is now well understood that genetics, metabolism, behavior, environment, culture, and socioeconomic status play a role in obesity, as well. Serotonin agonists have been used in the treatment of obesity for the appetite suppression that they produce. Drugs for obesity are considered effective if they demonstrate at least a 5% greater reduction in body weight as compared to placebo (no treatment). The majority of drugs approved to treat obesity have short-term indications for usage. A summary of medications for obesity is provided in Figure 39.11.

الأدوية المستعملة في معالجة السمنة (البداية) : يُطلق مصطلح “ السمنة ” على الأفراد ذوي منسب كتلة الجسم (BMI) ٣٠ كياوغرام/ م^٢ أو أكثر .

يُعدّ فقد توازن الطاقة سبباً جزئياً للسمنة ؛ على كل حال ، معروف الآن أنّ للوراثة والإستقلاب والسلوك والبيئة والثقافة والحالة الاجتماعية الاقتصادية دور في السمنة أيضاً .

تستعمل ناهضات السيروتونين في معالجة السمنة من أجل كبتها للشهية .

تكون أدوية السمنة فعّالة إذا أنقصت أكثر من ٥% من وزن الجسم مقارنةً مع غُفل (بدون علاج) . لمعظم الأدوية المثبتة لمعالجة السمنة توصيات الاستعمال قصير الأمد .

ملخص أدوية السمنة موفّر في الشكل ٣٩ . ١١ .

DRUG NAME	ROUTE OF ADMINISTRATION	COMMENTS
Nonspecific 5HT_{2C} receptor agonists:		
<i>Fenfluramine</i>	Oral	Discontinued by FDA
<i>Dexfenfluramine</i>	Oral	Discontinued by FDA
Specific 5HT_{2C} receptor agonist:		
<i>Lorcaserin</i>	Oral	10–20 mg/day, twice a day
Appetite suppressants:		
<i>Phentermine</i>	Oral	12–30 mg/day, once a day
<i>Diethylpropion</i>	Oral	25–75 mg/day, up to thrice a day
Lipase inhibitor:		
<i>Orlistat</i>	Oral	120–360 mg/day, thrice a day at 1 hour after meal
Glucagon-like peptide-1 (GLP-1) receptor agonist:		
<i>Liraglutide</i>	Subcutaneous	0.6–1.8 mg/day, once a day
Combination drugs:		
<i>Bupropion/naltrexone</i>	Oral	<i>Naltrexone</i> 8 mg/ <i>bupropion</i> 90 mg, 1–4 tablets/wk
<i>Pentermine/topiramate</i>	Oral	<i>Phentermine</i> = 3.75–15 mg/day, <i>topiramate</i> = 23–92 mg/day, once a day in morning

Figure 39.11

Summary of the drugs used for the treatment of obesity and their doses.

TABLE 16-5 Antiobesity drugs and their effects.

Drug or Drug Combination	Drug Group	Possible Mechanism of Action	Dosage	Toxicity
Orlistat	GI lipase inhibitor	Reduces lipid absorption	60–120 mg TID PO	Decreased absorption of fat-soluble vitamins, flatulence, fecal incontinence
Liraglutide	GLP-1 agonist	Decreases appetite	3 mg/d SC	Nausea, vomiting, pancreatitis
Lorcaserin	5-HT _{2c} agonist	Decreases appetite	10 mg PO BID	Headache, nausea, dry mouth, dizziness, constipation
Naltrexone/ bupropion	Opioid antagonist + antidepressant	Unknown	32 mg/ 360 mg PO TID	Headache, nausea, dizziness, constipation
Phentermine	Sympathomimetic	Norepinephrine release in CNS	30–37.5 mg/d PO	Increased BP, HR; arrhythmias, insomnia, anxiety
Phentermine/ topiramate	Sympathomimetic + antiseizure agent	Norepinephrine release plus unknown mechanism	3.75–15 mg/ 23–92 mg PO	Insomnia, dizziness, nausea, paresthesia, dysgeusia

BID, twice daily; BP, blood pressure; CNS, central nervous system; GI, gastrointestinal; HR, heart rate; PO, by mouth; SC, subcutaneously; TID, three times daily.

Although obesity can be defined as excess adipose tissue, it is currently quantitated by means of the body mass index (BMI), calculated from

رغم أنّ السُّمنة يمكن تعريفها بزيادة أنسج الشحمي ، فإنها تُقَدَّر حالياً بمنسب كتلة الجسم المحسوب من :

BMI = weight (in kilograms)/height² (in meters).

Using this measure, the range of

normal BMI is defined as 18.5–24.9 ;

overweight, 25–29.9 ;

obese, 30–39.9 ; and

morbidly obese (ie, at very high risk) , ≥ 40 .

(**Underweight** persons, ie, those with a BMI < 18 , also have an increased [but smaller] risk of health problems.) K

Some extremely muscular individuals may have a BMI higher than 25 and no excess fat; however, the BMI scale generally correlates with the degree of obesity and with risk.

A second metric, which may be an even better predictor of cardiovascular risk, is the ratio of waist measurement to body height ;

cardiovascular risk is lower if this ratio is less than 0.5.

Experts consider drug therapy to be justified in patients with increased risk factors and a BMI ≥ 27 and in those without comorbidities but with a BMI ≥ 30 . K

قد يكون لبعض الأفراد المفرطي العضلات BMI أكبر من ٢٥ وليس لديهم دهن زائد ؛ على كل حال يتعلق هذا المنسب عموماً بدرجة السمنة وبالاختطار .

ثمة مقياس ثاني ، قد يكون مُتَوَقَّع أفضل للاختطار القلبي الوعائي ، هو نسبة قياس الخصر (محيط الخصر) مقسوماً على الطول :

يكون الاختطار القلبي الوعائي أقل إذا كانت هذه النسبة أقل من 0.5 .

يبرّر الخبراء المعالجة الدوائية وفق الآتي :

١. عند المرضى ذوي عوامل اختطار زائد مع منسب كتلة جسم أكبر أو يساوي ٢٧ ؛

٢. عند أولئك بدون أمراض مشاركة إذا كان منسب كتلة الجسم عندهم أكبر أو يساوي ٣٠ .

A. Serotonin agonists

The first serotonin agonists used for weight loss, *fenfluramine* and *dexfenfluramine*, were withdrawn following an increase in potentially fatal adverse effects, including valvulopathy. Valvulopathy, which may lead to pulmonary hypertension, is linked to 5-HT_{2B} receptors. *Lorcaserin* [lor-KAS-er-in] is a serotonin agonist with selectivity for the 5-HT_{2C} serotonin receptor. In contrast to many other weight-loss drugs, it is used for chronic weight management.

أ. **ناهضات السيروتونين** : جرى سحب الـ *fenfluramine* والـ *dexfenfluramine* ، أول ناهضين للسيروتونين مستعملين لتنقيص الوزن ، بعد زيادة التأثيرات الضائرة المهددة للحياة ، متضمنةً **اعتلال الصِّمام** . اعتلال الصِّمام ، الذي قد يؤدي إلى فرط الضغط الرئوي ، يتعلق بالمستقبلات **5-HT_{2B}** .

الـ **Lorcaserin** ناهض للسيروتونين انتقائي على مستقبلات السيروتونين **5-HT_{2C}** . بخلاف الكثير من الأدوية المنقصة-للوزن ، يُستعمل للمعالجة المزمنة للوزن .

- 1. Mechanism of action:** *Lorcaserin selectively activates 5-HT_{2C} receptors, which are almost exclusively found in the central nervous system. This activation, in turn, stimulates pro-opiomelanocortin (POMC) neurons, which activate melanocortin receptors, thereby causing a decrease in appetite (Figure 39.12). If a patient does not lose at least 5% of their body weight after 12 weeks of use, the drug should be discontinued.*
- 2. Pharmacokinetics:** *Lorcaserin is extensively metabolized in the liver to two inactive metabolites that are then eliminated in the urine. Lorcaserin has not been studied for use in severe hepatic impairment and is not recommended in severe renal impairment.*

١. آلية الفعل : الـ **Lorcaserin** ينشط انتقائياً المستقبلات 5-HT_{2C} ، الموجودة استثنائياً تقريباً في الـ CNS . ينبه هذا التنشيط بدوره عصبونات طليعة-الكورتين الميلانيني الأفيوني (pro-opiomelanocortin) ، التي تنشط مستقبلات الكورتين الميلانيني ، وبالتالي تسبب نقصاً في الشهية (الشكل ٣٩ ١٢) . ينبغي التوقف عن تناول هذا الدواء إذا لم يفقد المريض على الأقل ٥% من وزنه بعد ١٢ أسبوع من استعماله .

٢. الحرائك الدوائية : يُستقلب الـ Lorcaserin في الكبد إلى مستقلبين غير فعالين يُطرحان في البول . لا يوصى به في الإختلال الكلوي الشديد ..

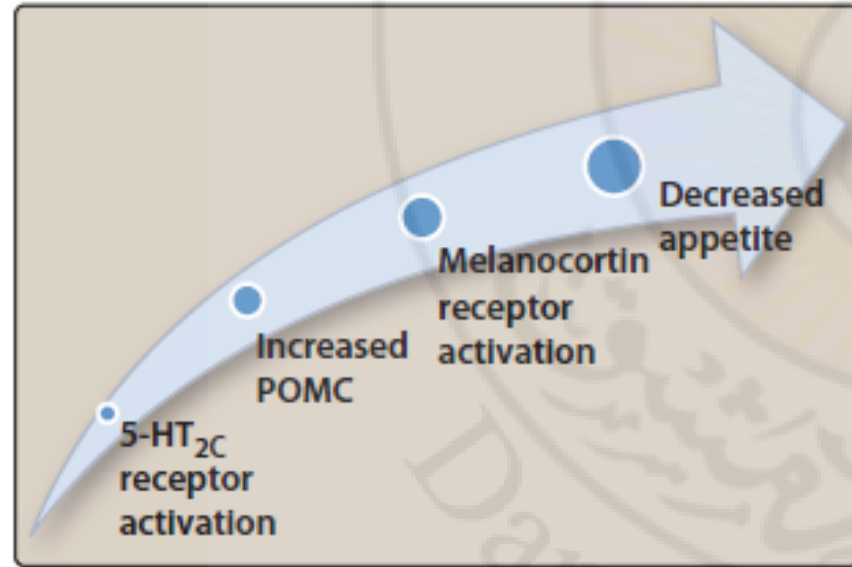


Figure 39.12

Lorcaserin mechanism of action.

POMC = pro-opiomelanocortin.

3. Adverse effects: The most common adverse effects observed with *lorcaserin* are *nausea, headache, dry mouth, dizziness, constipation, and lethargy*. Although rare, mood changes and suicidal ideation can occur. The development of life-threatening serotonin syndrome or neuroleptic malignant syndrome has been reported with the use of serotonin agonists. Therefore, patients should be monitored for the emergence of these conditions while on *lorcaserin*. *Because of the increased risk of serotonin syndrome, concomitant use of lorcaserin with selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, MAOIs, or other serotonergic drugs should be avoided.* As mentioned in the preceding text, valvulopathy has been associated with the use of 5-HT_{2B} receptor agonists. Although the incidence of valvulopathy was not significantly increased in studies of *lorcaserin* (5HT_{2c} receptor agonist), patients should still be monitored for the development of this condition. For that reason, individuals with a history of heart failure should use this agent with caution.

٣. **التأثيرات الضائرة :** يشيع الغثيان والصداع وجفاف الفم والدوخة والإمساك والنّوam . تَنَدّر تبدلات المزاج **وأفْتِكَار الانتحار** . يجري التبليغ عن تطور متلازمة السيروتونين المهددة للحياة أو متلازمة مضادّات الذهان الخبيثة مع استعمال ناهضات السيروتونين . لهذا ، ينبغي مراقبة المرضى وظهور هذه الحالات . ينبغي تجنب مُصاحبة استعمال الـ lorcaserin مع الـ SSRIs والـ SNRIs والـ MAOIs وغيرها من الأدوية السيروتونينية بسبب زيادة اختطار متلازمة السيروتونين .

كما نُؤهِ سابقاً ، يترباط اعتلال الصمّام مع استعمال ناهضات المستقبلات 5-HT_{2B} . رغم أنّ الـ lorcaserin ناهض للمستقبلات 5HT_{2c} ، ينبغي المراقبة من أجل تطور هذه

Serotonin Syndrome and Similar Syndromes

Excess synaptic serotonin causes a serious, potentially fatal syndrome that is diagnosed on the basis of a history of administration of a serotonergic drug within recent weeks and physical findings. It has some characteristics in common with neuroleptic malignant syndrome (NMS) and malignant hyperthermia (MH), but its pathophysiology and management are quite different (Table 16–4).

As suggested by the drugs that precipitate it, serotonin syndrome occurs when overdose with a single drug, or concurrent use of several drugs, results in excess serotonergic activity in the central nervous system. It is predictable and not idiosyncratic, but milder forms may easily be misdiagnosed. In experimental

animal models, many of the signs of the syndrome can be reversed by administration of 5-HT₂ antagonists; however, other 5-HT receptors may be involved as well. Dantrolene is of no value, unlike the treatment of MH.

NMS is idiosyncratic rather than predictable and appears to be associated with hypersensitivity to the parkinsonism-inducing effects of D₂-blocking antipsychotics in certain individuals. MH is associated with a genetic defect in the RyR1 calcium channel of skeletal muscle sarcoplasmic reticulum that permits uncontrolled calcium release from the sarcoplasmic reticulum when precipitating drugs are given (see Chapter 27).

TABLE 16–4 Characteristics of serotonin syndrome and other hyperthermic syndromes.

Syndrome	Precipitating Drugs	Clinical Presentation	Therapy ¹
Serotonin syndrome	SSRIs, second-generation antidepressants, MAOIs, linezolid, tramadol, meperidine, fentanyl, ondansetron, sumatriptan, MDMA, LSD, St. John’s wort, ginseng	Hypertension, hyperreflexia, tremor, clonus, hyperthermia, hyperactive bowel sounds, diarrhea, mydriasis, agitation, coma; onset within hours	Sedation (benzodiazepines), paralysis, intubation, and ventilation; consider 5-HT ₂ block with cyproheptadine or chlorpromazine
Neuroleptic malignant syndrome	D ₂ -blocking antipsychotics	Acute severe parkinsonism; hypertension, hyperthermia, normal or reduced bowel sounds; onset over 1–3 days	Diphenhydramine (parenteral), cooling if temperature is very high, sedation with benzodiazepines
Malignant hyperthermia	Volatile anesthetics, succinylcholine	Hyperthermia, muscle rigidity, hypertension, tachycardia; onset within minutes	Dantrolene , cooling

¹Precipitating drugs should be discontinued immediately. First-line therapy is in boldface font.

LSD, lysergic acid diethylamide, MAOIs, monoamine oxidase inhibitors; MDMA, methylenedioxy-methamphetamine (ecstasy); SSRIs, selective serotonin reuptake inhibitors.

B. Other agents for obesity

In addition to *lorcaserin*, several agents with varying mechanisms of action are available for weight loss and the management of obesity.

- 1. Appetite suppressants:** *Phentermine* [FEN-ter-meen] and *diethylpropion* [dye-eth-ill-PROE-pee-on] are appetite suppressants. They exert pharmacologic action by increasing the release of norepinephrine and dopamine from the nerve terminals and by inhibiting reuptake of these neurotransmitters, thereby increasing levels of neurotransmitters in the brain. The increase in norepinephrine signals a “fight-or-flight” response by the body, which, in turn, decreases appetite.

ب. الأدوية الإضافية للسمنة : ثمة أدوية إضافية ذات آليات فعل متغايرة متوافرة لإنقاص الوزن ومعالجة السمنة .

١. كابِتات الشهية : الـ **Phentermine** والـ **diethylpropion** كابِتِي شهية بإطلاقهما الـ N.Epi والـ DA من النهايات العصبية وتنشيط استرداد هذين الناقلين العصبيين ، فيزيدان مستوياتهما في الدماغ . الزيادة في الـ N.Epi تُشعر استجابة (المواجهة أو الجري) في الجسم ، التي بدورها تُنقص الشهية .

Tolerance to the weight loss effect of these agents develops within weeks, and weight loss typically plateaus. An increase in the dosage generally does not result in further weight loss, and discontinuation of the drug is usually recommended once the plateau is reached. The anorexiant is classified as a controlled substance due to the potential for dependence or abuse. Dry mouth, headache, insomnia, and constipation are common adverse effects. Heart rate and blood pressure may be increased with these agents. Therefore, these drugs should be avoided in patients with a history of uncontrolled hypertension, cardiovascular disease, arrhythmias, heart failure, or stroke. Concomitant use of anorexiant with monoamine oxidase inhibitors (MAOIs) or other sympathomimetics should be avoided.

يتطور التحمل للتأثير المنقص للوزن لهذه الأدوية خلال أسابيع ، فيتسطح منحنى تنقيص الوزن . زيادة الجرعات لا تؤدي إلى نقص إضافي للوزن ، ويوصى عادةً بتوقيف الدواء عند بلوغ التسطح .

تصنف المقمّهات بأنها مواد مُضَبَّطَة بسبب احتماليّة الاعتماد أو المعاقرة .

يُعدّ جفاف الفم والصداع والأرق والإمساك تأثيرات ضائرة شائعة . قد تزداد سرعة القلب وضغط الدم مع هذه الأدوية . لهذا ، ينبغي تجنب هذه الأدوية عند مرضى فرط الضغط غير المضبوط والداء القلبي الوعائي واضطرابات النظم وفشل القلب والسكتة .

ينبغي تجنب استعمال المقمّهات مع MAOIs وغيرها من محاكيّات الودي .

2. Lipase inhibitor: Orlistat [OR-lih-stat] is the only agent in a class of antiobesity drugs known as lipase inhibitors. It is indicated for weight loss or weight maintenance. Orlistat is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Administration of orlistat decreases fat absorption by about 30%. The loss of calories from decreased absorption of fat is the main cause of weight loss. Figure 39.13 shows the effects of orlistat treatment.

٢. **مثبطات الليباز** : الـ **Orlistat** : يوصى به لتتقيص الوزن أو المحافظة عليه . هو إستر حامض البينتانويك الذي يثبط إنزيمات الليباز المعدية والبنكرياسية ، وبالتالي ينقص تكسّر الدهن التغذوي إلى جزيئات أصغر يمكن امتصاصها .

إعطاء الأريلستات ينقص امتصاص الدهن حوالي ٣٠% . يُعدّ فقد السُعرات من تتقيص امتصاص الدهن السبب الرئيس لتتقيص الوزن . يظهر الشكل ٣٩ . ١٣ تأثيرات المعالجة بالأريلستات .

The clinical utility of orlistat is limited by gastrointestinal adverse effects, including oily spotting, flatulence with discharge, fecal urgency, and increased defecation. These effects may be minimized through a low-fat diet and the use of concomitant cholestyramine. Orlistat is contraindicated in pregnancy and in patients with chronic malabsorption syndrome or cholestasis. The drug also interferes with the absorption of fat-soluble vitamins and β -carotene. Patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K and β -carotene. Orlistat can also interfere with the absorption of other medications, such as amiodarone, cyclosporine, and levothyroxine, and clinical response to these medications should be monitored if orlistat is initiated. The dose of levothyroxine should be separated from orlistat by at least 4 hours.

الاستعمال السريري للأرليستات مُقَيَّد بالتأثيرات الضائرة الهضمية ، متضمنة التَّبَقُّع الزيتي والغازات مع إلْحَاحُ التَّغَوُّطِ .. يمكن تصغير هذه التأثيرات عبر النظام التغذوي القليل الدهن واستعمال الكوليستيرامين معه .

الأرليستات ممنوع الاستعمال أثناء الحمل ومرضى متلازمة سوء الامتصاص المزمن والركود الصفراوي .

يتداخل هذا الدواء أيضاً مع امتصاص الفيتامينات الذوابة في الدهن والبيتا—كاروتين . ينبغي نصح المرضى أخذ مُكَمِّلات مُتَعَدِّدة الفيتامينات تحتوي على (A, D, E, and K and β -carotene) . يتداخل أيضاً مع امتصاص أدوية مثل amiodarone و cyclosporine و levothyroxine .. ينبغي مبادعة جرعة الليفوتيروكسين عن الأرليستات ٤ ساعات على الأقل .

- 3. Glucagon-like peptide-1 (GLP-1) receptor agonist:** *Liraglutide* is an injectable GLP-1 receptor agonist that is indicated for obesity. See Chapter 24 for a full discussion of GLP-1 receptor agonists.
- 4. Combination therapy:** The combination of *phentermine* and *topiramate* has been approved for long-term use in the treatment of obesity. Initial studies of the anticonvulsant *topiramate* observed weight loss in patients taking the medication. Because of the sedating effects of *topiramate*, the stimulant *phentermine* was added to counteract sedation and promote additional weight loss. If a patient does not achieve a 5% weight loss after 12 weeks on the highest dose of this medication, then it should be discontinued. It is also important to note that this medication should not be stopped abruptly as seizures may be precipitated.

٣. **ناهض مستقبلات الببتيد المشابه للغلوكاجون (GLP-1) :** الـ **Liraglutide** القابل للحقن الموصى به لمعالجة البدانة .. **يستدعي افْتِكَار الانتحار**

٤. **المعالجة التوليفية :** بُرِهِنَ توليف الـ **phentermine** والـ **topiramate** للاستعمال الطويل—الأمد في السمنة . إذ أظهر مضاد الاختلاج الـ **topiramate** إنقاصاً للوزن للمرضى المعالجين . وبسبب التأثيرات المهدئة للتوبيراميت ، أُضيف **الفنترمين** ليعارض التهدئة ويعزز نقصاً إضافياً للوزن .

إن لم يُنجز المريض نقصاً في الوزن قدره ٥% بعد ١٢ أسبوع بالجرعة الأكبر ينبغي إيقاف تناول التوليف . من المهم أيضاً ملاحظة أنه لا ينبغي إيقاف هذا الدواء فجأةً لأن النوبات قد تحدث .

Topiramate has been associated with birth defects including cleft palate, and, thus, the combination of *phentermine/topiramate* is *contraindicated* in pregnancy. *Bupropion* and *naltrexone* is another combination therapy approved for chronic weight management. Important characteristics of the medications for obesity are summarized in Figure 39.14. f

يترباط استعمال الـ Topiramate مع عيوب ولادية متضمنةً الحَنَكُ المَشَقُوق (فَلَحُ حَنَكِيّ) ، وبالتالي ممنوع استعمال التوليف phentermine/topiramate أثناء الحمل .
الـ **Bupropion** والـ **naltrexone** معالجة توليفية ثانية مُبرهنة للمعالجة المزمّنة للوزن . يستدعي افْتِكَار الانتحار .
المميزات المهمة للأدوية المعالجة للسمنة ملخصة في الشكل ٣٩ . ١٤ .

DRUG	TARGET	MECHANISM OF ACTION	PHARMACOKINETICS	ADVERSE EFFECTS
Bupropion + naltrexone	Bupropion: CNS—POMC neuron stimulation Naltrexone: CNS—blocks autoinhibitory feedback of the hypothalamic melanocortin system	Combination regulates the mesolimbic reward system and results in appetite suppression	Extensive metabolism through CYP2D6	Nausea, headache, dry mouth, dizziness, constipation, suicidal ideation
Liraglutide	GLP-1 receptor agonist	Slows gastric emptying and increases satiety	Excretion through the kidneys and metabolism in the liver	Nausea and vomiting, pancreatitis, hypoglycemia, acute gall bladder disease, elevated heart rate, suicidal ideation
Lorcaserin	CNS—5-HT _{2C} receptor agonist	Appetite suppression	Extensive metabolism in the liver	Nausea, headache, dry mouth, dizziness, constipation, suicidal ideation, lethargy
Orlistat	GI system—inhibits gastric and pancreatic lipase	Fat absorption decreased by ~30%, which decreases overall caloric intake	Minimal systemic absorption	GI symptoms such as oily spotting, flatulence, fecal urgency, and increased defecation
Phentermine	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion through the kidneys	Dry mouth, headache, insomnia, constipation Possible heart rate and blood pressure increases
Diethylpropion	CNS—increase in NE and dopamine release and reuptake inhibition	Appetite suppression	Excretion mainly through the kidneys	Dry mouth, headache, insomnia, constipation Possible heart rate and blood pressure increases
Phentermine + topiramate	Phentermine: CNS—increase in NE and dopamine release and reuptake inhibition Topiramate: CNS—increase in GABA	Appetite suppression and increased satiety	Excretion primarily through the kidneys with limited hepatic metabolism	Paresthesia, altered taste, dizziness, insomnia, dry mouth, constipation Contraindicated in pregnancy

CNS = central nervous system; GABA = γ -aminobutyric acid; GI = gastrointestinal; GLP = glucagon-like peptide; NE = norepinephrine; POMC = pro-opiomelanocortin.

Figure 39.14

Characteristics of the medications for obesity.

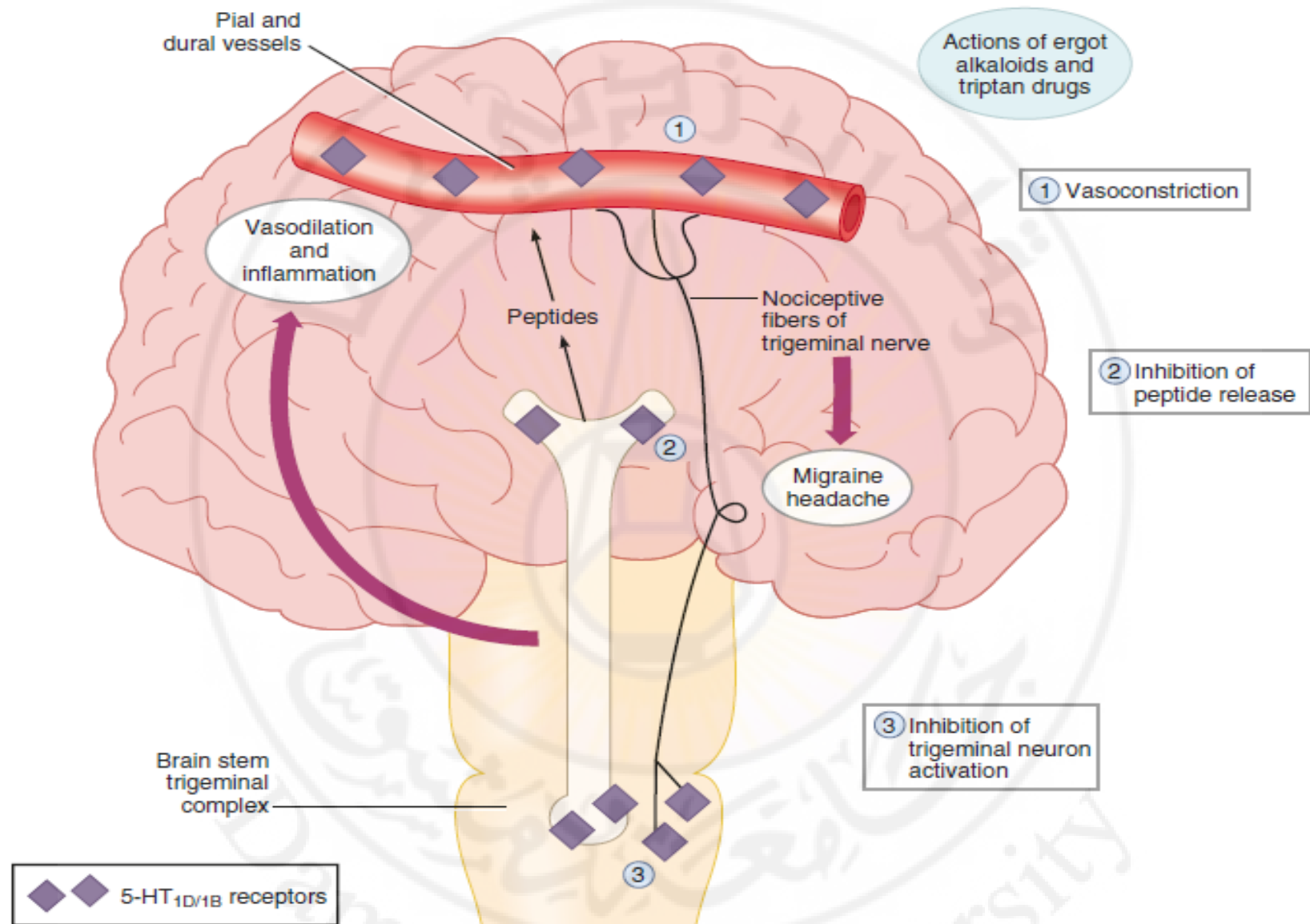


FIG. 29.1 Mechanisms of ergot alkaloids and triptan drugs used in the treatment of migraine headache disorder. Migraine attacks are thought to result from trigeminal neurovascular dysfunction. When neurons in the trigeminal complex release peptides such as substance P and calcitonin gene-related peptide (CGRP), this causes vasodilation and inflammation of pial and dural vessels. These events activate nociceptive trigeminal fibers and cause moderate to severe pain that is characteristic of migraine headaches. Ergot alkaloids and triptan drugs terminate the pain by activating serotonin 5-HT_{1B/1D} receptors at several sites: (1) They activate receptors on pial and dural vessels and thereby cause vasoconstriction. (2) They activate presynaptic receptors to inhibit the release of peptides and other mediators from trigeminal neurons. (3) They activate receptors in the brainstem, which is believed to inhibit the activation of trigeminal neurons responsible for migraine attacks. CGRP antagonists (not shown) are also effective in the treatment of migraine.

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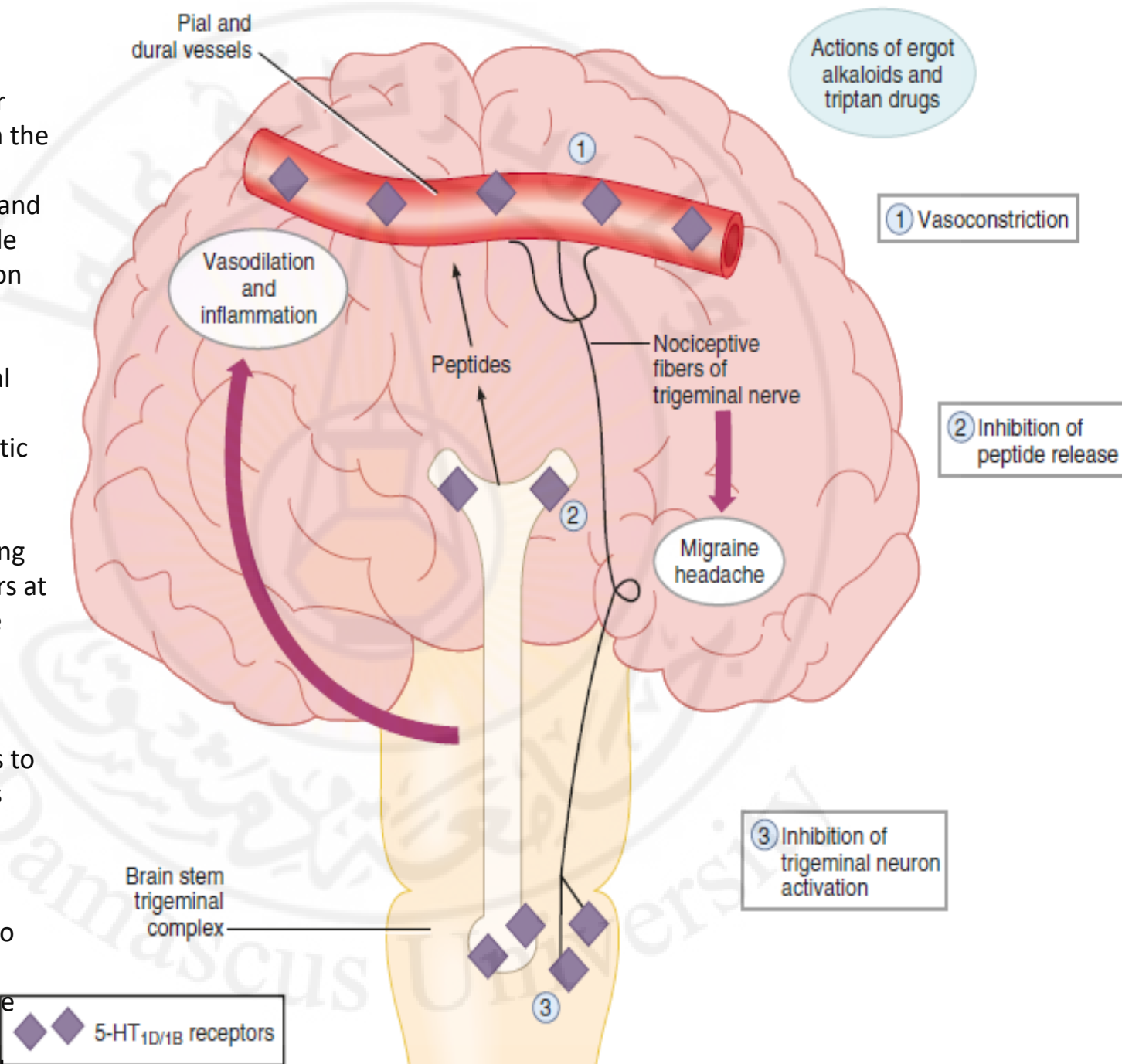
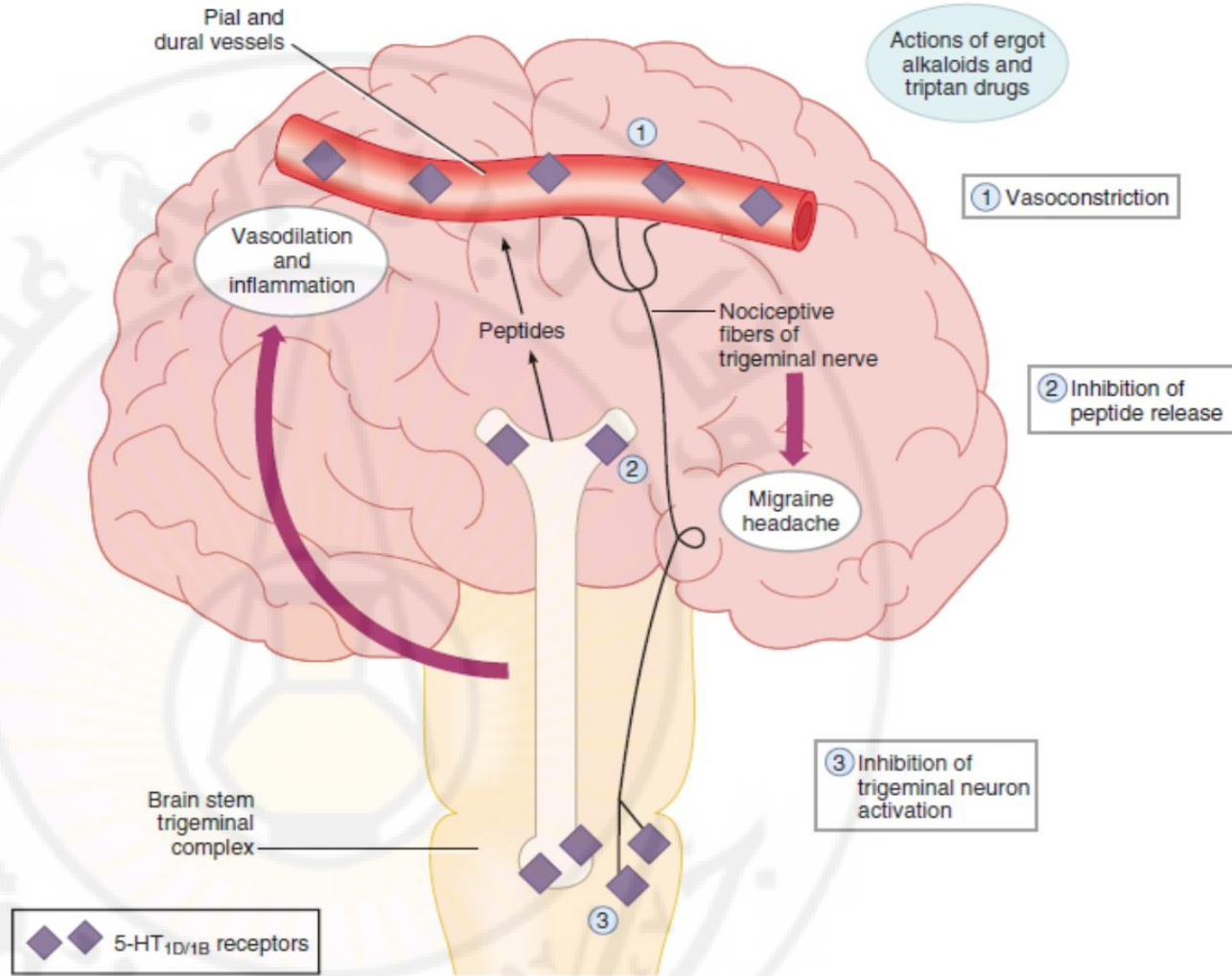


Fig. 29.1 Mechanisms of ergot alkaloids and triptan drugs used in the treatment of migraine headache disorder. Migraine attacks are thought to result from trigeminal neurovascular dysfunction. When neurons in the **trigeminal complex** release peptides such as substance P and calcitonin gene-related peptide (CGRP), this causes vasodilation and inflammation of pial and dural vessels. These events activate nociceptive trigeminal fibers and cause moderate to severe pain that is characteristic of migraine headaches. Ergot alkaloids and triptan drugs terminate the pain by activating serotonin 5-HT_{1B}/1D receptors at several sites: (1) They activate receptors on pial and dural vessels and thereby cause vasoconstriction. (2) They activate presynaptic receptors to inhibit the release of peptides and other mediators from trigeminal neurons. (3) They activate receptors in the brainstem, which is believed to inhibit the activation of trigeminal neurons responsible for migraine attacks. CGRP antagonists (not shown) are also effective in the treatment of migraine.



شكل ٢٩. ١. آليات قلوانيات الإرغوت والتريبتانات المستعملة في معالجة اضطراب صداع الشقيقة . تنجم هجمات الشقيقة عن خلل وعائي عصبي لمثلث التوائم . عندما تُطلق عصبونات مثلث التوائم ببتيديات مثل المادة P والببتيد المتعلق—بمورثة الكالسيثونين CGRP ، يسبب هذا توسيع أوعية والتهاب الأوعية الحنونة والجافية . تُنشِط هذه الأحداث ألياف مثلث التوائم المستقبلية للأذية وتسبب ألم متوسط إلى شديد مُميّز لصداع الشقيقة . **تُنهى قلوانيات الإرغوت والتريبتانات الألم بتنشيطها المستقبلات 5-HT_{1B}/1D عند مقرّات : (١) تُنشِط مستقبلات على الأوعية الحنونة والجافية فتضيق الأوعية . (٢) تُنشِط مستقبلات قبل المشبك لتنشط إطلاق ببتيديات من عصبونات مثلث التوائم . (٣) تُنشِط مستقبلات في جذع الدماغ ، ممّا يثبط تنشيط عصبونات مثلث التوائم المسؤولة عن هجمات الشقيقة .** مناهضات الـ CGRP (غير مرئية هنا) فعّالة أيضاً في معالجة الشقيقة .

TABLE 29.1 Classification and Pharmacologic Management of Headache Disorders

CLASSIFICATION	CHARACTERISTICS	DRUGS FOR PREVENTING HEADACHES	DRUGS FOR ABORTING HEADACHES
Primary Headaches			
Cluster headaches	Severe, unilateral, retro-orbital; clustered over time	Lithium and verapamil	DHE, ergotamine, glucocorticoids, lidocaine, oxygen, and sumatriptan
Migraine headaches	Moderate or severe, often unilateral, usually pulsatile; occur with or without aura	β -adrenoceptor antagonists, anticonvulsants, antidepressants, calcium channel blockers, NSAIDs, and serotonin 5-HT ₂ receptor antagonists CGRP drugs	DHE, ergotamine, isometheptene, NSAIDs, tramadol, and triptans ^a
Tension headaches	Mild or moderate, bilateral, non-pulsatile; exert bandlike pressure	Amitriptyline	Muscle relaxants and NSAIDs
Secondary Headaches			
	Characteristics vary, depending on the underlying cause ^b	None	None (treat underlying disorder)

DHE, Dihydroergotamine; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aTriptans include naratriptan, rizatriptan, sumatriptan, and zolmitriptan.

^bExamples of causes are hemorrhage, infection, neuropathy, stroke, and tumor.

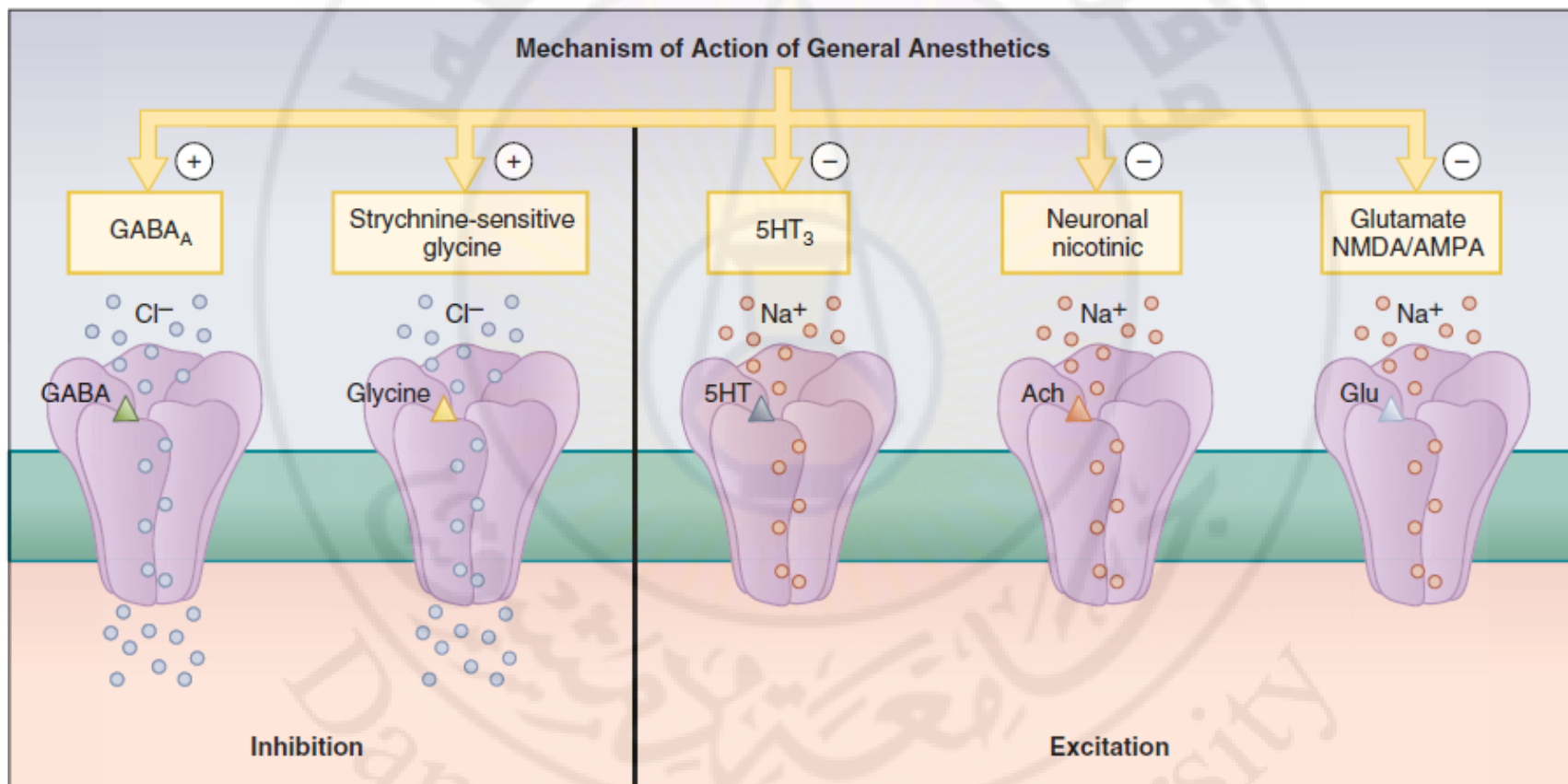


FIG. 21.3 Mechanism of action of general anesthetics. Like antiepileptic drugs, general anesthetics work at a variety of target sites. General anesthetics increase GABA and glycine inhibitory effects and decrease excitatory effects by blocking serotonergic, nicotinic, and glutaminergic neurotransmission.

5. A 35-year-old woman with a history of migraine reports to her physician that the last time she used her medicine to stop an acute attack, she felt numbness and tingling نُخز in her extremities and blanching تبييض and cyanosis of her fingers. Which one of the following medications did she take?

(A) butorphanol (B) sumatriptan (C) dihydroergotamine (D) tramadol (E) naproxen

5. **The answer is C:** dihydroergotamine. DHE is an ergot alkaloid, and these agents are known to cause vasoconstriction and paresthesia in the extremities, especially at high doses. Answer A, **butorphanol**, is an opioid analgesic and not associated with the woman's symptoms. Answer B, **sumatriptan**, is a triptan also used for acute attacks and can cause vasoconstriction, but not as commonly as observed with DHE. Answer D, **tramadol**, is a **dual action** opioid-antidepressant agent, helpful in the acute treatment of migraine but not producing the patient's constellation of adverse effects. Answer E, **naproxen**, is an NSAID agent that can cause increased release of norepinephrine and possible vasoconstriction, but it does not produce these effects as commonly as DHE

. 39.8 A 27-year-old married woman is asking about treatment options for obesity. She recently stopped taking her birth control medications, as she felt they were contributing to her weight gain. Which medication should be avoided in this patient?

A. Phentermine/topiramate B. Orlistat C. Diethylpropion D. Lorcaserin

Correct answer = A. Although patients should not take any medications to lose weight during pregnancy, the topiramate component of this medication is especially dangerous, since it can be teratogenic. Because this patient stopped her birth control medicine, she is at risk of becoming pregnant and developing birth defects while also on this medication.

39.6 A 29-year-old woman complains of migraine headaches associated with early onset vomiting. Currently, she uses ibuprofen as needed for her migraines, but it is not very effective. Which triptan would be ideal for this patient?

A. Naratriptan B. Zolmitriptan C. Frovatriptan D. Almotriptan

Correct answer = B. Although all of the triptans listed are available as an oral tablet, this patient suffers from **vomiting** associated with her migraines. **Zolmitriptan and sumatriptan are available as an intranasal dosage form, which would be ideal for this patient.**

Difficulty level: Medium.

14. A 43-year-old man with a long history of exertional angina was recently diagnosed with migraine. Which of the following antimigraine drugs would be contraindicated in this patient?

A. Aspirin B. Acetaminophen C. Sumatriptan D. Ibuprofen E. Propranolol

CLASSIFICATION OF DRUGS FOR HEADACHE DISORDERS

Drugs for Migraine Headaches

Drugs for migraine prevention

Antiepileptic drugs and antidepressants

- Valproic acid (DEPAKENE)
- Fluoxetine (PROZAC) also amitriptyline (ELAVIL)
- Phenelzine (NARDIL)

Nonsteroidal anti-inflammatory drugs

- Naproxen (NAPROSYN, ALEVE)
- Fenoprofen (NALFON)^a

Beta (β)-adrenoceptor antagonists

- Propranolol (INDERAL)
- Timolol (TIMOLIDE)

Calcium channel blockers

- Verapamil (CALAN)
- Nimodipine (NIMOTOP)

CGRP-targeted monoclonal antibodies

- Galcanezumab (EMGALITY)
- Erenumab (AIMOVIG)^b

Other agents for preventing migraine

- Gabapentin (NEURONTIN)
- Botulinum toxin A (BOTOX)

Drugs for migraine termination

Serotonin 5-HT receptor agonists

- Dihydroergotamine (DHE, MIGRANAL)^c
- Sumatriptan (IMITREX)^d
- Lasmiditan (REYVOW)

CGRP receptor antagonists

- Rimegepant (NURTEC)
- Ubrogepant (UBRELVY)

Other agents for migraine termination

- Isometheptene (MIDRID)
- Tramadol (ULTRAM)
- Butorphanol (STADOL NS)
- Naproxen (NAPROSYN, ALEVE)^e
- Acetaminophen with codeine (TYLENOL #3)^f
- Prochlorperazine (COMPAZINE)

Drugs for cluster and tension headaches

- See [Table 29.1](#).

^a Also flurbiprofen (ANSAL), ketoprofen (ORUDIS), and mefenamic acid (PONSTEL).

^b Also fremanezumab (AJOVY), and eptinezumab (VYEPTI).

^c Also ergotamine (ERGOMAR).

^d Also naratriptan (AMERGE), zolmitriptan (ZOMIG), rizatriptan (MAXALT), frovatriptan (FROVA), almotriptan (AXERT), and eletriptan (RELPAK); sumatriptan is also formulated as a nasal spray (ONZETRA XSAL) and as a transdermal iontophoresis patch (ZECURITY).

^e Also flurbiprofen (ANSAL), ketoprofen (ORUDIS), and mefenamic acid (PONSTEL).

^f Also acetaminophen with caffeine, butalbital, and codeine (FIORICET).

Fig. 29.1 Mechanisms of ergot alkaloids and triptan drugs used in the treatment of migraine headache disorder. Migraine attacks are thought to result

from trigeminal neurovascular dysfunction. When neurons in the trigeminal complex release peptides such as substance P and calcitonin gene-related peptide (CGRP), this causes vasodilation and inflammation of pial and dural vessels. These events activate nociceptive trigeminal fibers and cause moderate to

severe pain that is characteristic of migraine headaches. Ergot alkaloids and triptan drugs terminate the pain by activating serotonin 5-HT_{1B/1D} receptors at several sites: (1) They activate receptors on pial and dural vessels and thereby cause vasoconstriction. (2) They activate presynaptic receptors to inhibit the

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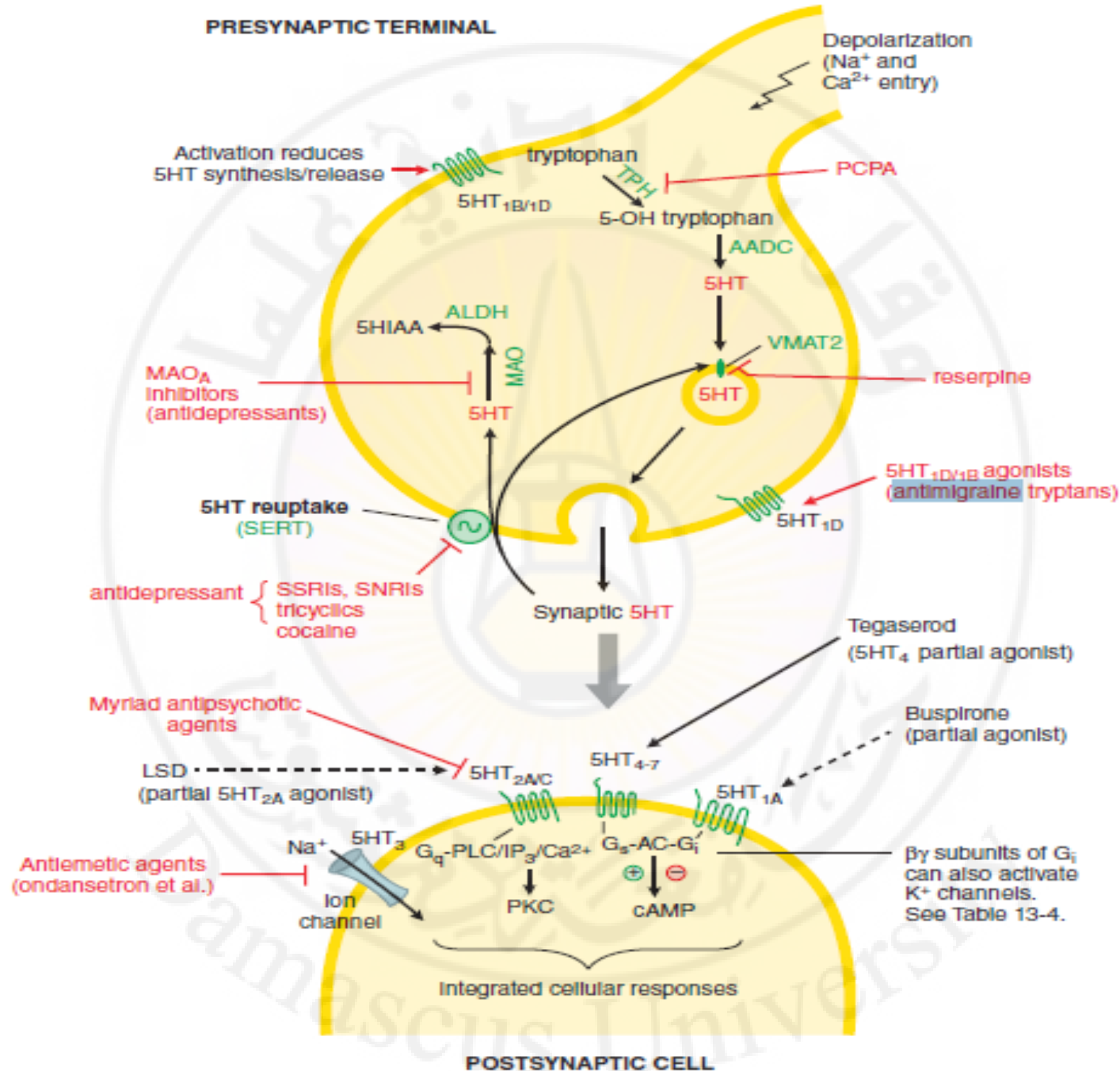


Figure 13-4 A serotonergic synapse. Presynaptic and postsynaptic molecular entities involved in the synthesis, release, signaling, and reuptake of serotonin are shown. MAO is shown extracellularly and in mitochondria within serotonergic nerve terminals.

K19. C. Postpartum Hemorrhage

The uterus at term is extremely sensitive to the stimulant action of ergot, and even moderate doses produce a prolonged and powerful spasm of the muscle quite unlike natural labor. Therefore, ergot derivatives should be used only for control of postpartum uterine bleeding and should never be given before delivery. Oxytocin is the preferred agent for control of postpartum hemorrhage, but if this peptide agent is ineffective, ergonovine maleate, 0.2 mg given intramuscularly, can be tried. It is usually effective within 1–5 minutes and is less toxic than other ergot derivatives for this application. It is given at the time of delivery of the placenta or immediately afterward if bleeding is significant.

Use of Ergot Alkaloids in Postpartum Hemorrhage

All of the natural ergot alkaloids markedly increase the motor activity of the uterus; however, ergonovine and its semisynthetic derivative methylergonovine have primarily been used as uterine-stimulating agents in obstetrics. As the dose is increased, contractions become more forceful and prolonged, resting tone is dramatically increased, and sustained contracture can result. This characteristic is compatible with their use postpartum or after abortion to control bleeding and maintain uterine contraction. Oxytocin (see Chapter 44) is now the more prevalent agent in controlling postpartum hemorrhage.

ببتيد مرتبط بجين الكالسيتونين (Calcitonin gene-related peptide))

الوصف

الببتيد المرتبط بجين الكالسيتونين هو ببتيدي ينتمي لعائلة الكالسيتونين ويوجد عند الإنسان على نوعين هما: ألفا: ويتكون من ببتيدي من ٣٧ حمض أميني ويوجد في الصبغي ١١. و

بيتا: ويتكون من ٣ أحماض أمينية عند الإنسان. [ويكيبيديا](#)

-- ماذا يعمل ؟

يطلق من محاور مثلث التوائم إلى أوعية الدم حيث يُكْتَفَف في توسيع الأوعية وتنشيط الأعصاب ثلاثية التوائم . الأدوية التي تستهدفه تعالج الشقيقة .

=

كيف يسبب شقيقة ؟

إحدى النظريات أنه يحسس الأعصاب المحيطية ، التي بدورها ترسل إشارات إلى الـ CNS تحفز الألم والحساسية للمنبهات الحسية المترابطة مع الألم . قد يحدث هذا لأنه عندما يرتبط الـ CGRP بمستقبلاته ، فإنه يُحَسِّس الأعصاب عبر زيادة معدل/سرعة تأججها ١٠ / ٢٨ . ٢٠٢١/

What does the calcitonin gene related peptide do?

CGRP is released from trigeminal axons onto blood vessels in the meninges where it is involved in vasodilation and activation of trigeminal neurons. CGRP targeting drugs likely act at this site to treat migraine

=

How does CGRP cause migraines?

One theory is that CGRP sensitizes peripheral nerves, which in turn send signals to the central nervous system (CNS) that trigger the pain and sensitivity to sensory stimuli associated with migraine. This may occur because when CGRP binds to its receptor, it sensitizes the nerves by increasing their rate of firing. 28/10/2021

What is the mechanism of action of CGRP?

The adenylate cyclase pathway mediates CGRP's vasodilatory action. CGRP contributes to neurogenic inflammation by activating the release of neurokinin A and substance P, which leads to plasma extravasation, and by interacting with **glial** and mast cells to release inflammatory agents. 03/03/2023

= What is the calcitonin gene related peptide neurons?

CGRP is produced in both peripheral and central neurons. It is a potent peptide vasodilator and can function in the transmission of **nociception**. In the spinal cord, the function and expression of CGRP may differ depending on the location of synthesis.

ماهي آلية فعل الـ CGRP ؟

يتواسط طريق الأدينيل سيكلاز الفعل الموسع للأوعية للـ CGRP .

يساهم الـ CGRP في التهاب الأعصاب عبر تنشيط إطلاق الكاينين العصبي—A والمادة P ، مما يؤدي إلى تسرب البلازما ،

وعبر التأثير مع **الدبق** والخلايا البدنية لإطلاق عوامل التهابية ٣ / ٣ / ٢٠٢٣ .

=

ما هي عصبونات الـ CGRP ؟

يُنتج الـ CGRP في **العصبونات المحيطية والمركزية** . إنه ببتيد موسع قوي للأوعية ويعمل في نقل **حس الأذى** .

قد تختلف وظيفة وتعبير الـ CGRP في الحبل النخاعي اعتماداً على موضع التصنيع .

= How does CGRP cause vasodilation?

Using a HEK293 cell line, it was shown that CGRP exhibits biased agonism, favoring the Gas pathway and thus vasodilation (Weston et al., 2016) where CGRP triggers nitric oxide (NO) production in the endothelial cells, acting to relax the underlying vascular smooth muscles, while PKA activation in the vascular smooth ...19/09/2018

= Is CGRP a neurotransmitter?

CGRP is the main neurotransmitter of the nociceptive sensory c fibers, but is also present in other sensory nerve fibers i.e., type A and B medium-sized neurons.

كيف يسبب الـ CGRP توسيع الأوعية ؟

تبين باستخدام الخط الخلوي HEK293 أنّ الـ CGRP يظهر تضاد متحيّز/عجيب مفضلاً الطريق Gas وبالتالي توسيع الأوعية (٢٠١٦) حيث يحفز الـ CGRP إنتاج NO في الخلايا البطانية ، عاملاً على استرخاء العضلات الملساء الوعائية المستبطنة ، بينما تنشط الـ PKA في العضلات الملساء الوعائية (٢٠١٨)

=

هل الـ CGRP ناقل عصبي ؟

إنّه ناقل عصبي رئيس للألياف C الحسية لمستقبلات الأذى ، لكنه أيضاً موجود في ألياف عصبية حسية إضافية ، أي ، العصبونات المتوسطة الحجم من النمط A و B .

Lorcaserin (*Belviq*) Withdrawn From US Market Due to Cancer Risk

M. Alexander Otto

February 13, 2020

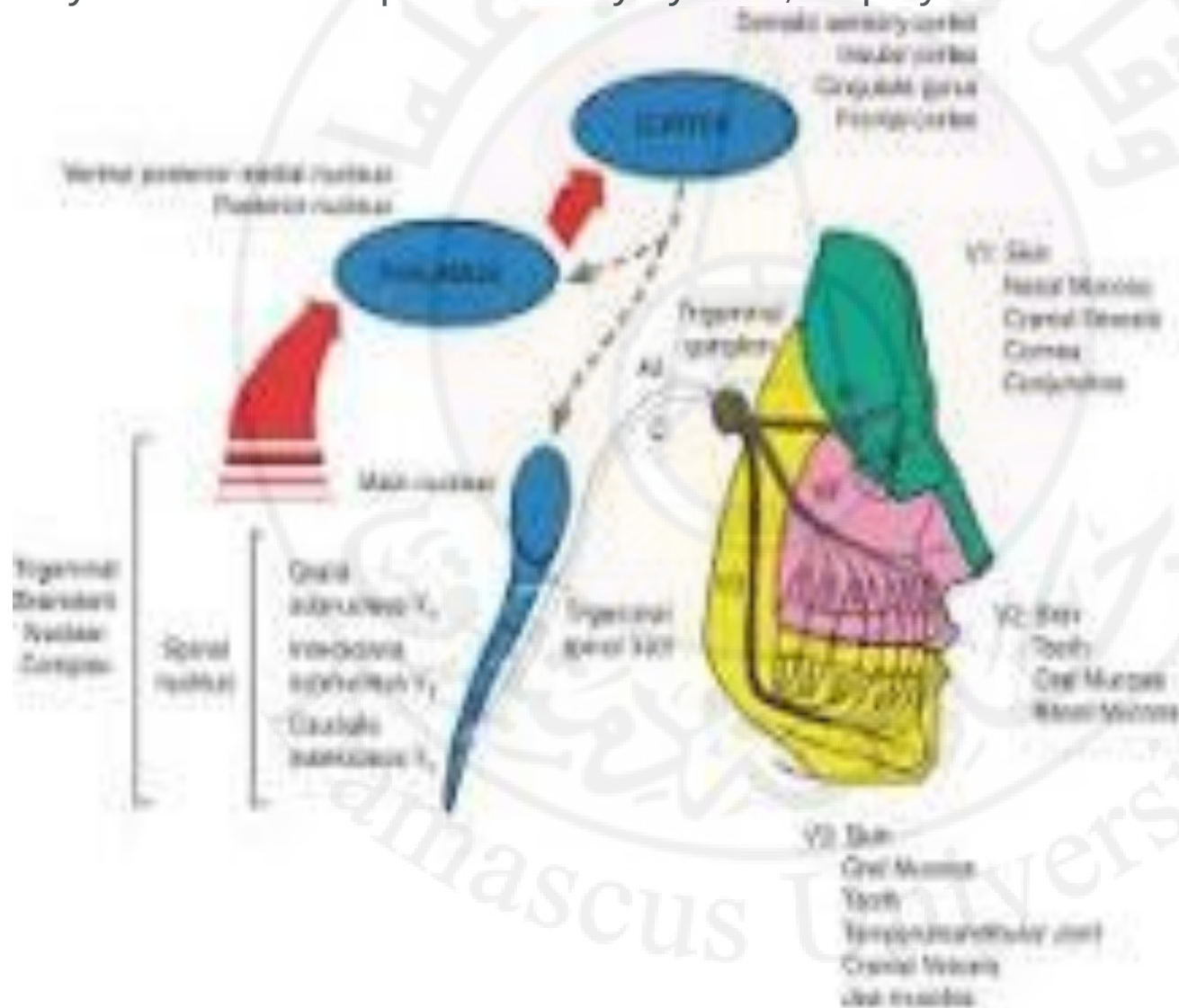
12

The Food and Drug Administration asked Eisai to voluntarily withdraw the weight-loss drug [lorcaserin](#) (Belviq and Belviq XR) on Feb. 13 after a post-marketing trial with more than 12,000 subjects revealed an increased occurrence of cancer.

In a Drug Safety Communication, the agency said "health care professionals should stop prescribing and dispensing lorcaserin to patients. Contact patients currently taking lorcaserin, inform them of the increased occurrence of cancer seen in the clinical trial, and ask them to stop taking the medicine

What is the trigeminal complex?

Definition. The trigeminal (V) brainstem nuclear complex (VBNC, Fig. 1) is the site of the first synapse of most V sensory primary afferents and of considerable sensory processing and modulation. Its anatomy and physiology, although generally similar to the spinal sensory system, display several differences.



كابتات المناعة Immunosuppressants

I. OVERVIEW.

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. The immune system is one of the most complex organ systems in the body, which can make it difficult to manipulate. Immunosuppressants are drugs that reduce the activation or efficacy of the immune system to treat certain conditions, such as autoimmune diseases, or to lower the body's ability to reject a transplanted organ. Autoimmune diseases can arise when the immune system mistakenly identifies an individual's own tissues as foreign and directs a destructive response against them. The goal of treatment for these diseases is to use drug therapy to stop this inappropriate and harmful process. In the case of organ transplantation, foreign tissue is purposely implanted into the recipient, but the goal remains the same—to use drug therapy to limit the damage inflicted by the immune system and potential rejection of the transplanted organ.

أولاً. النظرة العامة : كابتات المناعة أدوية تُنقص تنشيط أو نجاعة الجهاز المناعي بغرض معالجة حالات محددة ، مثل **أمراض المناعة الذاتية** ، أو بغرض **إنقاص قابلية الجسم رفض عضو مغروس/مزروع** .

تنشأ أمراض المناعة الذاتية عندما يَسْتَعْرِف جهاز المناعة نُسج ذاتية لفرد ما على نحو خاطئ أنها غريبة فيُوجّه استجابة تَحْريبيّة ضدها .
تتمثّل غاية معالجة هذه الأمراض باستعمال معالجة دوائية لإيقاف هذه العملية غير الملائمة والمؤذية .

يجري في حالة زرع الأعضاء غرس نسيج غريب في المُتلقّي ، لكنّ الغاية العلاجية بكابتات المناعة تظل نفسها—استعمال معالجة دوائية للحد من الضرر المُوجّه من جهاز المناعة ومنع إمكانية رفض العضو المزروع .

Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved surgical techniques and better tissue typing. Available drugs now more selectively inhibit rejection of transplanted tissues while preventing the patient from immunological compromise and prolonging the life of transplanted organs (Figure 38.1).

صار زرع الأعضاء والنسج (مثل الكلية والقلب ، أو نقي العظم) روتينياً بسبب الطرق الجراحية المطورة والتنميط (تَحْدِيدُ النَّمَطِ) الأفضل للنسيج .

تثبط الأدوية المتوافرة الآن على نحو انتقائي أكثر رفض النسيج المزروعة وتوقي المريض بنفس الوقت من نقص المناعة وتطيل حياة الأعضاء المزروعة (الشكل ٣٨ . ١) .

ANTIBODIES
Alemtuzumab
Antithymocyte globulins
Basiliximab
Rituximab
CALCINEURIN INHIBITORS
Cyclosporine
Tacrolimus
COSTIMULATION BLOCKER
Belatacept
mTOR INHIBITORS
Everolimus
Sirolimus
ANTIPROLIFERATIVES
Azathioprine
Mycophenolate mofetil
Mycophenolate sodium
ADRENOCORTICOIDS
Methylprednisolone
Prednisolone
Prednisone
OTHER
Bortezomib
Intravenous immunoglobulin

Figure 38.1

Immunosuppressant drugs.
mTOR = mammalian target of rapamycin. (For drug dosages, refer

Earlier drugs were nonselective, and patients frequently succumbed to infection due to suppression of both the antibody-mediated (humoral) and the cell-mediated arms of the immune system. Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed. Immunosuppressive drug regimens typically consist of two to four agents with different mechanisms of action that disrupt various levels of T-cell activation.

[Note: these agents may be used in the treatment of other disorders. For example, *cyclosporine* may be useful in the treatment of psoriasis, and various monoclonal antibodies have applications in a number of disorders, including rheumatoid arthritis, multiple sclerosis, Crohn's disease, and ulcerative colitis.]

كانت الأدوية الأولى غير انتقائية ، واستسلم المرضى كثيراً للعدوى بسبب كبت الجهاز المناعي المتواسط بالضدّ (الخلطي) والجهاز المناعي المتواسط بالخلايا .
يتمثل الأسلوب المبدئي للمعالجة الكابتة للمناعة اليوم بتعديل وظيفة الخلايا اللمفاوية باستعمال أدوية أو أضداد تهاجم بروتينات المناعة .

يجري عموماً تطبيق توليف من كاببات المناعة بجرعات صغيرة عادةً بسبب سمّياتها الشديدة عند استعمالها كمعالجة أحادية . إذ تتكون تدابير الأدوية الكابتة للمناعة نموذجياً من دوائين إلى أربعة ذات آليات فعل متفارقة تُعرقّل مستويات متنوعة من تنشيط الخلايا التائية

(ملاحظة : يمكن استعمال هذه الأدوية أيضاً في معالجة اضطرابات مثل استعمال السيكلوسبورين لمعالجة الصدفية والـ **MABs** في معالجة التهاب المفاصل الروماتويدي والتصلب المتعدد وداء كرون والتهاب القولون التقرحي..) .

The immune activation cascade can be described as a three-signal model (Figure 38.2). Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an **antigen-presenting cell (APC)**. Signal 1 alone is insufficient for T-cell activation and requires signal 2. Signal 2, also referred to as **co stimulation**, occurs when CD80 and CD86 (also known as B7.1 and B7.2) on the surface of APCs engage CD28 on T-cells. Both signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium–calcineurin pathway. These pathways trigger the production of cytokines such as interleukin (IL)-2. IL-2 then binds to the IL-2 receptor (also known as CD25) on the surface of other T-cells, thereby providing signal 3 activating the cell cycle via **mammalian target of rapamycin (mTOR)** and leading to T-cell proliferation.

يمكن وصف شلال تنشيط المناعة كطراز (نموذج) الإشعارات-الثلاث (الشكل ٣٨. ٢).
الإشعارة ١ تبدأ إثارة (تنبيه) الخلايا التائية عند مركب المستقبل **CD3** بواسطة **مُستَضِد** على **سطح خلية مُقدِّمة للمستضد (APC)**. لا تكفي الإشعارة ١ وحيدة لتنشيط الخلية التائية وتتطلب الإشعارة ٢.

تحدث **الإشعارة ٢**، المُشار إليها أيضاً أنها **تنبيه مشترك**، عندما تندمج الـ **CD80** والـ **CD86** (المعروفان أيضاً بالـ B7.1 والـ B7.2) على سطح الـ **APCs** بالـ **CD28** على سطح **الخلايا التائية**.

كلا الإشعارة ١ والإشعارة ٢ معاً تنشطان طرق داخل خلوية لنقل الإشعارة، أحدها طريق الكالسيوم—**كالسينيورين**. هذه الطرق تعزز إنتاج سيتوكينات مثل **IL-2**. ثم يرتبط هذا بمستقبلته **IL-2 receptor** (المعروفة أيضاً بـ **CD25**) على سطح **خلايا تائية** إضافية، موفراً بذلك **إشعارة ٣** منشطة لدورة الخلية عبر الهدف الثديي للـ **rapamycin (mTOR)** ومؤدية إلى تكاثر الخلايا التائية.

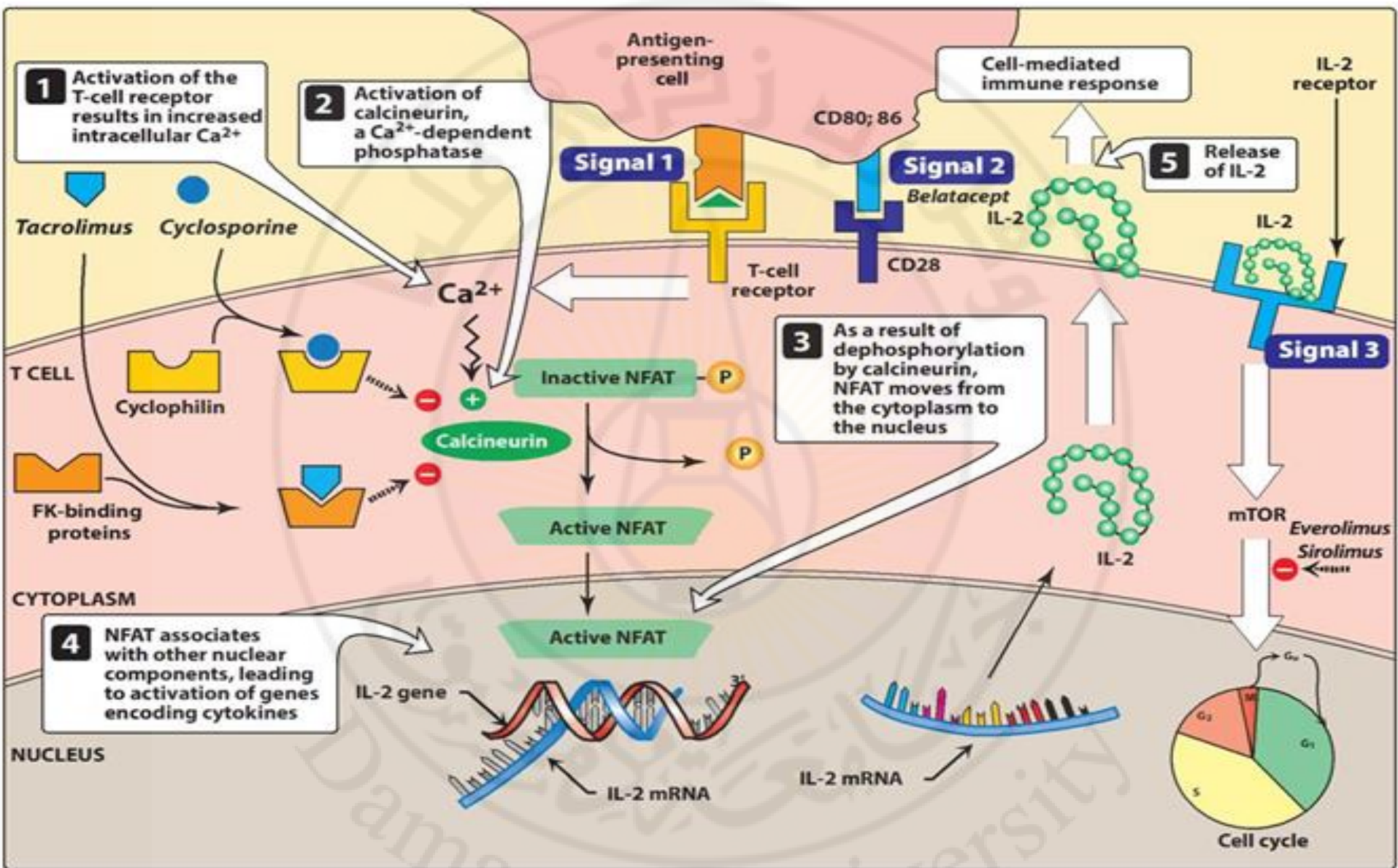


Figure 38.2

Mechanism of action of immunosuppressive agents. IL-2 = interleukin 2; mRNA = messenger RNA; mTOR = mammalian target of rapamycin; NFAT = nuclear factor of activated T.

Immunosuppressants can be broadly categorized by their place in therapy and their mechanism of action. More potent immunosuppressant drugs, such as monoclonal and polyclonal antibodies, are often used in **induction therapy**, which powerfully suppresses the immune system at the time of transplant, allowing the new organ to start functioning in the recipient and preventing early graft rejection. Maintenance immunosuppressant drugs, on the other hand, are less potent and provide long-term immunological protection for the transplanted organs, with lower risk of infection than with the induction drugs. As noted above, maintenance immunosuppressant medications are frequently combined in regimens to maintain adequate immunosuppression while minimizing adverse effects.

يمكن تصنيف كابطات المناعة بمنزلتها في المعالجة وآلية فعلها .

تستعمل كابطات المناعة الأكثر فاعلية ، مثل الأضداد وحيدة النسيلة والأضداد مُتَعَدِّدة النَّسَائِل ، عادةً في المعالجة الأولى (الأوليّة)/المُحَرِّضَة للاستجابة السريّة ، التي تكبت جهاز المناعة بقوّة عند الزرع ، سامحة للعضو الجديد البدء بوظيفته عند المُتلقّي وممانعةً رفض الطعم المبكر .

من جهة ثانية ، كابطات المناعة المُدَاوِمَة (الصيانيّة) أقل فاعلية وتوفر تحصين مناعي طويل-الأمد للأعضاء المزروعة ، مع اختطار أقل للعدوى مقارنةً مع الأدوية الأولى .

كثيراً ما تُؤلّف كابطات المناعة المداومة لتصغير التأثيرات الضائرة .

II. INDUCTION AND REJECTION IMMUNOSUPPRESSANT MEDICATIONS

The use of antibodies plays a central role in prolonging allograft survival. [Note: An allograft is transplant of an organ or tissue from one person to another who is not genetically identical.] Antibodies are prepared by immunization of either rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies or monoclonal antibodies) or by hybridoma technology (producing antigen-specific monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing cells with tumor cells. Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically useful amounts of the desired antibody.

ثانياً. أدوية المعالجة الأولى الكابتة للمناعة والرفض المناعي :

يطيل استعمال الأضداد بقاء الطَّعْمِ الخَيْفِيّ (زرع عضو أو نسيج من شخص لآخر غير متطابق وراثياً/جينياً) .

تُحَضَّرُ الأضداد بتمنيع **الأرانب** أو **الأحصنة** بخلايا لِمَفَانِيَّةٍ بشرية (إنتاج مزيج من أضداد مُتَعَدِّدُ النَّسَائِلِ أو وحيدة النسيلة) أو بتكنولوجيا الورم الهجين (إنتاج أضداد وحيدة النسيلة نوعية-للمستضد) .

تُنتَجُ الأورام الهجينة بدمج خلايا فأرية منتجة-للأضداد مع خلايا ورم . يجري انتقاء الخلايا الهجينة وتنسيلها ، ويمكن تحديد نوعية الأضداد للنسائل .

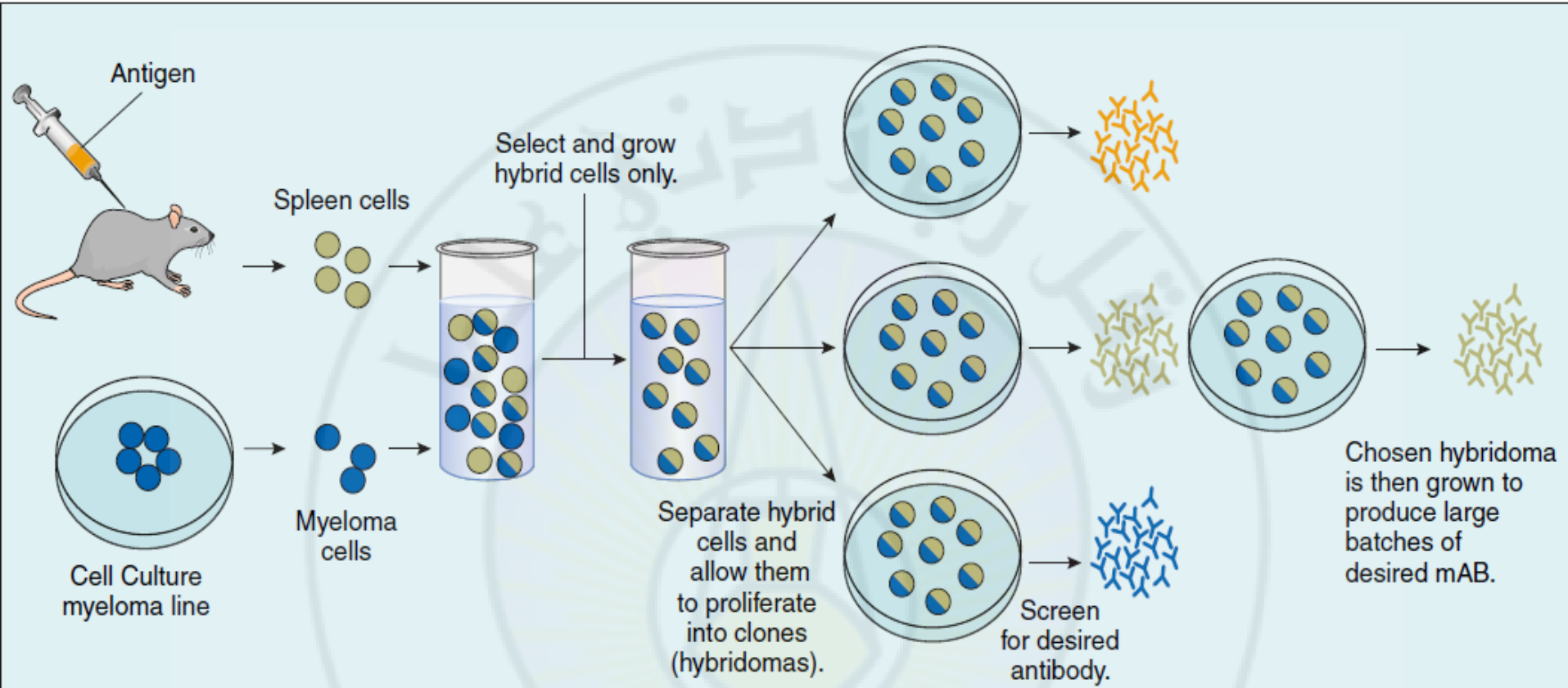


Fig. 46.1 Manufacture of monoclonal antibody drugs. The antigen of interest is injected into mice for development of targeted antibodies. After an immune response occurs, mice are sacrificed, and antibody-producing B cells are removed from the spleen. Immortalized myeloma cells are mixed with the mouse B cells and fused to create hybridoma cells. The hybridoma cells are selected for in the cell culture and unfused cells die off. The remaining cells are screened for those emitting the specific antibody to the antigen of interest. The selected antibody-producing hybridoma cells are grown in vast quantities and the culture media periodically drained off and the monoclonal antibodies purified and packaged for administration .

صناعة الـ MABs : يُحقن المُستضد المطلوب في الفأر لتطوير الأضداد الـهَدَف . يُضخّى بالفأر بعد حدوث استجابة مناعية وتُزال الخلايا الـ B المُنتجة—للضدّ من الطحال . تُمزج خلايا ورم النقي المُخلّدة مع الخلايا B للفأر وتُدمج لتصنيع خلايا ورم هجين . تُنتقى خلايا الورم الهجين من مستنبت الخلايا و تُزال الخلايا غير المندمجة الميتة . تُتحرّى الخلايا الباقية من أجل الخلايا القاذفة للضد النوعي للمستضد المطلوب . تُنمّى خلايا الورم الهجين المُنتجة—للضد بكميّات كبيرة ، ويُنزع/يُصرف الوسط الزراعي دورياً وتُنقى الـ MABs وتعلّب/تُرزم للإعطاء .

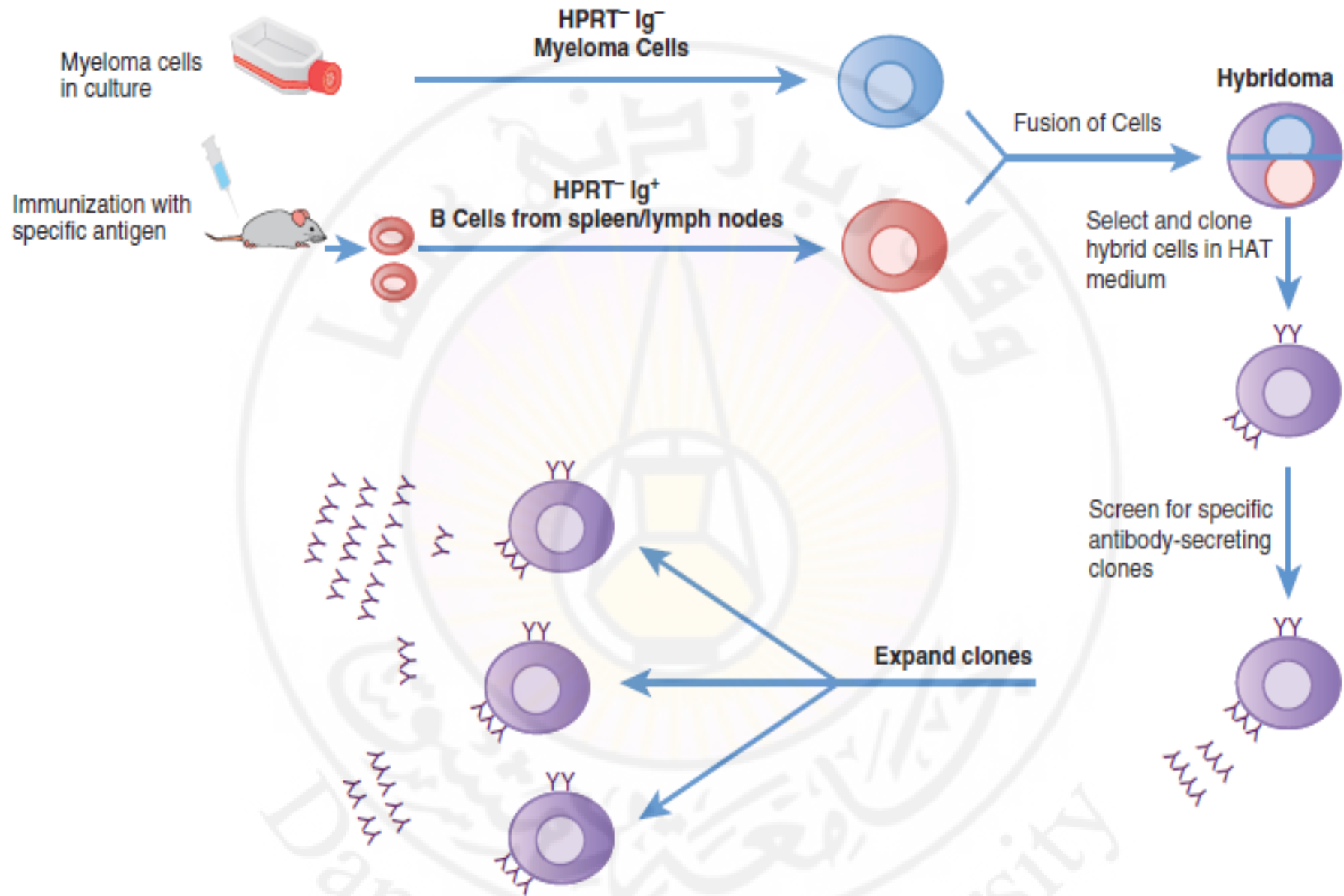


Figure 35-3 *Generation of mAbs.* Mice are immunized with the selected antigen, and the spleen or lymph node is harvested and B cells separated. These B cells are fused to a suitable B-cell myeloma selected for its ability to grow in medium supplemented with HAT (hypoxanthine, aminopterin, and thymidine). Only myeloma cells that fuse with B cells can survive in HAT-supplemented medium. The hybridomas expand in culture. Hybridomas of interest are selected based on a specific screening technique and then cloned by limiting dilution. The mAbs can be used directly as supernatants or ascites fluid for experimental use but are purified for clinical use.

Recombinant DNA technology can also be used to replace part of the mouse gene sequence with human genetic material, thus “humanizing” the antibodies and making them less antigenic. The names of monoclonal antibodies conventionally contain “xi” or “zu” if they are chimerized or humanized, respectively. The suffix “-mab” (monoclonal antibody) identifies the category of drug. The polyclonal antibodies, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific (Figure 38.3).

تستخدم تكنولوجيا الدّنا المأشوب أيضاً لاستبدال جزء من تتالي مورثة فأرية بمادة مورثية بشرية ، وبالتالي «أنسنة» الأضداد وجعلها أقل مُستضدّية .

تحتوي أسماء الأضداد وحيدة النسيلة “xi” أو “zu” إذا كانت **خيمريّة** (وجود خلايا مختلفة المنشأ الوراثي) أو **مؤنسنة** على التوالي .

أما اللاحقة **(monoclonal antibody) “-mab”** فتستعرف تصنيف الدواء .

إنتاج الأضداد مُتعدّد النّسائل أقلّ تكلفة نسبياً ، لكنها متغايرة وأقل نوعية ، على عكس الأضداد وحيدة النسيلة التي تكون متجانسة ونوعية (الشكل ٣٨ . ٣) .

DRUG	CLASS	MECHANISM OF ACTION	INDICATIONS	ADVERSE EFFECTS
<i>Alemtuzumab</i>	Humanized monoclonal antibody (CD52)	Binds to CD52 on B and T lymphocytes, causing T- and B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), severe and prolonged leukopenia, neutropenia, thrombocytopenia, infections (CMV, HSV, and other viruses/fungi)
<i>Antithymocyte globulins</i>	Polyclonal antibodies	T-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), leukopenia, thrombocytopenia, pulmonary edema, infections due to CMV or other viruses, skin rash
<i>Basiliximab</i>	Chimeric monoclonal antibody	Binds to CD25 (IL-2R) and inhibits IL-2 mediated T-cell proliferation (nondepleting)	Induction	Generally well tolerated vs. placebo
<i>Bortezomib</i>	Proteasome inhibitor	Proteasome inhibition leads to plasma cell depletion	Treatment of antibody-mediated rejection	Leukopenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, peripheral neuropathy, hypotension, hepatotoxicity (less common)
<i>Intravenous Immunoglobulin (IVIg)</i>	Immune globulin	Antibodies, B cells	Induction for highly sensitized patients, treatment of rejection	Infusion-related reactions, headache, hypotension, hemolytic anemia, pulmonary edema, thromboembolic events, aseptic meningitis, acute renal failure
<i>Methylprednisolone</i>	Corticosteroid	Nonspecific interleukin and TNF inhibition	Induction, treatment of rejection, maintenance	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
<i>Rituximab</i>	Chimeric monoclonal antibody	CD20 ⁺ B-cell depletion	Induction, treatment of rejection	Infusion-related effects (chills, fever), infections (reactivation of hepatitis B virus, CMV, and other viruses/fungi), PML, leukopenia, thrombocytopenia, mucocutaneous reactions

CMV = cytomegalovirus; HLD = hyperlipidemia; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; PML = progressive multifocal leukoencephalopathy; TNF = tumor necrosis factor.

Figure 38.3

Medications used for induction and/or rejection immunosuppressant therapy.

A. Antithymocyte globulins . Antithymocyte globulins are polyclonal antibodies produced by isolating γ -globulin fractions of serum obtained from rabbits or horses after immunization with human thymocytes. They cause depletion of circulating T-cells and apoptosis of activated T-cells. Rabbit preparations are preferred over horse preparations because of greater potency and less toxicity.

Antithymocyte globulin, rabbit is primarily used at the time of transplantation to prevent early allograft rejection, along with other immunosuppressive agents. It may also be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. It is usually used for 3 to 10 days to produce profound lymphopenia that may last beyond 1 year.

The antibodies are slowly infused intravenously and their half-life extends from 3 to 9 days. Premedication with corticosteroids, *acetaminophen*, and antihistamines may help reduce infusion-related reactions. Prolonged use may be associated with profound immunosuppression and an increased risk of opportunistic infections **and/or post-transplant lymphoproliferative disease (PTLD).**

أ. الغلوبولينات المضادة للمفاويات : أضداد مُتَعَدِّدة النَّسَائِل تُنتَج بعزل أجزاء ال- γ -globulin من مصل الأرانب أو الأحصنة بعد تمنيعها بخلايا تَوْتِيَّة (خلايا لمفية في التوتة) بشرية . تسبب استنفاد الخلايا التائية الجائلة واستماتة الخلايا التائية المنشطة . تفضل مستحضرات الأرانب على الأحصنة لأنها أكثر فاعلية وأقل سميّة .

تستعمل مستحضرات الأرنب المضادة للغلوبولين وقت الزرع لمنع رفض الطعم المبكر ، مع كابحات مناعة إضافية . تستعمل أيضاً لمعالجة نوائب الرفض الشديدة أو الرفض الحاد المقاوم—للكورتيكوستيرويد . تستعمل ٣—١٠ أيام لإحداث قلة لمفاويات واضحة تدوم أكثر من ١ عام .

تُسَرَّب الأضداد ببطء في الوريد ويمتد عمرها النصفى ٣—٩ يوم . يساعد استبقاها بالكورتيكوستيرويد والأسيتامينوفين ومضادات الهيستامين **إنقاص التفاعلات المتعلقة—** **بالتسريب .** قد يترابط طول استعمالها مع كبت مناعة شديد وزيادة اختطار عداوى انتهازية و/أو داء تكاثر اللمفاويات بعد الزرع .

B. Basiliximab. Basiliximab is a chimeric (murine/human) monoclonal antibody that functions as an immunosuppressive agent. **Basiliximab** is a monoclonal antibody to the high-affinity **IL-2 receptor** expressed on activated T cells. **Basiliximab** binds to the α -subunit of the receptor and **prevents IL-2 binding**. By this action, IL-2-mediated activation of lymphocytes is prevented, and the response of the immune system to **alloantigens** (e.g., those present in transplanted allografts) is impaired. A short course of basiliximab is used in combination with other agents as induction immunotherapy immediately after **renal transplantation**.

Basiliximab significantly **lowers circulating lymphocytes** and **prevents acute transplant rejection**.

ب. **Basiliximab** : ضد وحيد النسيلة خيمري (فأري/بشري) كابيت للمناعة . ذو ألفة كبيرة لمستقبلات الـ IL-2 المعبرة على الخلايا T المنشّطة . يرتبط بالوحيدة—الألفا للمستقبلات فيمنع ارتباط الـ IL-2 وبهذا يمنع تنشيط اللمفاويات المتواسط—بالـ IL-2 ، فتختل استجابة الجهاز المناعي للمستضدات الخيفية لـ **alloantigens** (مثال ، الموجودون في الطعوم الخيفية المزروع) .

يستعمل مقرر علاجي قصير لهذا الدواء بالتوليف مع غيره كمعالجة مناعية أولية حالاً بعد زرع الكلية .

ينقص جداً اللمفاويات الجائلة و يمنع الرفض الحاد للزرع .

XXV. IMMUNOSUPPRESSANT DRUGS

Antibodies:

<i>Alemtuzumab</i>	IV: 12 mg/day
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Antithymocyte globulins

<i>Basiliximab</i>	IV: Adult = 20 mg 12 hourly, children = 10 mg 12 hourly
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<i>Rituximab</i>	IV: 250–500 mg/m ²
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Calcineurin inhibitors:

<i>Cyclosporine</i>	Oral: 2–15 mg/kg/ day IV: 3–5 mg/kg/day
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<i>Tacrolimus</i>	Oral: 0.05–0.2 mg/kg 12 hourly 0.03% and 0.1% topical ointment
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Costimulation blocker:

<i>Belatacept</i>	IV: 5–10 mg/kg
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mTOR Inhibitors:

<i>Everolimus</i>	Oral: 2.5–20 mg/day
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<i>Sirolimus</i>	Oral: 1 mg/m ² /day
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Antiproliferatives:

<i>Azathioprine</i>	Oral: 1–5 mg/kg/day
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<i>Mycophenolate mofetil</i>	Oral: 1 g twice a day
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<i>Mycophenolate sodium</i>	Oral: Adult: 720 mg twice a day, children: 400–720 mg twice a day
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Adrenocorticoids:

<i>Methylprednisolone</i>	Oral: 4–32 mg/day IV: 0.5–1 g
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<i>Prednisolone</i>	Oral: 5–60 mg/day IM/Intra-articular: 10–40 mg/day
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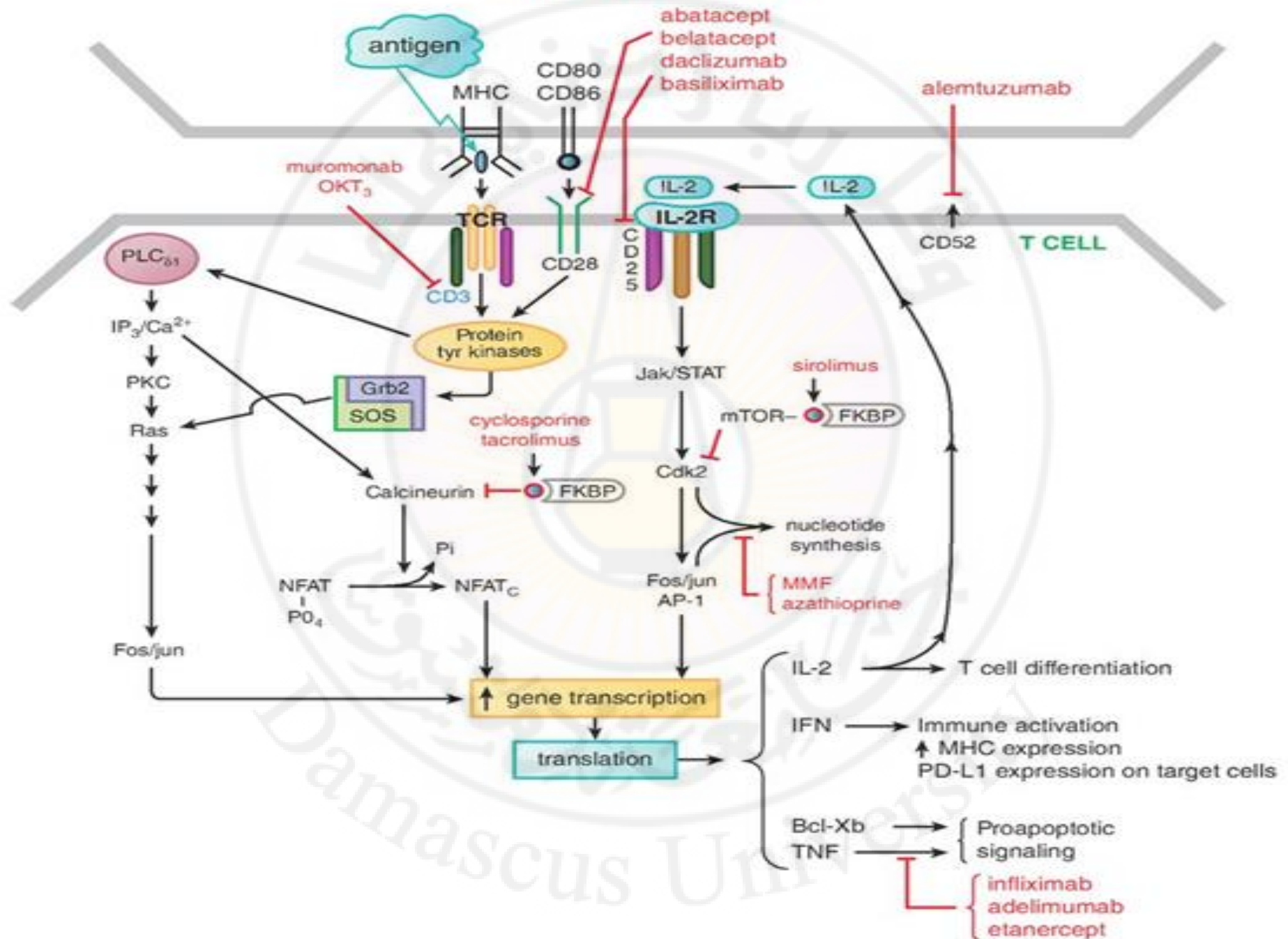
<i>Prednisone</i>	Oral: Adult = 0.5–2 mg/kg/day, children: 0.05–2 mg/kg/day
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Others:

<i>Bortezomib</i>	IV: 1.3 mg/m ²
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<i>Intravenous immunoglobulin</i>	IV : 300–1000 mg/kg
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Antigen-Presenting Cell



C. Alemtuzumab is a CD52-directed cytolytic **monoclonal antibody** approved for the treatment of patients with relapsing forms of MS. Because of its potentially **life-threatening adverse effects** of autoimmune, infusion reactions, and increased malignancies, alemtuzumab should only be used in patients who have not responded to two or more other treatments for MS.

Alemtuzumab binds to **CD52**, a cell surface glycoprotein found on all B and T lymphocytes, natural killer cells, monocytes, and macrophages. Following cell surface binding to T and B lymphocytes, alemtuzumab results in **antibody-dependent cellular cytotoxicity** and **complement-mediated lysis**. It is indicated for the **treatment of MS**. Alemtuzumab may cause bleeding, hypertension, and kidney failure.

ج. **Alemtuzumab** ضد وحيد النسيلة حالّ للخلية مُوجّه—بالـ CD52 مبرهن لمعالجة الشكل الناكس من التصلب اللويحي MS .

يرتبط الـ **Alemtuzumab** بالـ CD52 البروتين السّكري الموجود على سطح الخلية لكل اللمفاويات البائية والتائية ، والخلايا القاتلة الطبيعية والوحيدات والبلاعم/البالعات . بعد الارتباط بسطح الخلايا البائية والتائية يؤدي الـ alemtuzumab إلى انحلال خلية مُعتمِد—على الضد و انحلال مُتواسط—بالمُتممة .

تأثيراته الضائرة مهددة—للحياة يزيد الخباثات يسبب نزف وفرط ضغط وفشل كلية ..

D. Rituximab is an anti-CD-20 cytolytic agent indicated for the treatment of non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia, RA, Wegener granulomatosis, and pemphigus vulgaris. Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis by complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC).

Rituximab is a chimeric (*xi*) human-mouse *mAb* used to treat tumor (*tu*). **Rituximab was the first monoclonal** antibody drug approved for targeted cancer treatment.

د. **Rituximab** : ضد وحيد النسيلة خيمري (*xi*) (فأري-بشري) مضاد للـ CD-20 حالّ للخلية يستهدف المستضد CD20 المُعبّر على سطح الخلايا اللمفاوية البائية B الطلائع والناضجة . يتواسط عند ارتباطه بالـ CD20 انحلال الخلية—البائية بالسمية الخلوية المعتمدة على المتممة (CDC) والسمية الخلوية المعتمدة على الضد (ADCC) .

مستعمل لعلاج السرطان (*tu*) موصى به لمعالجة اللمفوما غير الهودجكينية (NHL) والابيضاض (اللوكيميا) اللمفاوي المزمن والتهاب المفاصل الروماتويدي RA ، والأورام الحبيبية لويغنز ، والفقاع الشائع .

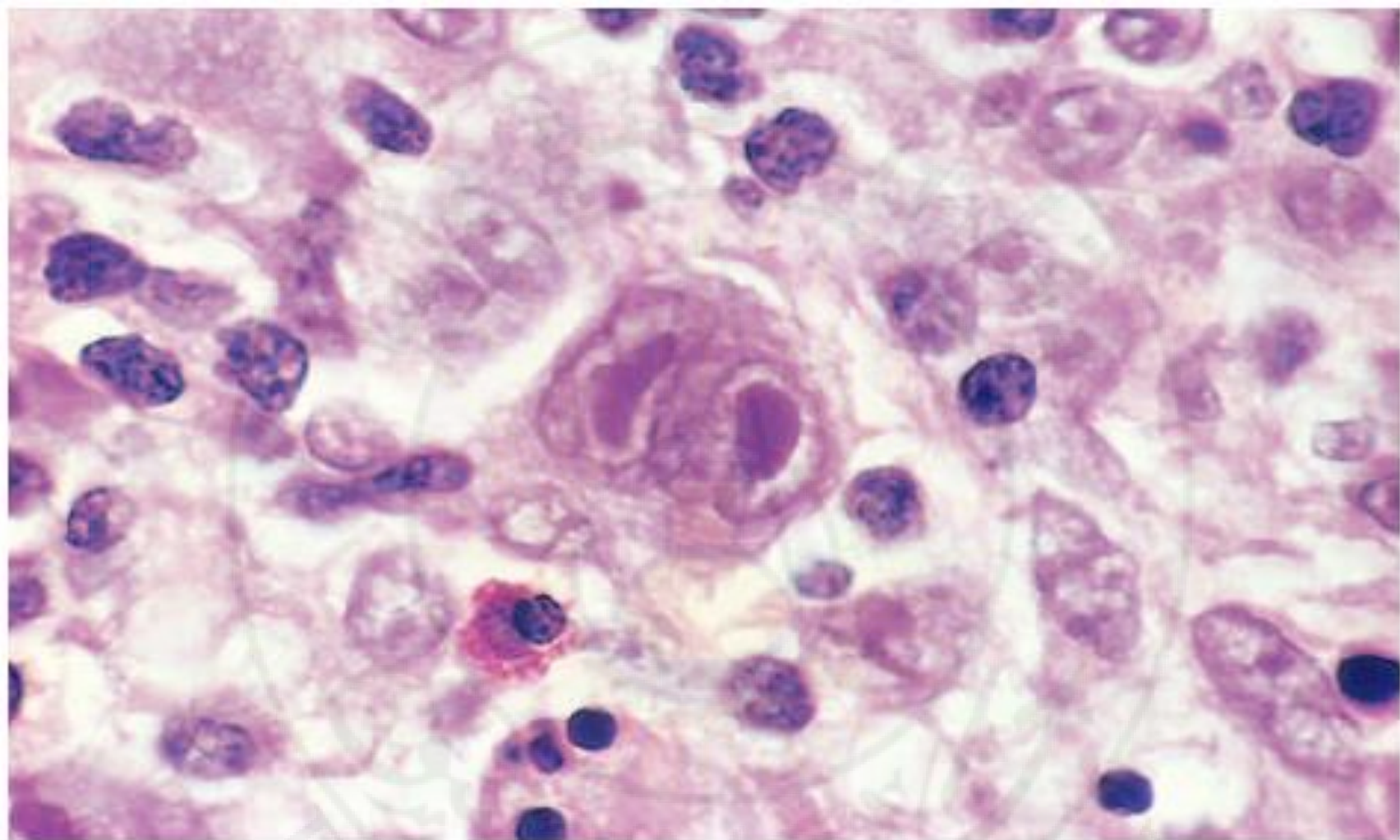


Fig. 12.20 Hodgkin lymphoma—lymph node. A binucleate Reed-Sternberg cell with large, inclusion-like nucleoli and abundant cytoplasm is surrounded by lymphocytes, macrophages, and an eosinophil. (Courtesy of Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

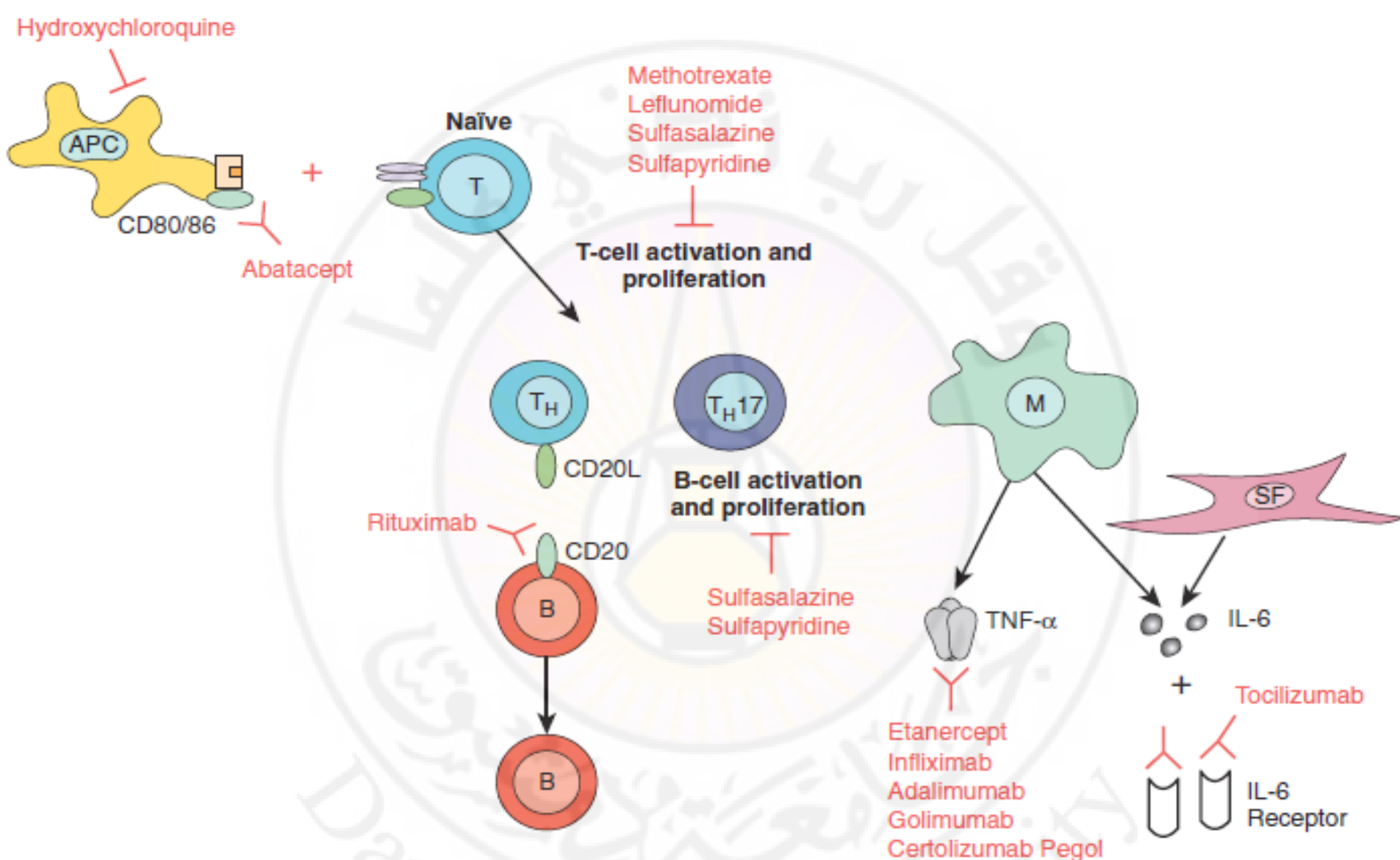


FIG. 35.2 Disruption of the Inflammatory Pathway by DMARDs. The nonspecific conventional DMARDs (methotrexate, leflunomide, sulfasalazine, and sulfapyridine) inhibit the proliferation and activation of T and B cells, whereas hydroxychloroquine affects the activation of antigen-presenting cells (APCs). The biological and targeted DMARDs interact with specific cytokines such as tumor necrosis factor- α (TNF- α), cytokine targets such as the interleukin-6 (IL-6) receptor, or cell surface proteins such as CD20 expressed by B-lymphocytes to potentially inhibit inflammation.

Bortezomib was the first small molecule **proteasome inhibitor** to be developed for cancer treatment. The drug prevents the degradation and recycling of proteins (proapoptotic proteins) by the proteasome of cancer cells, leading to protein accumulation and cell death. Bortezomib is used to treat **multiple myeloma** and **mantle cell lymphoma**. Other small molecule proteasome inhibitors include **carfilzomib** and **ixazomib**. They are both approved for the treatment of multiple myeloma.

Inhibition of Proteasome enzymes which then causes buildup of undegraded proteins which leads to apoptosis and inhibition of cancer growth.

و. الـ **Bortezomib** أول جزيء صغير **مثبط للبروتيزوم** يُطوّر لمعالجة السرطان .

يمنع تدرك البروتينات (البروتينات المؤيدة للموت المبرمج) بواسطة بروتيزوم خلايا السرطان ، مُؤدياً إلى تراكم البروتين وموت الخلية . يستعمل البروتيزوم لعلاج **الورم النقي المتعدد** و **لمفوما الخلايا الليمفاوية/القشرية mantle cell lymphoma** . تتضمن مثبطات البروتيزون الصغيرة الجزيء الإضافية **carfilzomib** and **ixazomib** . مصدوقان لمعالجة ورم النقي المتعدد .

يسبب تثبيط إنزيمات البروتيزوم تعزيز/زيادة/تجمع بروتينات غير متدركة تؤدي إلى موت مبرمج وتثبيط نمو السرطان .

bortezomib (Proapoptotic Agent)
proteasome degrades proapoptotic proteins

F. **Intravenous immunoglobulin (IVIG)** . contains immunoglobulins prepared by human plasma pooled from many donors. It has an immunomodulatory effect and is often used for autoimmune diseases, pretransplant desensitization protocols, and treatment of AMR. The immunomodulatory effects on T- and B-cells occur at high doses. The mechanism of action is not well defined, but high doses of IVIG appear to induce B-cell apoptosis and modulate B-cell signaling. It also inhibits binding of antibodies to the transplanted graft and activation of the complement system. The serum half-life of IVIG is about 3 to 4 weeks.

Adverse effects of IVIG include headache, fever, chills, myalgias, and hypotension/hypertension, which can be reduced by slowing the infusion rate. Serious adverse effects are rare and can include aseptic meningitis, acute renal failure, and thrombotic events.

و. **الغلوبولين المناعي الوريدي** : يحتوي على غلوبولينات مناعية محضرة من بلازما بشرية مُجمّعة من متبرعين كثر .

له تأثير مُعدّل مناعياً ويستعمل عادةً في أمراض المناعة الذاتية وفي بروتوكولات إزالة التَحَسُّس قبل الزرع ومعالجة الرفض المتواسط—بالضد (AMR) . تحدث التأثيرات المعدلة للمناعة على الخلايا التائية والبائية مع الجرعات الكبيرة ..

الجرعات الكبيرة تحرض استماتة الخلايا البائية وتُحوّر إشعارة الخلايا البائية . يثبط أيضاً ارتباط الأضداد مع الطعم المزروع وتنشيط جهاز المتممة .

عمر النصف المصلي ٣—٤ أسابيع .

تتضمن التأثيرات الضائرة صداع وحمى ونفضات (حمى مترافقة برعدة) وآلام عضلية ونقص/زيادة الضغط ، الذي يمكن إنقاظه بإبطاء سرعة التسريب . التأثيرات الضائرة الخطيرة نادرة وتتضمن التهاب السحايا العقيم وفشل كلوي حاد وأحداث خثارية .

III. MAINTENANCE IMMUNOSUPPRESSANT

MEDICATIONS. Maintenance immunosuppressants are intended to provide adequate immunosuppression to prevent allograft rejection, while minimizing infection, malignancy, and drug-induced adverse effects. Often they are combined in regimens of two to four drugs, using medications with different mechanisms of action to minimize drug toxicity. These drugs can be further divided into four main classes: 1) calcineurin inhibitors (*cyclosporine* and *tacrolimus*), 2) co-stimulation blockers (*belatacept*), 3) mTOR inhibitors (*sirolimus* and *everolimus*), and 4) antiproliferatives (*mycophenolate* and *azathioprine*) (*Figure 38.4*).

ثالثاً. أدوية المُداوَمَة في كبت المناعة : يُقصد منها توفير كبت مناعة كافٍ لمنع رَفْضُ الطَّعْمِ الخَفِيفِ ، وبنفس الوقت تصغير العدوى والخبثاء والتأثيرات الضائرة المُحرَّضَة — بالدواء .

تُؤَلَّف عادةً ٢—٤ أدوية ذات آليات فعل مختلفة لتصغير السمية الدوائية .

يمكن تقسيم هذه الأدوية إضافياً إلى أربعة أصناف رئيسة :

- (١) مثبطات الكالسينيورين (*cyclosporine* و *tacrolimus*) ،
- (٢) محصرات التنبيه—المشترك (*belatacept*) ،
- (٣) مثبطات الـ mTOR (*sirolimus* و *everolimus*) و
- (٤) مضادات التكاثر (*mycophenolate* و *azathioprine*) (الشكل ٣٨ . ٤) .

DRUG	CLASS	INDICATIONS	PHARMACOKINETICS	ADVERSE EFFECTS
<i>Azathioprine</i>	Antiproliferative	SOT (renal), RA	Activated by glutathione S-transferase DDIs (<i>allopurinol, warfarin</i>)	Myelosuppression, nausea, vomiting, diarrhea, pancreatitis, hepatotoxicity
<i>Belatacept</i>	Costimulation blockade	SOT (renal)	Elimination half-life ~10 days	Anemia, leukopenia
<i>Cyclosporine</i>	Calcineurin inhibitor	SOT (renal, liver, heart), psoriasis, RA, acute GVHD	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, hirsutism, gingival hyperplasia, neurotoxicity, nephrotoxicity
<i>Everolimus</i>	mTOR inhibitor	SOT (renal, liver), oncology	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression
<i>Methyl-prednisolone, prednisolone, prednisone</i>	Corticosteroid	Numerous indications	Activated to <i>prednisolone</i>	HTN, HLD, hyperglycemia, peripheral edema, mood disturbance, osteoporosis, weight gain
<i>Mycophenolate</i>	Antiproliferative	SOT (renal, liver, heart)	Metabolism by glucuronidation DDI (bile acid sequestrants)	Leukopenia, thrombocytopenia, nausea, vomiting, diarrhea
<i>Sirolimus</i>	mTOR inhibitor	SOT (renal), lymphangioleiomyomatosis	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD (particularly TG, TC), stomatitis, proteinuria, impaired wound healing, rash, myelosuppression, pneumonitis
<i>Tacrolimus</i>	Calcineurin inhibitor	SOT (renal, liver, heart)	Metabolism by CYP3A4 Numerous DDIs	HTN, HLD, hyperglycemia, hyperkalemia, alopecia, neurotoxicity (hand tremor, headache, seizure), nephrotoxicity

DDI = drug-drug interaction; GVHD = graft-versus-host disease; HLD = hyperlipidemia; HTN = hypertension; mTOR = mammalian target of rapamycin; RA = rheumatoid arthritis; SOT = solid organ transplant; TC = total cholesterol; TG = triglycerides.

Figure 38.4
Medications used for maintenance immunosuppressant therapy.

A. Calcineurin inhibitors. *cyclosporine and tacrolimus* block signal transduction through the calcium– calcineurin pathway, activated downstream of signal 1, to impair T-cell activation. Calcineurin, a calcium-dependent protein phosphatase, dephosphorylates the transcription factor **Nuclear Factor of Activated T-cells (NFAT)**, allowing NFAT to enter the T-cell nucleus and bind to DNA, leading to transcription and production of cytokines, including IL-2. *Cyclosporine binds to cyclophilin, whereas tacrolimus binds a protein called FK-binding protein (FKBP).* These drug–protein complexes inhibit the activity of calcineurin, thereby preventing T-cell activation. *Tacrolimus is the preferred calcineurin inhibitor due to its decreased rate of allograft rejection as compared to cyclosporine.* Although it is approved for renal, liver, and heart transplant, *tacrolimus* is the mainstay of maintenance immunosuppressants for all solid organ transplants.

أ. مثبطات الكالسينيورين : cyclosporine و tacrolimus ((FK 506)) يحصران نقل الإشعاع عبر طريق الكالسيوم— الكالسينيورين ، المنشط بتيار الإشعاع ١ ، ليُخلَا بتنشيط الخلايا التائية فيثبطا إنتاج الـ IL-2 .

الكالسينيورين هو بروتين فسفاتاز معتمد—على الكالسيوم ، يزيل فسفرة عامل الانتساخ (العامل النووي للخلايا التائية المنشطة «NFAT») ، مما يسمح للـ NFAT بأن يدخل نواة الخلية التائية ويرتبط بالدنا ، مؤدياً إلى نسخ وإنتاج السيتوكينات ، متضمنةً IL-2 .

يرتبط السيكلوسبورين بالسيكلوفيلين ، بينما يرتبط التاكروليموس مع بروتين يدعى FK-binding protein (FKBP) . يثبط معقدي الدواء—البروتين هذين نشاط الكالسينيورين ، فيمنعان بالتالي تنشيط الخلية التائية .

يفضل التاكروليموس بسبب نقص معدل رفض الطعم الخيفي مقارنةً مع السيكلوسبورين . يعد التاكروليموس ركن أساسي من كابتات المناعة المداومة لكل زروعات الأعضاء الصلبة رغم أنه مبرهن لزراع الكلية والكبد والقلب .

Enzymes CYP3A4, CYP3A5, and P-glycoprotein (P-gp) expressed in the gastrointestinal tract and liver are responsible for the interindividual variability in oral absorption and metabolism of *cyclosporine* and *tacrolimus*. Dosing titration is based on 12-hour trough levels, with goal trough levels varying between different organs, time from transplant, and transplant center-specific protocols.

One of the primary limitations to the use of calcineurin inhibitors is nephrotoxicity, which has led to the development of regimens using these agents in combination with other immunosuppressant drugs. As with all immunosuppressants, infections are possible with the use of calcineurin inhibitors, and recipients are often given prophylactic medications post-transplant. Hirsutism, or excessive hair growth, is a common adverse effect of *cyclosporine*.

سبب التباين بين الأفراد في امتصاص واستقلاب السيكلوسبورين والتاكروليموس هو الـ CYP3A4 والـ CYP3A5 والـ **P-gp** المعبّرة في السبيل الهضمي والكبد . .
يتمثل أحد القيود الأولية في استعمال مثبطات الكالسينيورين بالسمية الكلوية ، التي أدت إلى تطوير تدابير تستعمل هذه الأدوية بالتوليف مع غيرها من كابحات المناعة .
يمكن حدوث عداوى مع استعمال مثبطات الكالسينيورين ، ويعطى المتلقين عادةً أدوية وقائية بعد-الزرع . الشعرانية ، أو نمو الشعر الزائد شائعة مع السيكلوسبورين .

B. **Belatacept** is a monoclonal antibody preparation directed against **CD80 glycoprotein** on antigen-presenting cells (APCs) and blocks the costimulation of T cell lymphocytes. The activated T cells are the primary mediators of immunologic rejection. **Belatacept** is indicated for use in **renal transplant** patients in combination with **basiliximab** induction, **mycophenolate**, and **corticosteroids**.

ب. مُحصِر التنبيه المشترك **Belatacept** : ضد وحيد النسيلة مُوجّه ضد الـ **CD80 glycoprotein** على الخلايا الجالبة—للمستضد (APCs) فيحصِر التنبيه المُشترَك للخلايا اللمفاويّة T . إذ أنّ الخلايا T المُنشّطة هي الوسائط الأولى للرفض المناعي .
يوصى به للاستعمال لمرضى زرع الكلية بالتوليف مع **basiliximab** معالجة أوليّة ، والـ **mycophenolate** والـ **corticosteroids** .

C. mTOR inhibitors

Sirolimus [sih-RO-lih-mus] (also known as *rapamycin*) and *everolimus* [e-ve-RO-lih-mus] inhibit the protein mTOR, blocking the signal transduction pathway activated by signal 3. Progression into the cell cycle and T-cell proliferation is subsequently prevented (Figure 38.5). The mTOR inhibitors are commonly used in multidrug regimens, frequently to minimize the dose of calcineurin inhibitors and spare their nephrotoxic adverse effects.

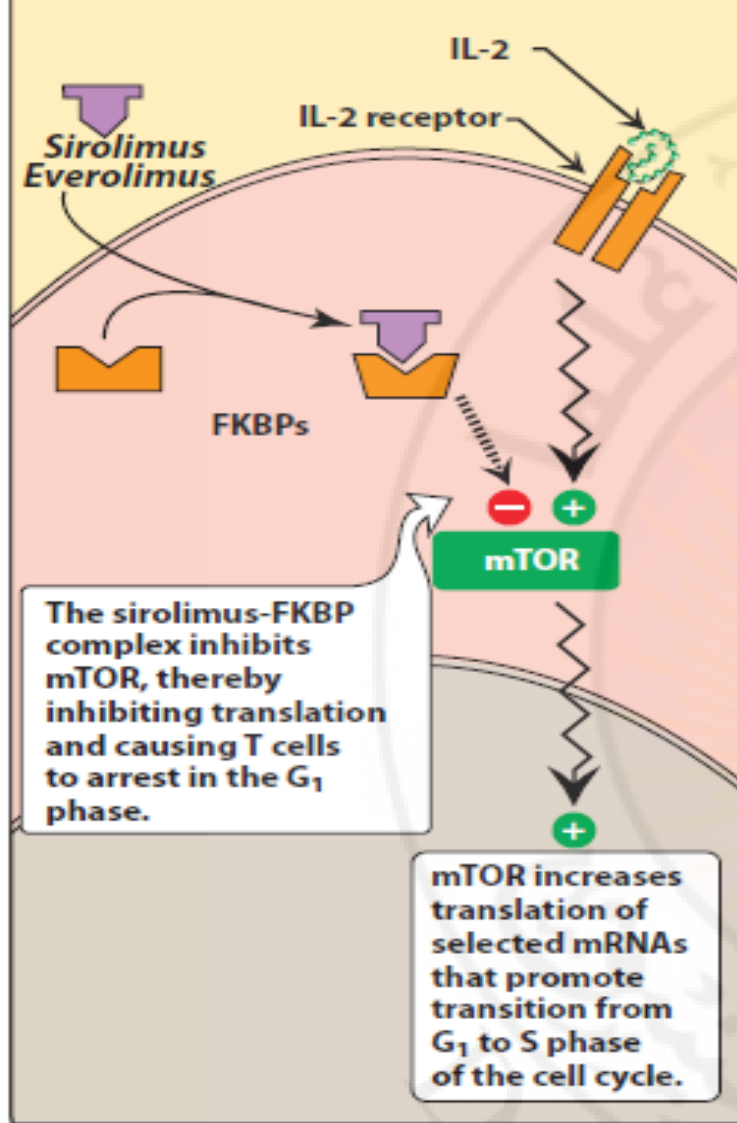


Figure 38.5

Mechanism of action of *sirolimus* and *everolimus*. FKBP = FK-binding protein; IL = interleukin; mRNA = messenger RNA; mTOR = mammalian target of rapamycin.

ج. **مثبطات الـ mTOR** : يثبط الـ **Sirolimus** (المعروف أيضاً **rapamycin**) والـ **everolimus** البروتين **mTOR** ، فيحصران طريق نقل الإشعاع المُنشَّط بالإشعاع ٣ . هذا يمنع بالتالي التقدم في دورة الخلية وتكاثر الخلايا التائية (الشكل ٣٨ . ٥) . تستعمل مثبطات الـ mTOR في تدابير تعديد الأدوية ، لتصغير جرعة مثبطات الكالسينيورين ومنع تأثيراتها الضائرة السامة للكلية .

Like the calcineurin inhibitors, both *sirolimus* and *everolimus* are metabolized by CYP3A4, are substrates for P-gp, and are subject to numerous drug–drug interactions. Both agents require drug monitoring of **trough** concentrations to optimize therapy. *Sirolimus* has a longer half-life than the calcineurin inhibitors or *everolimus*, and is dosed only once daily, which may improve medication compliance. The antiproliferative action of *sirolimus* is also valuable in cardiology where *sirolimus*-coated stents are used to inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells. *Everolimus* is also used in oncology to treat many different types of cancer, including breast, renal cell, and neuroendocrine tumors. However, the doses for tumor treatment are higher than those used in transplantation.

الـ **Sirolimus** والـ **everolimus** ، مثل مثبطات الكالسينيورين ، يستقلبان بالـ CYP3A4 ، وهما ركيزتان للـ **P-gp** ، ويخضعان لتأثرات دوائية كثيرة . يتطلبان مثلهما مراقبة تراكيز **الغور** (المنخفض) للمعالجة المثلّية .

للسيروليموس عمر-نصف أكبر من مثبطات الكالسينيورين أو إيفيروليموس ، ويعطى مرة في اليوم ، مما يحسن الامتثال .

الفعل المضاد للتكاثر للسيروليموس ذو قيمة في **طَبُّ الْقَلْبِ** حيث تستعمل وإقيات الطُّعْم المغلفة—بالسيروليموس لتنشيط عَوْدَةُ التَّضَيُّقِ للأوعية الدموية **بإنقاصها تكاثر الخلايا البطانية** .

يستعمل الإفيروليموس بجرعات أكبر أيضاً في **عِلْمُ الْأَوْرَام** لمعالجة أورام الثدي وخلايا الكلية والأورام العصبية الصّماوية .

D. Antiproliferatives. The antiproliferatives *azathioprine* [ay-za-THYE-oh-preen] and *mycophenolate* [mye-koe-FEN-oh-late] block lymphocyte proliferation by inhibiting nucleic acid synthesis. *Azathioprine*, which was one of the first agents to achieve widespread use in organ transplantation, is a prodrug that is converted first to 6-mercaptopurine (6-MP) and then to the corresponding nucleotide analog, thioinosinic acid. The analog is incorporated into nucleic acid chains and blocks further elongation of the DNA. *Mycophenolate* is a potent, reversible, noncompetitive inhibitor of *inosine monophosphate dehydrogenase*, which blocks the de novo formation of guanosine phosphate (Figure 38.6). Because lymphocytes are unable to utilize the salvage pathway of nucleotide synthesis, *mycophenolate* effectively blocks T- and B-cell proliferation by eliminating de novo production of guanosine.

د. مضادات التكاثر : **azathioprine** و **mycophenolate** يحصران تكاثر اللمفاويات بتثبيطهما تصنيع الحامض النووي ..

الأزاثيوبرين المستعمل في زرع الأعضاء طليعة دواء يُحوّل إلى 6-mercaptopurine (6-MP) ثم إلى المشابه النوكليوتيدي حامض الثيوزينوزينيك . يُضمّن هذا المشابه في سلاسل الحامض النووي و يحصر الإطالة الإضافية للدنا .

الميكوفينولات مثبط فعّال لا تنافسي عكوس لنازعة هيدروجين الإينوزين أحادي الفسفات ، مما يحصر التكوين الجديد لفسفات الغوانوزين (الشكل ٣٨ . ٦) . بما أنّ اللمفاويات غير قابلة لاستخدام الطريق الإنقادي لتصنيع النوكليوتيد ، فإنّ الميكوفينولات يحصر بقوة تكاثر الخلايا التائية والبائية عبر إنهاء الإنتاج الجديد للغوانوزين .

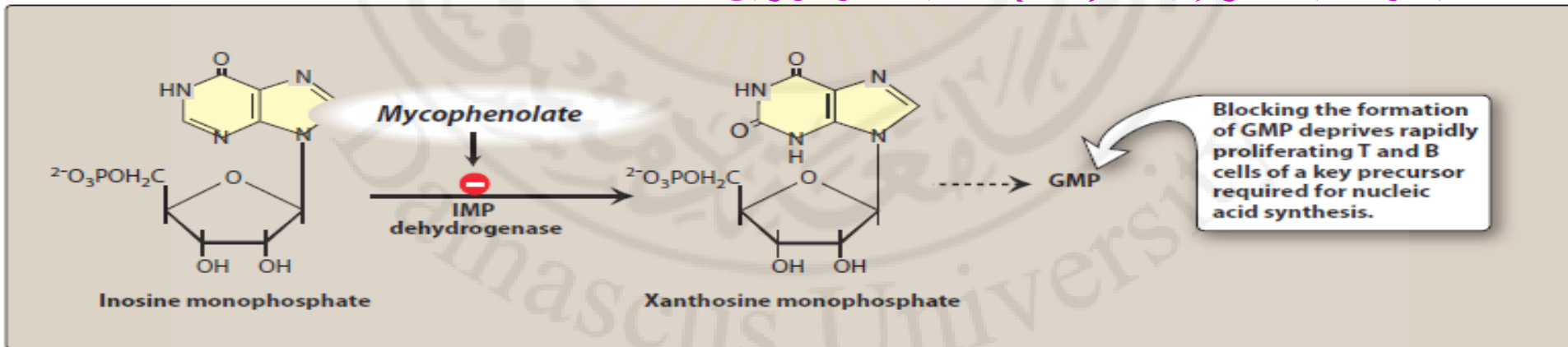


Figure 38.6

Mechanism of action of *mycophenolate*. GMP = guanosine monophosphate; IMP = inosine-5'-monophosphate.

These medications are used as adjunctive immunosuppressant agents, primarily with calcineurin inhibitors with or without corticosteroids. However, *mycophenolate has largely replaced azathioprine* in this role due to its improved safety and efficacy profile. The main dose-limiting adverse effect of azathioprine is *bone marrow suppression*. *Allopurinol inhibits the metabolism of azathioprine, thereby enhancing the adverse effects of azathioprine. Thus, concomitant use of allopurinol requires a significant reduction in azathioprine dose.*

Mycophenolate is available in two formulations: 1) as a prodrug mycophenolate mofetil and 2) as an active drug mycophenolic acid. Mycophenolate mofetil is rapidly hydrolyzed in the gastrointestinal tract to mycophenolic acid. Glucuronidation of mycophenolic acid in the liver produces an inactive metabolite, but enterohepatic recirculation occurs, prolonging the effect of the drug. Mycophenolic acid is an enteric-coated tablet designed to theoretically reduce the gastrointestinal upset commonly experienced with mycophenolate mofetil.

تستعمل هذه الأدوية كابتات مناعة مساعدة ، خصوصاً مع مثبطات الكالسينيورين مع أو بدون كورتيكوستيروئيدات . على كل حال ، حلّ المييكوفينولات محل الآزاثيوبرين في هذا الدور بسبب مأمونيته ونجاعته . التأثير الضائر المهم المحدد-بالجرعة للأزاثيوبرين هو كبت نقي العظم . يثبط الألوپورينول استقلال الآزاثيوبرين ، فيزيد تأثيراته الضائرة . لهذا فإن الاستعمال المشترك مع الألوپورينول يتطلب إنقاص جرعة الآزاثيوبرين .

يتوافر المييكوفينوليت في مستحضرين :

(١) كطليعة دواء **mycophenolate mofetil** و

(٢) **حامض المييكوفينوليت** .

يُحلّمه الأول سريعاً في جهاز الهضم إلى حامض المييكوفينوليك . يعطي الانضمام الغلوكوروني لحامض المييكوفينوليك في الكبد مستقلب متعطل ، لكن يحدث دوران معدي معوي يطيل تأثير الدواء . حامض المييكوفينوليك قرص مغلف-معوي مصمم نظرياً لإنقاص الانزعاج الهضمي الشائع مع الـ **mycophenolate mofetil** .

E. Cytotoxic agents for immunosuppression

Some of the cytotoxic agents used in anticancer therapy have also showed immunosuppression by suppressing clonal expression of T and B lymphocytes; therefore, they are employed in immunosuppression. *Azathioprine, chlorambucil, and cyclophosphamide are used in various autoimmune conditions. Methotrexate has been used as a first-line agent in conditions such as severe psoriasis, myasthenia gravis, uveitis, and pemphigus.*

هـ. **الأدوية السامة للخلية من أجل كبت المناعة** : أظهرت بعض الأدوية السامة للخلية المستعملة في المعالجة المضادة للسرطان كبت المناعة عبر كبت التعبير النسيلى للمفاويات التائية والبائية ؛ لهذا ، تُطبَّق في كبت المناعة .

الـ **Azathioprine** والـ **chlorambucil** والـ **cyclophosphamide** تستعمل في حالات مناعة ذاتية متنوعة .

يستعمل الـ **Methotrexate** خط أول في حالات مثل الصَدَفِيَّة والوهن العضلي والتهاب العنبيَّة والفُقاع .

F. Corticosteroids

The corticosteroids (see Chapter 26) were the first pharmacologic agents to be used as immunosuppressives, both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are *prednisone* and *methylprednisolone*, whereas *prednisone* and *prednisolone* are used for autoimmune conditions. [Note: In transplantation, they are used in combination with agents described previously in this chapter.] The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma.

و. الكورتيكوستيرويدات : أوّل كابِتات المِناعة في زرع الأعضاء والاضطرابات المِناعية الذاتية المتنوعة . لا تزال إحدى الأركان الأساسية في تخفيف نوايب الرفض .

الـ **prednisone** والـ **methylprednisolone** هما الأشيع في زرع الأعضاء ، بينما يستعمل الـ **prednisone** والـ **prednisolone** في حالات المِناعة الذاتية .

(ملاحظة : تستعمل في الزرع بالتوليف مع أدوية سابقة في هذا الفصل) .

تستعمل الستيرويدات لكبت الرفض الحادّ للطعوم الخفيفة للأعضاء الصلبة وفي داء الطُّعْم المزمن حَيالَ الثويّ . إضافةً أنها فعّالة ضدّ ضرب واسع من حالات المِناعة الذاتية ، متضمنةً التهاب المفاصل الروماتويدي المعاند و الذئبة الحُمائيّة المجموعيّة والتهاب المفاصل الصدغي والربو .

The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T-lymphocytes are most affected. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor. The complex passes into the nucleus and regulates the transcription of DNA. Among the genes affected are those involved in inflammatory responses. The use of these agents is associated with numerous adverse effects. For example, they are diabetogenic and can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension with prolonged use. Consequently, efforts are being directed toward reducing or eliminating the use of steroids in the maintenance of allografts.

آلية الفعل : تتأثر اللمفاويات التائية بالكورتيكوستيرويدات . إذ أنّ الستيرويدات قادرة على إنقاص جمهرات اللمفاويات عبر الانحلال أو إعادة التوزع . بدخولها الخلايا ترتبط بمستقبلة القشرانية السكرية . ثم يمرّ المعقد إلى النواة ويُنظّم انتساخ الدنا . من المورثات المتأثرة تلك المكتنفة في الاستجابات الالتهابية .

يتربط استعمال هذه الأدوية مع تأثيرات ضائرة كثيرة . على سبيل المثال ، هي محدثة للسكري وتسبب فرط كوليستيرول الدم وسادّ وتخلخل العظم وفرط ضغط الدم مع طول الاستعمال . بالتالي ، ثمة جهود تُوجّه لإنقاص أو إنهاء استعمال الستيرويدات في المُداوَمَة في الطعوم الخيفية .

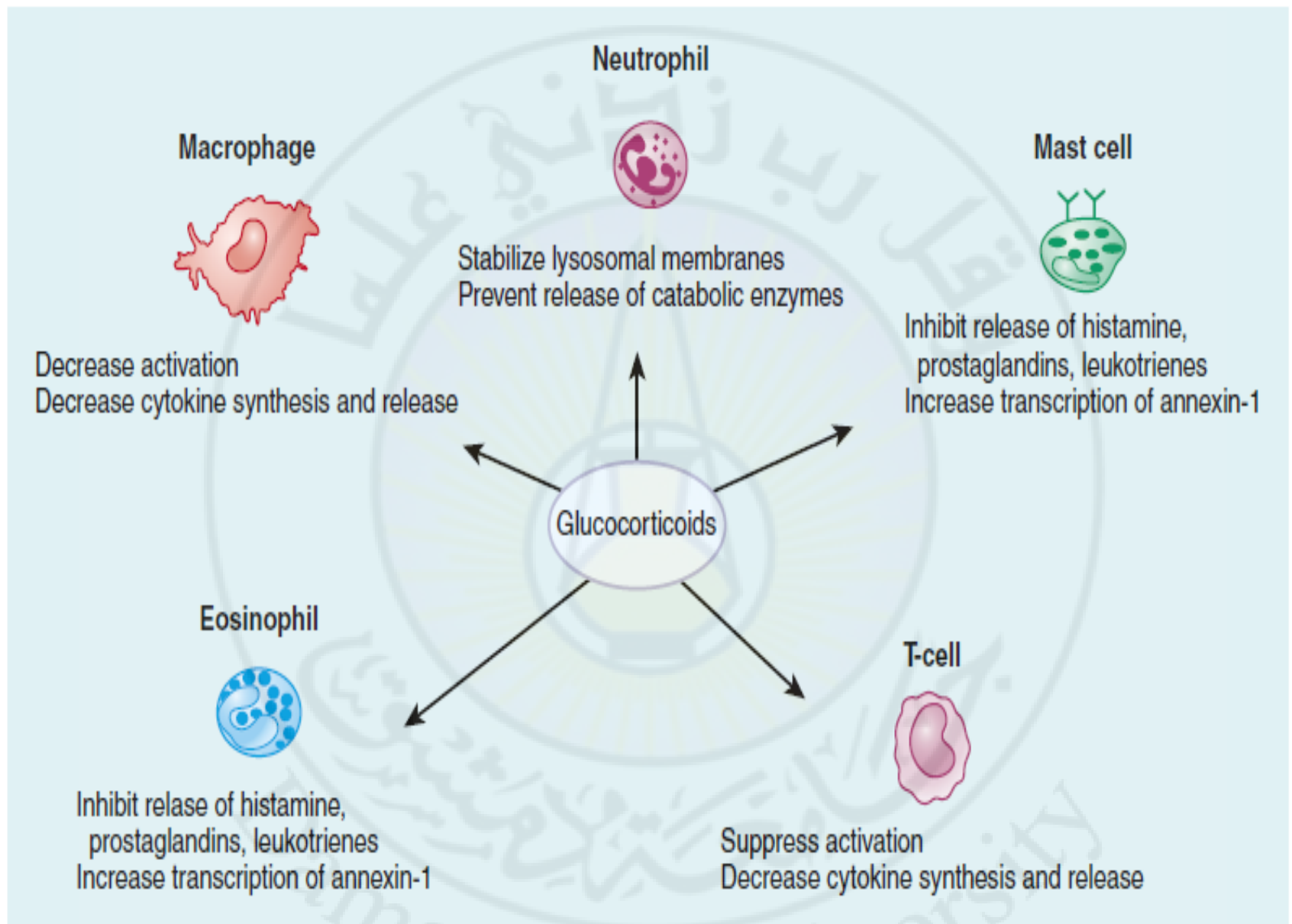


FIG. 33.3 Anti-inflammatory actions of glucocorticoids. Glucocorticoids act by suppressing T-cell activation, decreasing cytokine production and release, and preventing mast cells and eosinophils from releasing various chemical mediators of inflammation, including histamine, prostaglandins, leukotrienes, and other substances that cause tissue damage, vasodilation, and edema. They also have a number of actions on neutrophils and macrophages that reduce the chemical mediators of inflammation. Glucocorticoids have additional anti-inflammatory effects described in the text.

IV. THERAPEUTIC DRUG MONITORING

OF IMMUNOSUPPRESSANTS

Immunosuppressants require therapeutic drug monitoring because of their narrow therapeutic index and significant inter-individual variability in blood concentrations, especially for cyclosporine, tacrolimus, sirolimus, and mycophenolic acid. This variability in blood levels can be because of factors such as age, gender, drug–disease interactions, drug–nutrient interactions, renal and hepatic insufficiency, inflammation and infection, and polymorphism. For details, see Chapter 1.

f

رابعاً. المراقبة الدوائية العلاجية لكابتات المناعة : تتطلب كابتات المناعة مراقبة دوائية علاجية بسبب ضيق مناسبها العلاجية والتغاير المعتد في تراكيزها الدموية بين الأفراد ، خصوصاً للسيكلوسبورين والتاكروليموس والسيروليموس وحامض المييكوفينوليك . قد يكون سبب هذا تغاير في مستويات الدم عوامل مثل العمر والجنس والتأثرات المرضية—الدوائية والتأثرات الغذائية—الدوائية والقصور الكلوي والكبد والالتهاب والعدوى وتعدّد الأشكال الوراثي .

s. Anti-inflammatory Effects

The anti-inflammatory effects of glucocorticoids are primarily attributable to their multiple actions on several types of leukocytes (see Fig. 33.3).

تُعزى تأثيرات الـ GCs المضادة—للالتهاب أولياً لأفعالها على أنماط من الكريات البيض (شكل ٣٣. ٣).

First, glucocorticoids suppress the activation of **T lymphocytes** by interleukins and nuclear factor κ B (NF- κ B), a **transcription factor for proinflammatory cytokine genes**.

أولاً. تثبط الـ GCs تنشيط اللمفاويات T باللوكوترينينات والعامل النووي—الكابا ب (NF- κ B) ، عامل الانتساخ من أجل مورثات السيتوكينات المؤيدة للالتهاب .

Second, they suppress the production of cytokines by activated helper T cells. Cytokines play a major role in inflammation by recruiting and activating eosinophils and by stimulating antibody production by B cells. Glucocorticoids inhibit the production of proinflammatory cytokines by **increasing the transcription** of a gene for a protein that blocks NF- κ B, as noted earlier.

ثانياً. تثبط إنتاج السيتوكينات من الخلايا T المساعدة المنشّطة . تؤدي السيتوكينات دور مهم في الالتهاب عبر تجنيد وتنشيط اليوزينات وعبر تنبيه إنتاج الضد من الخلايا B . تثبط الـ GCs إنتاج سيتوكينات مؤيدة للالتهاب عبر زيادتها انتساخ مورثة لبروتين يحصر الـ NF— κ B ، مثل ما ذُكر سابقاً .

Third, glucocorticoids decrease the release of various chemical mediators of inflammation, including histamine, prostaglandins, leukotrienes, and other substances from mast cells, eosinophils, and inflamed tissue. They decrease the synthesis of prostaglandins and leukotrienes by increasing the **transcription of annexin-1** (previously named *lipocortin-1*), which **inhibits phospholipase A**, the first step in the eicosanoid pathway (see [Chapter 26](#)).

ثالثاً . تُنْقِصُ الـ GCs إطلاق وسائط التهاب متنوعة ، متضمنة الـ H والـ PGs والـ LTs من الخلايا البدينة واليوزينات والنسيج المُلتَهَب .. تُنْقِصُ تصنيع الـ PGs والـ LTs بزيادتها انتساخ الـ **annexin—1** (المُسَمَّى سابقاً *lipocortin-1*) الذي يُثَبِّطُ الفسفوليپاز A ، الخطوة الأولى في طريق الأيكوزانويد ..

Fourth, glucocorticoids **stabilize lysosomal membranes** of neutrophils and prevent the release of catabolic enzymes (e.g., acid phosphatase) from these organelles; this limits cytotoxic effects of inflammation.

رابعاً . تُثَبِّتُ الأغشية اليلحلولية للعَدَلَات وتمنع إطلاق إنزيمات هدم/تقويض (مثل فسفاتاز الحمض) من هذه العُضَيَّات ؛ يَحُدُّ هذا من تأثيرات الالتهاب السامة للخلية .

Fifth, glucocorticoids cause vasoconstriction and decrease capillary permeability by **increased synthesis of annexin-1** leading to **decreased prostacyclin** by the mechanism outlined previously. They also decrease the synthesis of proinflammatory cytokines and other substances released from eosinophils in blood vessels as noted previously, and both actions **reduce the vasodilation and plasma extravasation** that are the signs of inflammation.

خامساً. تسبب الـ GCs تضيق أوعية وتنقص النفوذية الوعائية بزيادتها تصنيع الإنوكسين **annoxin-1** مؤديةً إلى نقص البروستاسيكلين بآلية سبق ذكرها . تنقص تصنيع سيتوكينات مؤيدة للالتهاب ومواد أخرى منطلقة من اليوزينات في الأوعية الدموية كما لوحظ سابقاً ، وكلا الفعلين ينقص توسع الأوعية وتسرب البلازما وهي علامات التهاب .

Finally, glucocorticoids decrease activation of macrophages and decrease the synthesis and release of cytokines from these cells.

Glucocorticoids also have multiple effects on **circulating leukocytes**. Pharmacologic doses of glucocorticoids suppress lymphoid tissue and reduce the number of circulating lymphocytes. They also reduce the concentration of circulating eosinophils, basophils, and monocytes, while at the same time increasing the concentration of erythrocytes, platelets, and polymorphonuclear leukocytes.

أخيراً. تنقص الـ GCs تنشيط البالعات وتنقص تصنيع وإطلاق السيتوكينات من هذه الخلايا .
للـ GCs أيضاً تأثيرات عديدة على الكريات البيض الجائلة . تثبط الجرعات الفارماكولوجية للـ GCs النسيج اللمفاوي وتنقص عدد اللمفاويات الجائلة . تنقص أيضاً تركيز اليوزينات الجائلة والأسسات والوحيدات ، وتزيد تركيز الكريات الحمر والصفائح والكريات البيض المتعددة الشكل النووي .

D. Rituximab. [ri-TUX-i-mab] is a chimeric monoclonal antibody against the antigen CD20 on pre B-cells, mature B-cells, and memory B-cells. Rituximab causes B-cell depletion by inducing B-cell lysis and blocking B-cell activation and eventual maturation to antibody-forming plasma cells. Existing plasma cells do not express the CD20 antigen and, therefore, are unaffected by rituximab. The drug is approved for use in the treatment of B-cell lymphomas, post-transplant lymphoproliferative disease (PTLD), PTLD, and rheumatoid arthritis. The benefit of using rituximab in transplantation is for antibody removal, which has been utilized in ABO (blood type) incompatible transplants, desensitization protocols, and treatment of antibody-mediated rejection (AMR).

Intravenous administration of rituximab leads to rapid and sustained depletion of B-lymphocytes, with B-cell counts returning to normal within 9 to 12 months. Rituximab has a boxed warning for reactivation of JC virus leading to progressive multifocal leukoencephalopathy (PML) which has been reported in the nontransplant population. Activation of hepatitis B infection has also been reported following treatment, and hepatitis serologies should be monitored. **(CDC&ADCC)**

د. **Rituximab** : ضدّ وحيد النسيلة خيمري ، تجاه المستضد CD20 على طلائع الخلايا البائية والبائية الناضجة وخلايا الذاكرة البائية . يستنفذ الخلايا البائية بتحريضه انحلالها وإحصاره لتنشيطها وللإنضاج النهائي لخلايا البلازما المكوّنة للأضداد .

وجود الخلايا البلازمية لا يُعبّر المستضد CD20 ، ولهذا لا تتأثر بالريتوكسيماب .
مبرهن لمعالجة لمفوما الخلايا البائية والـ **PTLD** والتهاب المفاصل الروماتويدي .

تتمثل منفعة في الزرع في إزالة الضد ، المستخدم في زرعات الـ ABO (نمط دم) المتنافرة ، وبروتوكولات إزالة التّحسّس ومعالجة الرفض المتواسط بالـضد (**AMR**) .

يسبب إعطاؤه الوريدي نفاذ سريع ومستدام للمفاويات البائية مع عودة عددها للطبيعي في ٩—١٢ شهر . يحمل تحذير الإطار الأسود من أجل إعادة تنشيط فيروس JC المؤدي إلى اعتلال بِيضَاء الدِّماغ العَديد البَوَر المُتَرَقِّي المبلغ عنه في مجتمع عدم الزرع .

ثمة تقارير عن تنشيط عدوى التهاب الكبد بعد المعالجة ، وينبغي رصد مصلّيات التهاب الكبد .

E. Bortezomib

AMR involves the production of high levels of antibodies by plasma cells, either newly made from B-cells or from those that existed prior to transplant. One mechanism to control AMR is to target antibody production by plasma cells. *Bortezomib [bor-TEZ-oh-mib]* is a *proteasome* inhibitor that leads to cell cycle arrest and apoptosis of normal plasma cells, thereby decreasing antibody production in sensitized patients.

Bortezomib is approved for the treatment of multiple myeloma, but it has been adapted for use in the treatment of AMR in transplant patients. It can be administered via intravenous bolus or subcutaneous injection, so it has a low potential for infusion-related reactions. Bortezomib is metabolized primarily by cytochrome P450 enzymes and hepatic dysfunction has rarely been reported when multiple cycles are given.

هـ. **Bortezomib** : يكتنف الرفض المتواسط—بالضد (AMR) إنتاج مستويات كبيرة من الأضداد بواسطة خلايا البلازما ، إمّا مصنوعة حديثاً من الخلايا البائية أو من تلك الموجودة قبيل الزرع . تتمثل إحدى آليات مكافحة الـ AMR بإستهداف إنتاج الضد من الخلايا البلازمية .

هذا الدواء مثبت للبروتوزوم ، مما يؤدي إلى وقف دورة الخلية واستماتة الخلايا البلازمية الطبيعية ، وبالتالي إنقاص إنتاج الضد عند المرضى المُحَسَّسين .

مبرهن لمعالجة الورم النقيّ المتعدّد ، لكن يجري تكييفه للاستعمال في معالجة الرفض المتواسط—بالضد AMR عند مرضى الزرع . بلعة وريدية أو تحت الجلد .. يستقلب بالسيتوكروم ونادراً ما يسبب خلل وظيفة الكبد عند إعطائه في دورات عديدة .

bortezomib (Proapoptotic Agent)
proteasome degrades proapoptotic proteins

B. Costimulation blocker. *Belatacept* [bel-a-TA-sept], a second-generation costimulation blocker, is a recombinant fusion protein of CTLA-4, which, like CD28, binds to CD80 and CD86 on APCs. Binding of *belatacept* to CD80 and CD86 prevents CD28 from binding to those molecules and, thus, inhibits signal 2 of the T-cell activation pathway. *Belatacept* is approved for kidney transplantation in combination with *basiliximab*, *mycophenolate mofetil*, and *corticosteroids*. This drug can substitute for calcineurin inhibitors to avoid the detrimental long-term nephrotoxic, cardiovascular, and metabolic complications seen with *cyclosporine* and *tacrolimus*. [Note: The first-generation costimulation blocker *abatacept* is approved for rheumatoid arthritis.]. T-lymphocyte-associated antigen 4 (CTLA-4),

ب. **مُحَصِّر التنبية المشترك** : الـ **Belatacept** ، مُحَصِّر من الجيل الثاني ، بروتين اندماج مأشوب للـ **CTLA-4** (T-lymphocyte-associated antigen 4) ، الذي ، مثل الـ **CD28** ، يرتبط بالـ **CD80** والـ **CD86** على الـ **APCs** . ارتباط البيلاتاسيبت بالـ **CD80** والـ **CD86** يمنع الـ **CD28** من الارتباط بتلك الجزيئات وبالتالي يثبط الإشارة ٢ لطريق تنشيط الخلايا التائية .

مبرهن لزرع الكلية بالتوليف مع باسيليكسيماب و mycophenolate mofetil وكورتيكوستيرويدات .

بديل لمثبطات الكالسينيورين لتجنب أضرار مضاعفات السمية الكلوية الطويلة-الأمد والقلبية الوعائية والاستقلابية الملاحظة مع السيكلوسبورين والتاكروليموس .

(ملاحظة : محصر التنبية المشترك من الجيل الأول abatacept مبرهن للـ RA) .

Belatacept is the first IV maintenance immunosuppressant and is dosed in two phases. Initially, it is administered four times in the first month at a higher dose to build up drug levels and then decreased to once-monthly dosing. After 4 months, the dose is also decreased. Monthly dosing may be beneficial in patients for whom medication compliance is an issue.

*Clearance of belatacept is not affected by age, sex, race, renal, or hepatic function. Belatacept increases the risk of **post-transplant lymphoproliferative disease (PTLD)** , particularly of the central nervous system. Therefore, it is contraindicated in patients who are seronegative to Epstein-Barr virus (EBV), a common cause of (PTLD). Serological titers to EBV are typically obtained to confirm exposure.*

الـ Belatacept أول كابيت مناعة مداوم وريدي ويُجرّع في طورين . بدئياً ، يُعطى أربع مرّات في الشهر الأول بجرعة كبيرة لتأسيس مستويات الدواء ثم ينقص إلى تجريع مرّة— شهرياً . بعد ٤ شهور ، تنقص الجرعة أيضاً . التجريع شهرياً قد ينفع عند المرضى الذين يمثل امتثالهم معضلة .

لا تتأثر تصفية البيلاتاسبيت بالعمر والجنس والعرق والوظيفة الكلوية أو الكبدية . يزيد اختطار الـ PTLD (داء التكاثر اللمفي بعد الزرع) وخصوصاً الـ CNS . لهذا ، يعد ممنوع الاستعمال عند المرضى سلبيّ المصل تجاه الـ Epstein-Barr virus (EBV) ، سبب شائع للـ PTLD .

يُحصل على المعايرة المصلية لهذا الفيروس نموذجياً لتأكيد التعرض .

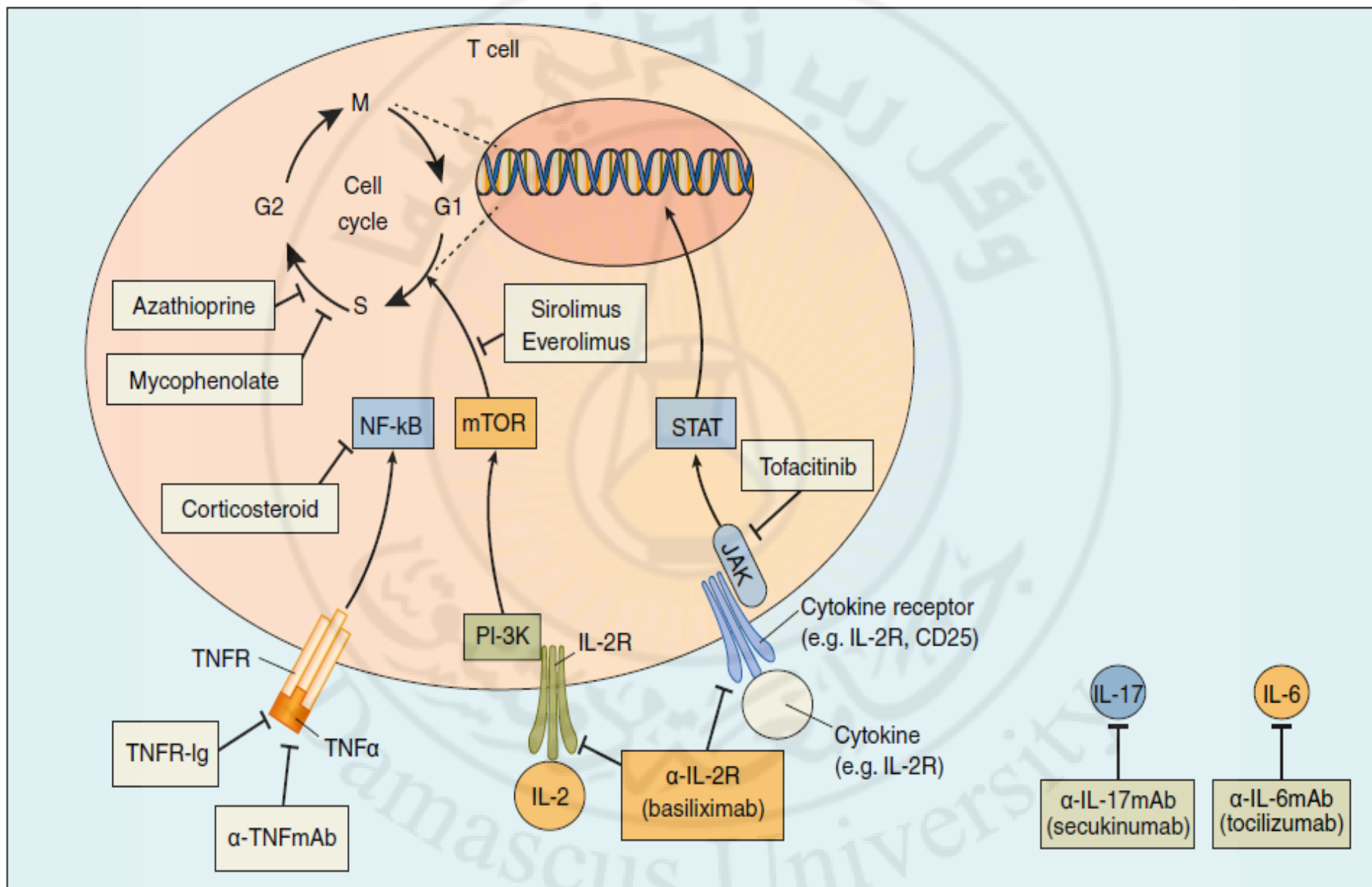


FIG. 46.3 Mechanism of action of drugs used to treat organ rejection. Sites of action for various drugs used for the treatment of organ rejection are shown. See text for further details.

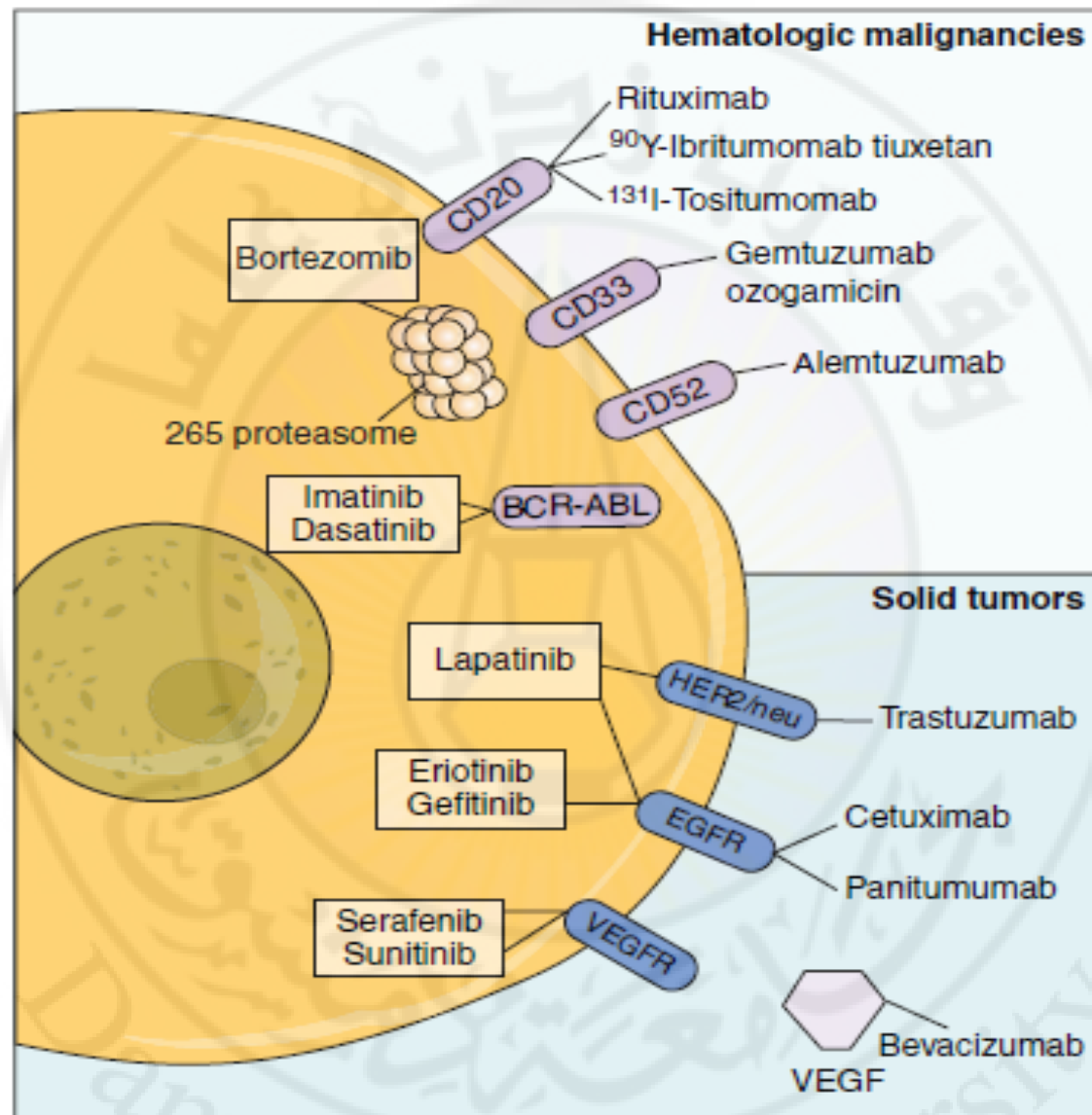


FIG. 46.2 Mechanisms of action of antineoplastic monoclonal antibodies and small molecule inhibitors. Diagram shows targets for select monoclonal antibody drugs and small molecule inhibitors that are used to treat hematologic cancers (top half) or solid tumors (bottom half). Cluster of differentiation (CD) proteins, CD20, CD33, and CD52, the 26S proteasome, the BCR-ABL fusion gene product and receptor kinases are shown.

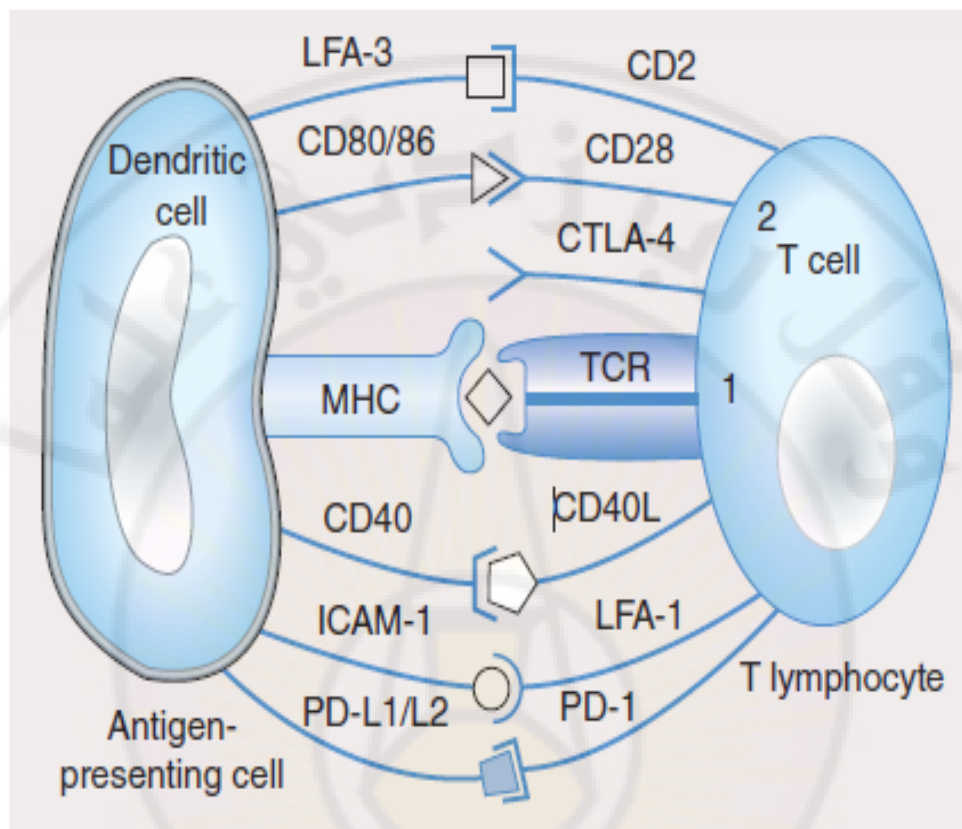


FIGURE 55-2 T-cell activation by an antigen-presenting cell requires engagement of the T-cell receptor by the MHC-peptide complex (signal 1) and binding of the costimulatory molecules (CD80, CD86) on the dendritic cell to CD28 on the T cell (signal 2). The activation signals are strengthened by CD40/CD40L and ICAM-1/LFA-1 interactions. In a normal immune response, T-cell activation is regulated by T-cell–derived CTLA-4 and PD-1. CTLA-4 binds to CD80 or CD86 with higher affinity than CD28 and sends inhibitory signals to the nucleus of the T cell, while ligation of PD-1 by PD-L1 or -L2 also inhibits T cell proliferation.

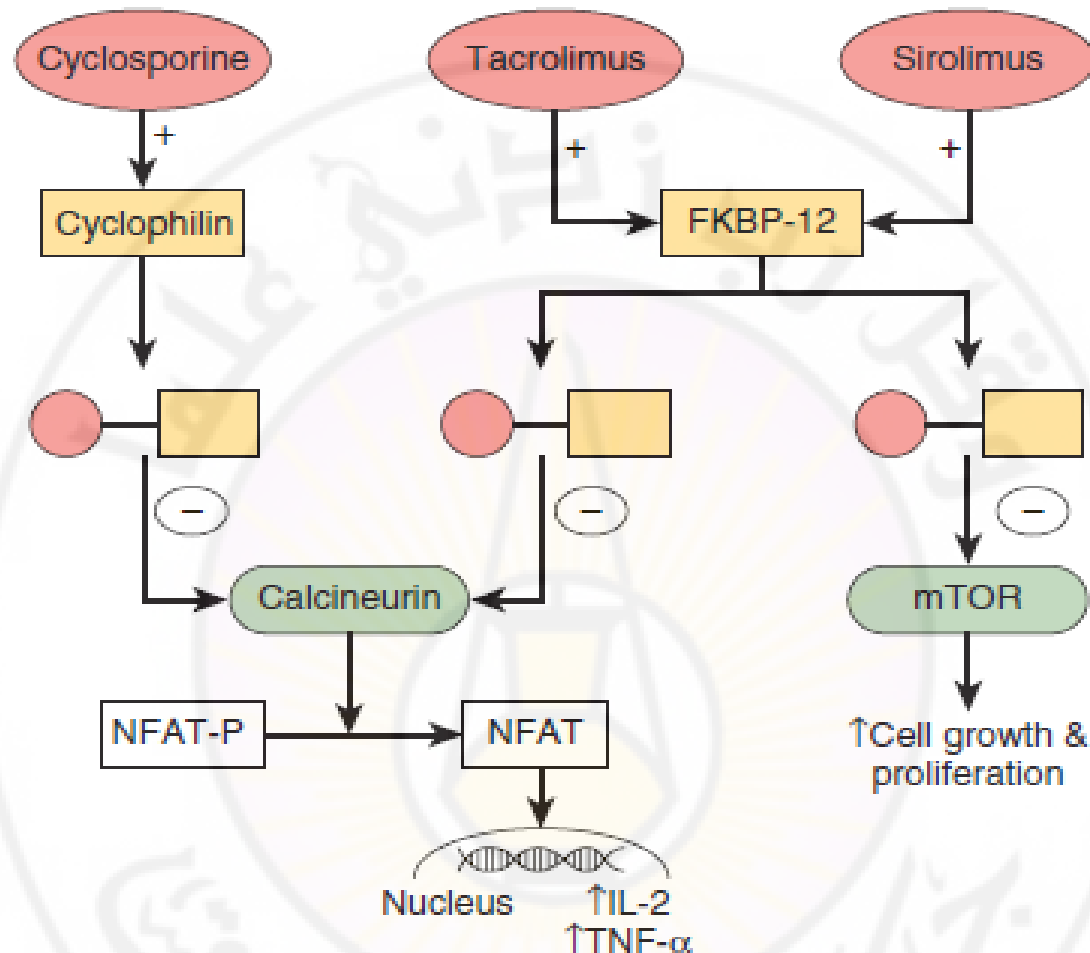


FIG. 34.4 Mechanism of Action of Calcineurin and mTOR Inhibitors. Calcineurin normally functions to dephosphorylate phosphorylated nuclear factor for activated T cells (NFAT-P) through its phosphatase activity, leading to translocation of NFAT into the nucleus, where it can bind to DNA and increase the expression of several proinflammatory cytokines, including IL-2 and TNF- α . Cyclosporine and tacrolimus are calcineurin inhibitors that bind to the immunophilins cyclophilin and FKBP-12, respectively, to form a complex that inhibits calcineurin. mTOR is a serine/threonine kinase involved in cell cycle progression. Sirolimus binds to the immunophilin FKBP-12, and the resulting complex inhibits mTOR, leading to the cell cycle arrest of B and T cells.

Antigen-Presenting Cell

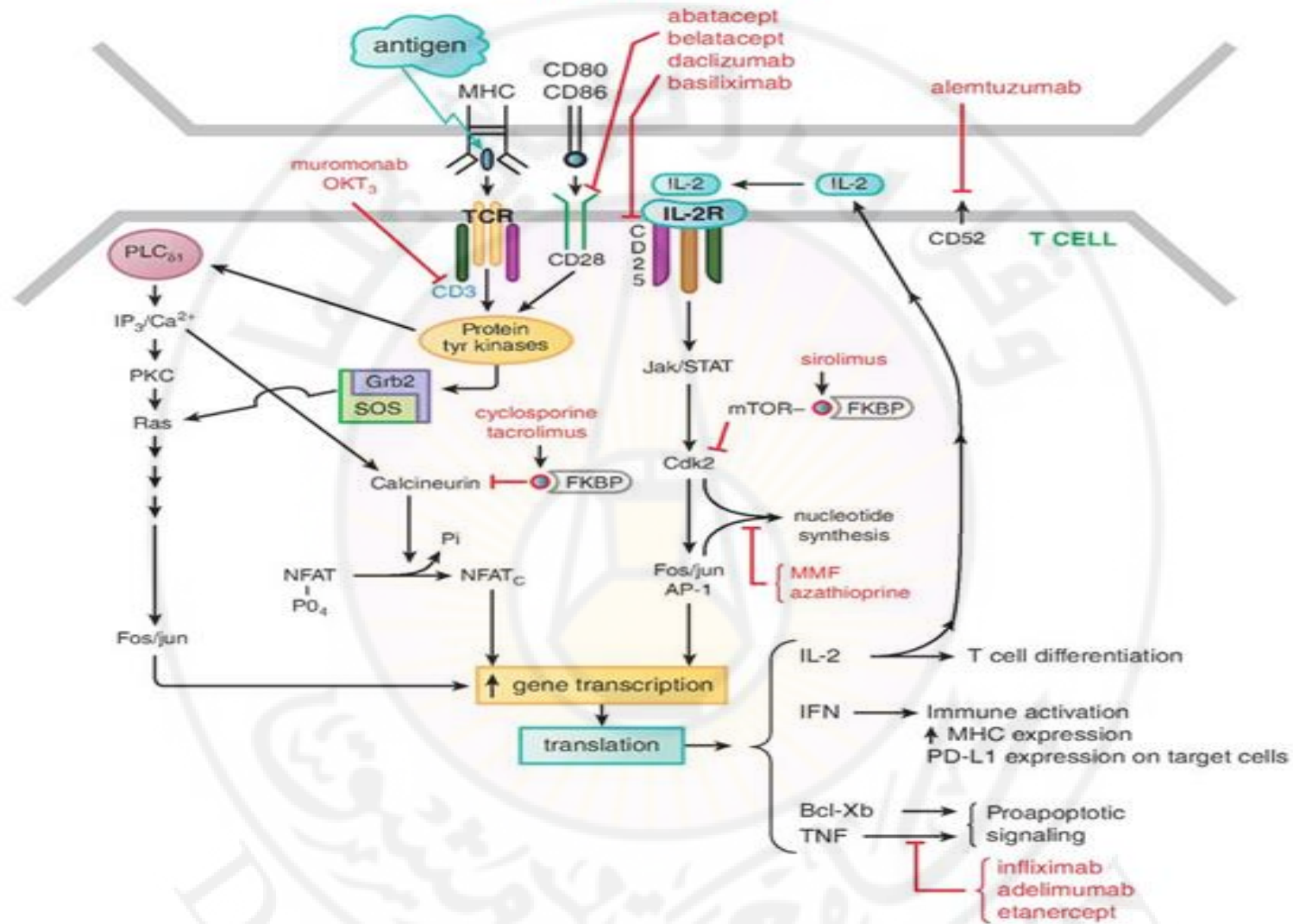


Figure 35–2 T-cell activation and sites of action of immunosuppressive agents. The TCR recognizes antigens bound to the MHC. A costimulatory signal is required for T-cell activation: The CD80/CD86-CD28 interaction from the APC to the T cell. Activation leads to IL-2 production (in a positive-feedback loop) and a host of other events, some of which are bracketed in the lower right-hand corner. Numerous agents are available to suppress T-cell activation. Cyclosporine and tacrolimus bind to immunophilins (cyclophilin and FKBP, respectively), forming a complex that inhibits the phosphatase calcineurin and the calcineurin-catalyzed dephosphorylation that permits translocation of NFAT into the nucleus. NFAT is required for transcription of IL-2 and other growth and differentiation-associated cytokines (lymphokines). Sirolimus (rapamycin) works downstream of the IL-2R, binding to FKBP; the FKBP-sirolimus complex binds to and inhibits the mTOR, a kinase involved in cell cycle progression (proliferation). MMF and azathioprine inhibit nucleic acid synthesis, thereby inhibiting T-cell proliferation. The antibody muromonab (OKT3) inhibits TCR function via interaction with its CD3 component. Daclizumab and basiliximab block IL-2 signaling by interacting with the alpha subunit of the IL-2R complex (CD25). Several antibodies can block the systemic effects of released TNF. Alemtuzumab, by binding to CD52, marks the cell for destruction, thereby depleting CD52⁺ cells.

TABLE 55–2 The cytokines.

Cytokine	Properties
Interferon- α (IFN- α)	Antiviral, oncostatic, activates NK cells
Interferon- β (IFN- β)	Antiviral, oncostatic, activates NK cells
Interferon- γ (IFN- γ)	Antiviral, oncostatic, secreted by and activates or up-regulates Th1 cells, NK cells, CTLs, and macrophages
Interleukin-1 (IL-1)	T-cell activation, B-cell proliferation and differentiation
Interleukin-2 (IL-2)	T-cell proliferation, Th1, NK, and LAK cell activation
Interleukin-3 (IL-3)	Hematopoietic precursor proliferation and differentiation
Interleukin-4 (IL-4)	Th2 and CTL activation, B-cell proliferation
Interleukin-5 (IL-5)	Eosinophil proliferation, B-cell proliferation and differentiation
Interleukin-6 (IL-6)	HCF, Th2, CTL, and B-cell proliferation
Interleukin-7 (IL-7)	CTL, NK, LAK, and B-cell proliferation, thymic precursor stimulation
Interleukin-8 (IL-8)	Neutrophil chemotaxis, proinflammatory
Interleukin-9 (IL-9)	T-cell proliferation
Interleukin-10 (IL-10)	Th1 suppression, CTL activation, B-cell proliferation
Interleukin-11 (IL-11)	Megakaryocyte proliferation, B-cell differentiation
Interleukin-12 (IL-12)	Th1 and CTL proliferation and activation
Interleukin-13 (IL-13)	Macrophage function modulation, B cell proliferation
Interleukin-14 (IL-14)	B-cell proliferation and differentiation
Interleukin-15 (IL-15)	Th1, CTL, and NK/LAK activation, expansion of T-cell memory pools
Interleukin-16 (IL-16)	T-lymphocyte chemotaxis, suppresses HIV replication
Interleukin-17 (IL-17)	Stromal cell cytokine production
Interleukin-18 (IL-18)	Induces Th1 responses
Interleukin-19 (IL-19)	Proinflammatory
Interleukin-20 (IL-20)	Promotes skin differentiation
Interleukin-21 (IL-21)	Promotes proliferation of activated T cells, maturation of NK cells
Interleukin-22 (IL-22)	Regulator of Th2 cells
Interleukin-23 (IL-23)	Promotes proliferation of Th1 memory cells
Interleukin-24 (IL-24)	Induces tumor apoptosis, induces Th1 responses
Interleukin-27 (IL-27)	Stimulates naive CD4 cells to produce IFN- γ
Interleukin-28 and -29 (IL-28, IL-29)	Antiviral, interferon-like properties
Interleukin-30 (IL-30)	p28 subunit of IL-27
Interleukin-31 (IL-31)	Contributes to type I hypersensitivities and Th2 responses
Interleukin-32 (IL-32)	Involved in inflammation
Interleukin-34 (IL-34)	Stimulates monocyte proliferation via the CSF-1 receptor (CSF-1R)
Interleukin-35 (IL-35)	Induces regulatory T cells (iT _{reg} 35)
Tumor necrosis factor- α (TNF- α)	Oncostatic, macrophage activation, proinflammatory
Tumor necrosis factor- β (TNF- β)	Oncostatic, proinflammatory, chemotactic
Granulocyte colony-stimulating factor	Granulocyte production
Granulocyte-macrophage colony-stimulating factor	Granulocyte, monocyte, eosinophil production
Macrophage colony-stimulating factor	Monocyte production, activation
Erythropoietin (epoetin, EPO)	Red blood cell production
Thrombopoietin (TPO)	Platelet production

Note: Many interleukin activities overlap and can influence and be influenced by each other.

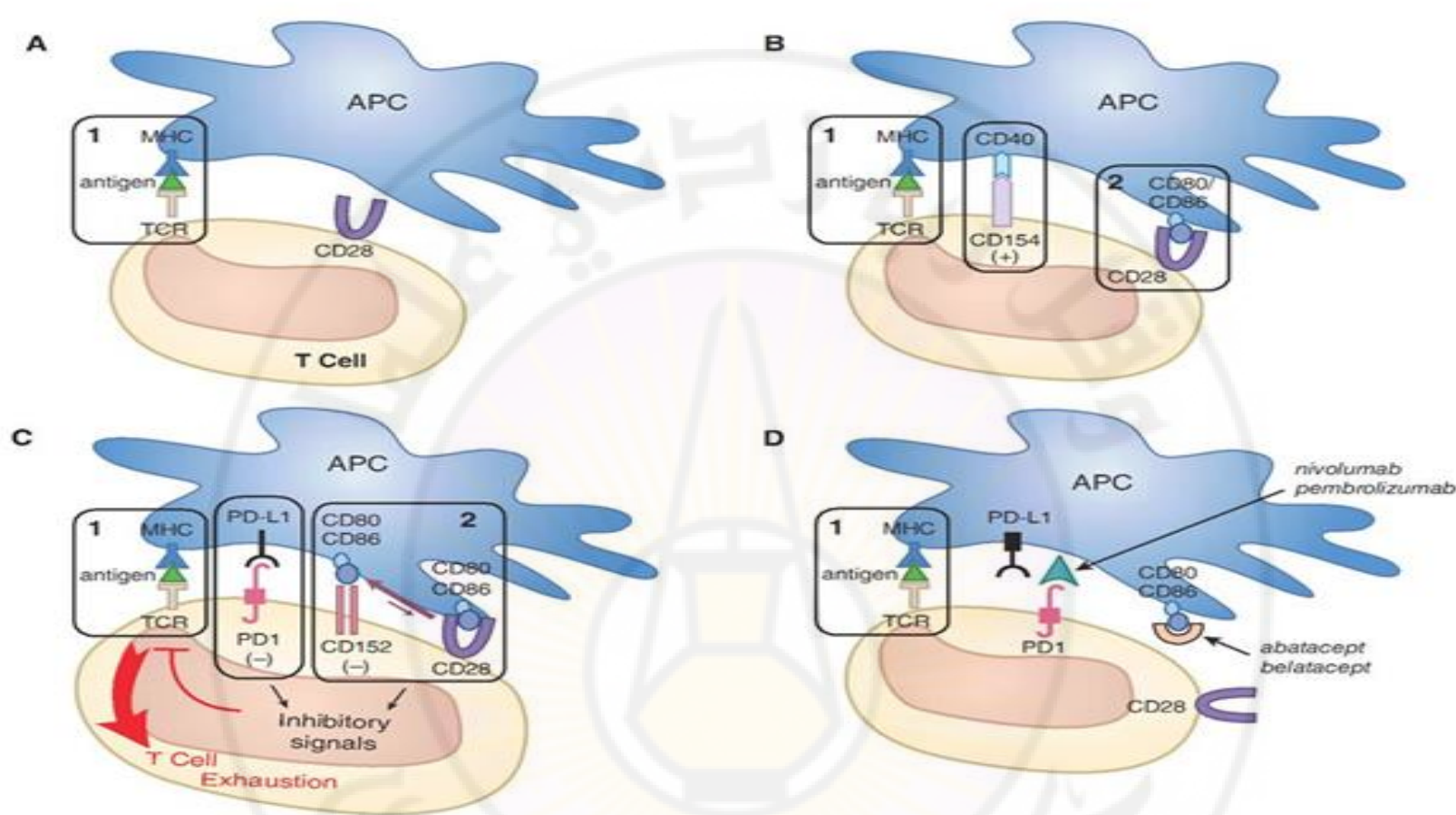


Figure 35-4 T-cell activation: costimulation and coinhibitory checkpoints. Numerous membrane CD proteins may be expressed on the APC and the T cell that lead to signaling interactions between ligands and receptors. These interactions can enhance or reduce the activation state of the T cell. Two signals are required for T-cell activation: presentation of an antigen ligand to the TCR and signaling by an additional “costimulatory” pair. **A.** The primary signal, *signal 1*, is the interaction of the TCR with the MHC-antigen complex on the APC. Activation requires a second, costimulatory interaction. **B.** *Signal 2*, the costimulatory interaction between CD28 on the T cell (the costimulatory receptor) and the costimulatory ligand on the APC, CD80/CD86, leads to T-cell activation. Additional costimulatory signals, such as the interaction of CD154 with CD40 on the APC, can further enhance T-cell activation (+). In the absence of costimulation, a T cell can become anergic or unresponsive. **C.** Additional APC–T-cell interactions can occur after T-cell activation, and some can be inhibitory, providing *immune checkpoints* that are important for reducing autoimmunity and for regulating the size and extent of immune responses. For example, the interaction of CD152 (CTLA4) with CD80/86 produces inhibitory signals that attenuate T-cell activation and proliferation (–). CD28 and CD152 compete for binding to CD80/CD86. As the figure suggests, the affinity of CD152 for CD80/CD86 exceeds that of CD28, and the equilibrium lies toward the formation of the inhibitory signaling complex, CD152–CD80/CD86. T cells may express varying amounts of another important modifier, PD1 (CD279). When liganded by PD-L1, PD1 produces inhibitory signals (↑ protein phosphatase activity, ↓ signaling by TCR, ↓ MAPK activity; see Figure 35-2) and reduces T-cell proliferation, leading to T-cell exhaustion, a state of hyporesponsiveness. When PD1 is highly expressed, as during conditions of chronic viral infection and cancer, suppression of T-cell activity via this pathway can be very effective; this pathway can facilitate continued viral replication and tumor progression. **D.** These immune checkpoints are useful sites for pharmacological regulation of T-cell activation. For instance, the agents abatacept and belatacept are fusion proteins that contain the CTLA4 domain of CD154 and act as decoys. These agents block costimulation of T cells by binding CD80/CD86 (see additional examples in Figure 35-2). Nivolumab and pembrolizumab are antibodies to PD1 and block interaction of PD1 with PD-L1, thereby blocking the immune suppression that would normally ensue and producing a state of immune hyperactivity. Checkpoint inhibitors that enhance immune responses are being used in cancer therapy (see Chapter 67). Antibodies can also be designed to be stimulatory ligands at checkpoints, to aid in generating a state of immune suppression that would be useful in treating autoimmune diseases.

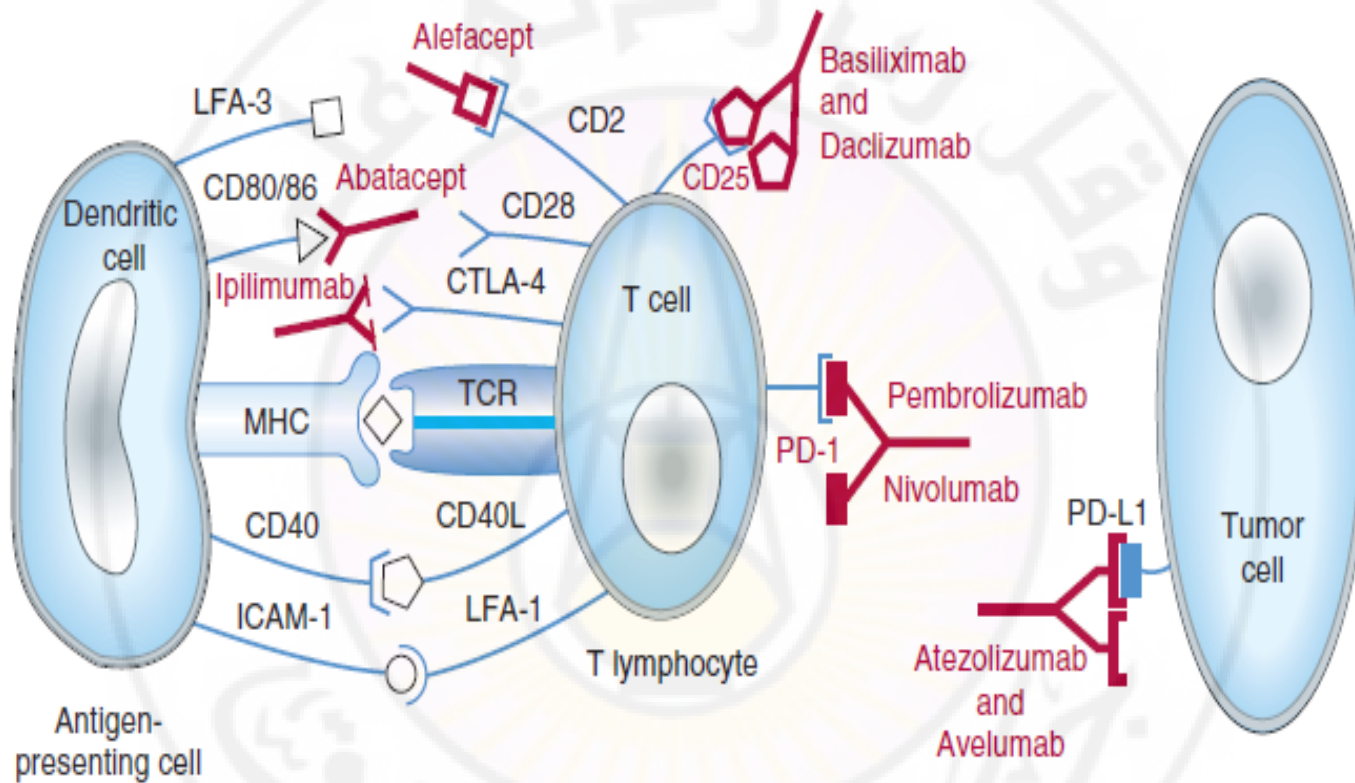
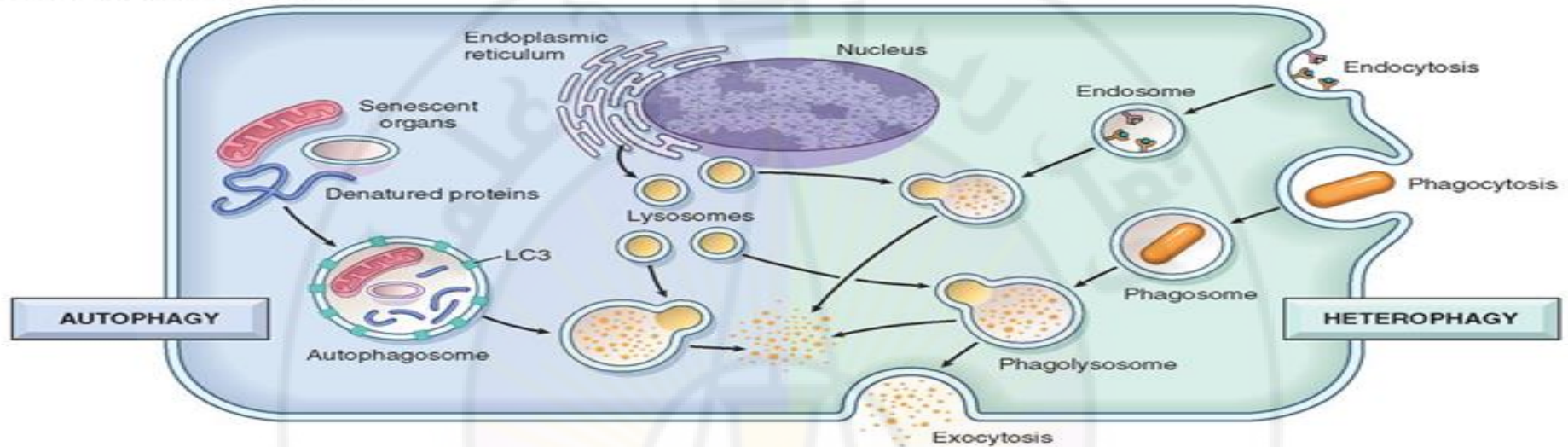


FIGURE 55-7 Actions of some monoclonal antibodies (*shown in red*). CTLA-4-IgFc fusion protein (CTLA-4-Ig, abatacept) binds to CD80/86 on DC and inhibits T-cell costimulation. Alefacept inhibits activation of T cells by blocking the interaction of LFA-3 and CD2. Basiliximab and daclizumab block IL-2 from binding to the IL-2 receptor (CD25) on T cells, preventing activation; CD25 is also important for the survival of T regulatory cells. T-cell activation can be maintained or restored if CTLA-4 interaction with CD80/86 is blocked using an anti-CTLA-4 antibody (ipilimumab); ipilimumab inhibits CTLA-4 signaling and prolongs activation. Pembrolizumab and nivolumab bind to PD-1, while atezolizumab binds to PD-L1. Each of these three Mabs inhibits the negative signal delivery by PD-1, also prolonging T cell activation.

A LYSOSOMAL DEGRADATION



B PROTEASOMAL DEGRADATION

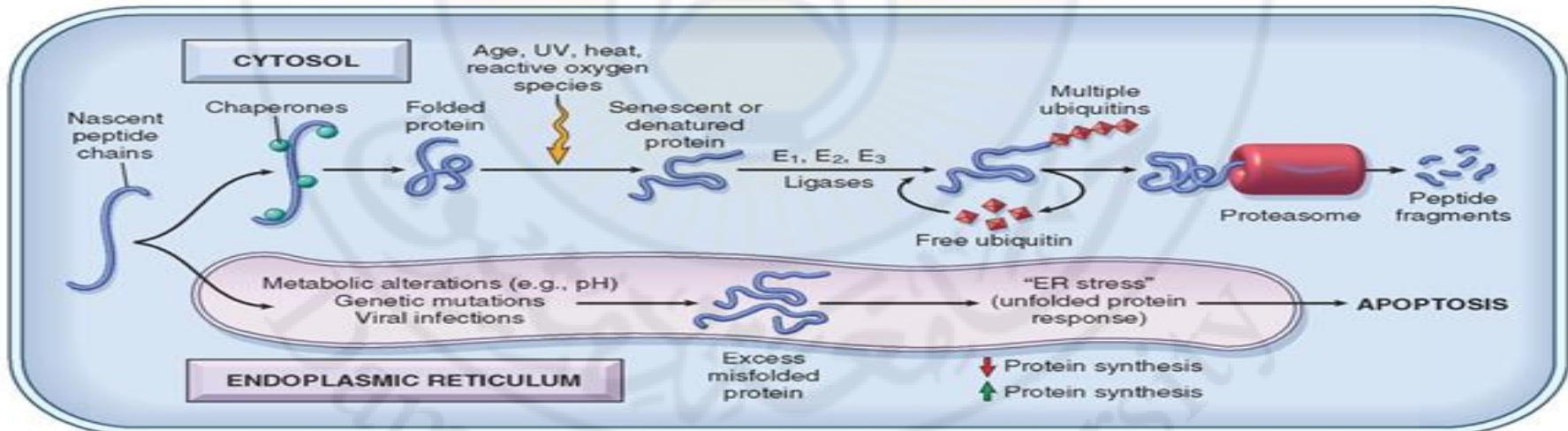


Fig. 1.10 Intracellular catabolism. (A) Lysosomal degradation. In heterophagy (right side), lysosomes fuse with endosomes or phagosomes to facilitate the degradation of their internalized contents (see Fig. 1.8). The end products may be released into the cytosol for nutrition or discharged into the extracellular space (exocytosis). In autophagy (left side), senescent organelles or denatured proteins are targeted for lysosome-driven degradation by encircling them with a double membrane derived from the ER and marked by LC3 proteins (microtubule-associated protein 1A/1B-light chain 3). Cell stressors such as nutrient depletion or certain intracellular infections can also activate the autophagocytic pathway. (B) Proteasome degradation. Cytosolic proteins destined for turnover (e.g., transcription factors or regulatory proteins), senescent proteins, or proteins that have become denatured because of extrinsic mechanical or chemical stresses can be tagged by multiple ubiquitin molecules (through the activity of E1, E2, and E3 ubiquitin ligases). This marks the proteins for degradation by proteasomes, cytosolic multisubunit complexes that degrade proteins to small peptide fragments. High levels of misfolded proteins within the ER trigger a protective unfolded protein response engendering a broad reduction in protein synthesis, but specific increases in chaperone proteins that can facilitate protein refolding. If this is inadequate to cope with the levels of misfolded proteins, apoptosis is induced.

B PROTEASOMAL DEGRADATION

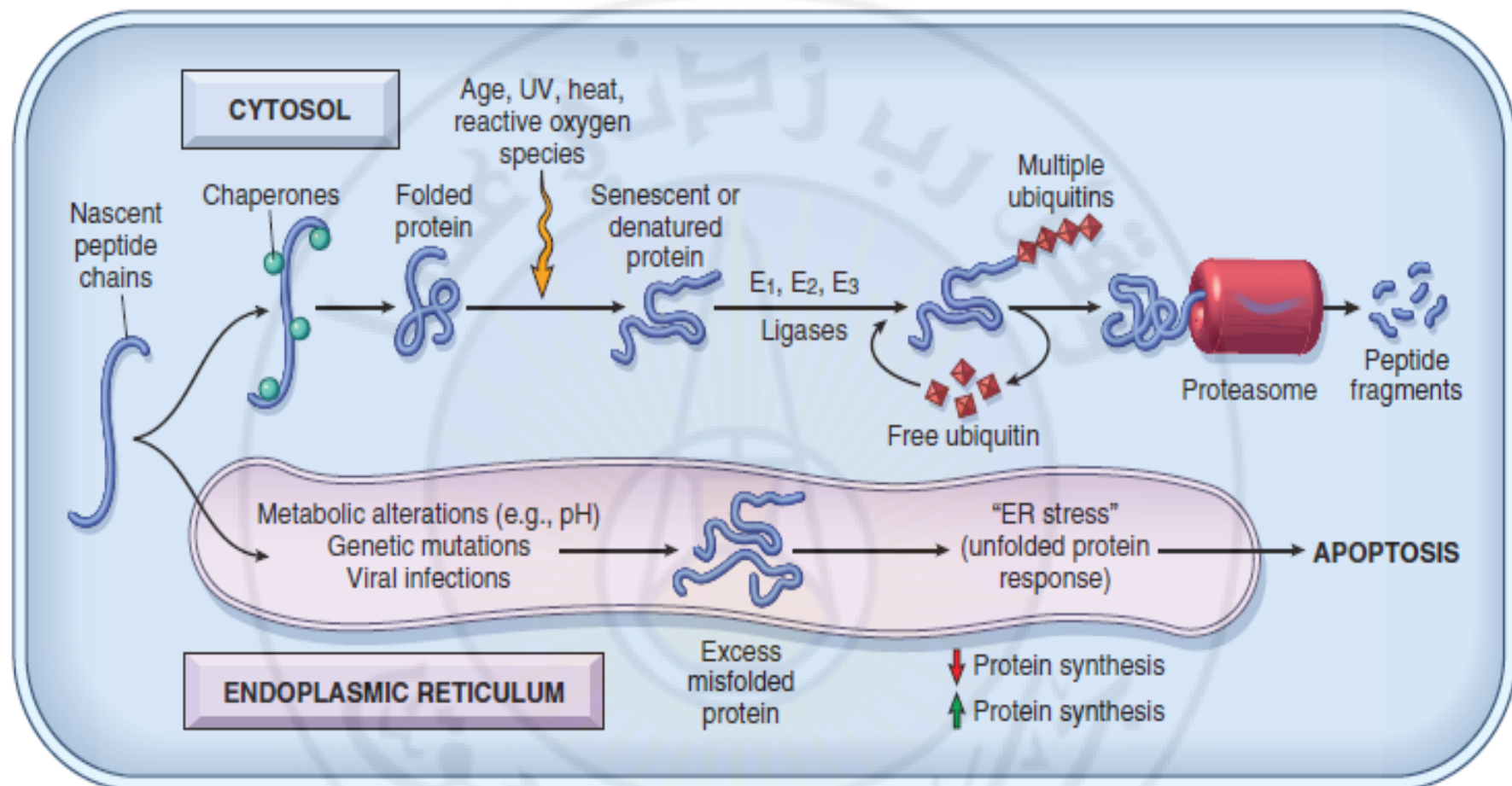


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TABLE 34.2 Biopharmaceuticals Used for Immunosuppression

Target/Factor	Type of Molecule	Generic Name	Action/Indications
Multiple human T-cell Ags	Polyclonal	Anti-thymocyte globulin (ATG)	Depletes lymphocytes/transplantation
TNF- α	Recombinant humanized mAb	Adalimumab	Binds to TNF- α /autoimmune disorders: Crohn disease, ulcerative colitis, psoriasis, RA
	Chimeric mAb	Infliximab	Inhibits TNF- α binding to its receptor/autoimmune disorders: Crohn disease, ulcerative colitis, psoriasis, RA
	Recombinant fusion protein	Etanercept	Binds to TNF- α ; functions as a decoy receptor/autoimmune disorders: psoriasis, RA
IL-1	Recombinant IL-1 receptor antagonist (IL-1RA)	Anakinra	Blocks IL-1 from binding to its receptor/RA
IL-1 β	Human mAb	Canakinumab	Binds IL-1 β , preventing it from interacting with its receptor/rare autoimmune disorders ^a
IL-2 receptor α chain on activated T cells (CD25)	Chimeric mAb	Basiliximab	Prevents T-cell replication and activation of B cells/transplantation
	Humanized mAb	Daclizumab	
IL-17A	Human mAb	Secukinumab	Binds IL-17A, preventing it from interacting with its receptor/psoriasis, multiple sclerosis
CD3 ϵ chain	Murine mAb	Muromonab-CD3	Depletes T cells/transplantation
CD2	Human fusion protein	Alefacept	Binds CD2 on T cells, interfering with T-cell activation/psoriasis
CD80	Human fusion protein	Abatacept	Binds CD80 on APCs, preventing its interaction with its receptor (CD28) on naïve T cells/RA
		Belatacept	
CD52 glycoprotein	Humanized mAb	Alemtuzumab	Prolonged T- and B-cell depletion/chronic lymphocytic leukemia

^aFor the treatment of cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease.
mAb, Monoclonal antibody; *RA*, rheumatoid arthritis.

TABLE 35-1 ■ SITES OF ACTION OF SELECTED IMMUNOSUPPRESSIVE AGENTS ON T-CELL ACTIVATION

DRUG	SITE (AND MECHANISM) OF ACTION
Glucocorticoids	Glucocorticoid response elements in DNA (regulate gene transcription)
Cyclosporine	Calcineurin (inhibits phosphatase activity)
Tacrolimus	Calcineurin (inhibits phosphatase activity)
Azathioprine	DNA (false nucleotide incorporation)
Mycophenolate mofetil	Inosine monophosphate dehydrogenase (inhibits activity)
Sirolimus	mTOR, protein kinase involved in cell-cycle progression (inhibits activity)
Everolimus	mTOR, protein kinase involved in cell-cycle progression (inhibits activity)
Belatacept	Costimulatory ligands (CD80 and CD86) present on antigen presenting cells (inhibits activity)
Alemtuzumab	CD52 protein, widely expressed on B cells, T cells, macrophages, NK cells (induces lysis)
Muromonab-CD3	T-cell receptor complex (blocks antigen recognition)
Daclizumab, basiliximab	IL-2R (block IL-2-mediated T-cell activation)

Table 18.5 Mechanism of action of immunosuppressants commonly used following renal transplantation

Drug	Mechanism	Comment
Steroids	Bind to steroid receptors and inhibit gene transcription and function of T-cells, macrophages and neutrophils	Prophylaxis against and reversal of rejection
Ciclosporin	Forms complex with intracellular protein cyclophilin → inhibits calcineurin. Ultimately inhibits interleukin-2 synthesis and T-cell activation	Long-term maintenance therapy against rejection
Tacrolimus	Forms complex with an intracellular protein → inhibits calcineurin	Long-term maintenance therapy against rejection Rescue therapy in severe or refractory rejection
Sirolimus	Inhibits interleukin-2 cell signalling → blocks T-cell cycling and inhibits B-cells	Usually used in combination with ciclosporin ± steroids
Mycophenolate	Inhibits inosine monophosphate dehydrogenase → reduces nucleic acid synthesis → inhibits T- and B-cell function	Usually used in combination with ciclosporin/tacrolimus ± steroids
Azathioprine	Incorporated as a purine in DNA → inhibits lymphocyte and neutrophil proliferation	Usually used in combination with ciclosporin/tacrolimus ± steroids
Muromonab (OKT3, mouse monoclonal anti-CD3)	Binds to CD3 complex → blocks, inactivates or kills T-cell. Short $t_{1/2}$	Prophylaxis against rejection Reversal of severe rejection
Polyclonal horse/rabbit antithymocyte or antilymphocyte globulin (ATG, ALG)	Antibodies against lymphocyte proteins → alter T- and B-cell activity	Prophylaxis against rejection Reversal of severe rejection
Humanised or chimaeric anti-CD25 (basiliximab and daclizumab)	Monoclonal antibodies that bind CD25 in interleukin-2 complex → prevent T-cell proliferation	Prophylaxis against acute rejection in combination with ciclosporin and steroids

**TABLE 70-9 ■ MECHANISM OF ACTION FOR
SELECTED CYTOTOXIC, IMMUNOSUPPRESSIVE, AND
IMMUNOMODULATORY DRUGS**

Methotrexate	Dihydrofolate reductase inhibitor
Fluorouracil	Blocks methylation in DNA synthesis
Cyclophosphamide	Alkylates and cross-links DNA
Mechlorethamine hydrochloride	Alkylating agent
Carmustine	Cross-links in DNA and RNA
Vinblastine	Inhibits microtubule formation
Bleomycin	Induction of DNA strand breaks
Azathioprine	Purine synthesis inhibitor
Mycophenolate mofetil	Inosine monophosphate dehydrogenase inhibitor
Cyclosporine	Calcineurin inhibitor
Tacrolimus	Calcineurin inhibitor
Pimecrolimus	Calcineurin inhibitor
Sirolimus	mTOR inhibitor
Imiquimod	Interferon α induction via toll-like receptor 7
Dapsone	Inhibits neutrophil migration, oxidative burst
Thalidomide	Cytokine modulation

Drug Facts for Your Personal Formulary: *Immunosuppressants and Tolerogens*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Glucocorticoids		
• Prednisone The liver converts prednisone to prednisolone.	Prevent and treat transplant rejection, treat GVHD in bone marrow transplant, autoimmune disease, rheumatoid arthritis, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus	• Broad effects on cellular immunity • Affects transcription of many genes; ↓ NF-κB activation, ↓ pro-inflammatory cytokines IL-1 and IL-6 • ↓ T-cell proliferation, cytotoxic T-lymphocyte activation and neutrophil and monocyte function • Can cause ↑ blood glucose, hypertension, Cushingoid habitus, ↑ weight, ↑ risk of infection, osteoporosis, glaucoma, cataracts, depression, anxiety, psychosis • Long-term treatment ⇒ adrenal suppression; withdraw slowly on alternate days
• Prednisolone	Rheumatoid arthritis, uveitis, ulcerative colitis, multiple sclerosis, vasculitis, sarcoidosis, systemic lupus erythematosus	• As above
• Methylprednisolone	Systemic lupus erythematosus, multiple sclerosis	• As above
• Dexamethasone	Rheumatoid arthritis, idiopathic thrombocytopenic purpura	• As above
Calcineurin Inhibitors		
• Cyclosporine	Transplant rejection prophylaxis, transplant rejection rescue therapy, rheumatoid arthritis, psoriasis and other skin diseases, xerophthalmia	• Use algorithms to delay dosing until renal function OK in kidney transplant patients • Monitor C_0 to avoid side effects • Side effects: tremor, hallucinations, drowsiness, coma, nephrotoxicity, hypertension, hirsutism, hyperlipidemia, gum hyperplasia • Metabolized by CYP3A ⇒ drug interactions • Severe interactions with antiarrhythmics
• Tacrolimus	Transplant rejection prophylaxis, transplant rejection rescue therapy	• GI absorption is incomplete and variable • Side effects include nephrotoxicity, neurotoxicity, GI complaints, and hypertension • Glucose intolerance and diabetes mellitus • Monitor blood levels to avoid nephrotoxicity
Antiproliferative and Antimetabolic Agents		
• Azathioprine	Purine metabolism inhibitor, adjunct for prevention of organ transplant rejection, rheumatoid arthritis	• Renal clearance has little effect on efficacy or toxicity • Side effects include bone marrow suppression (leukopenia > thrombocytopenia > anemia) • Susceptibility to infections, hepatotoxicity, alopecia, GI toxicity • Avoid allopurinol
• Mycophenolate mofetil	Purine metabolism inhibitor, prophylaxis of transplant rejection, used off label for systemic lupus erythematosus, multiple sclerosis, sarcoidosis	• Side effects include GI (diarrhea and vomiting) and hematologic (leukopenia, pure red cell aplasia) problems • Contraindicated in pregnancy
• Sirolimus	mTOR inhibitor, prophylaxis of organ transplant rejection, incorporated into stents to inhibit occlusion	• Monitor blood levels • Hyperlipidemia • Anemia, leukopenia, thrombocytopenia • GI effects, mouth ulcers, hyperkalemia • Anticancer effects • Metabolized by CYP3A; requires close attention to drug interactions
• Everolimus	mTOR inhibitor, astrocytoma, breast cancer, kidney and liver transplant rejection prophylaxis, pancreatic neuroendocrine tumor, renal angiomyolipoma, renal cell cancer	• Pharmacokinetics distinct from sirolimus • Toxicity similar to sirolimus
• Temsirolimus	mTOR inhibitor	
T-cell costimulatory blocker		
• Belatacept	Prevention of renal transplant rejection	• Due to an increased risk of post-transplant lymphoproliferative disorder predominantly involving the CNS, progressive multifocal leukoencephalopathy, and serious CNS infections, administration of higher than the recommended doses or more frequent dosing is NOT recommended.

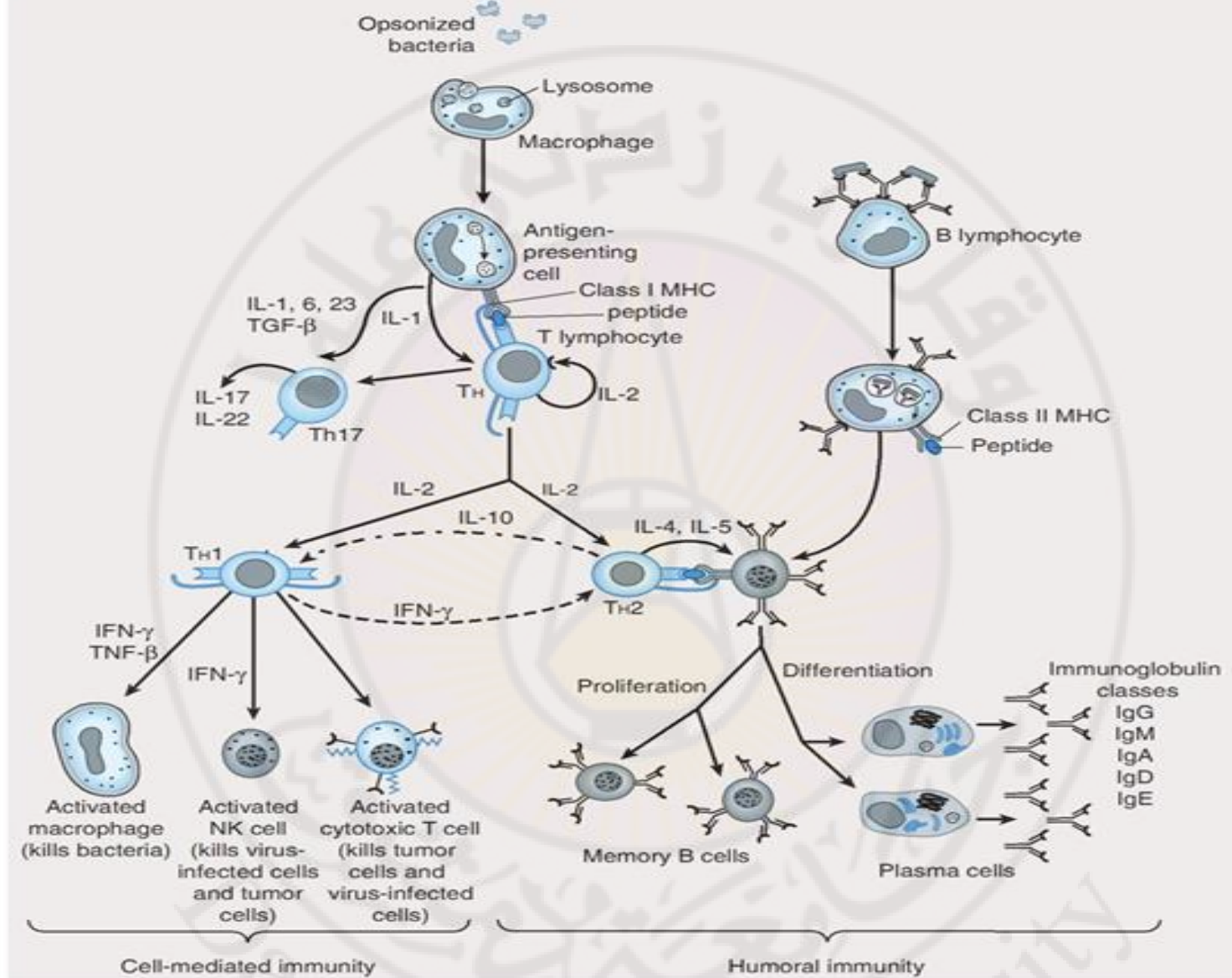


FIGURE 55-3 Scheme of cellular interactions during the generation of cell-mediated and humoral immune responses (see text). The cell-mediated arm of the immune response involves the ingestion and digestion of antigen by antigen-presenting cells such as macrophages. Activated T_H cells secrete IL-2, which causes proliferation and activation of cytotoxic T lymphocytes as well as T_H1 and T_H2 cell subsets. T_H1 cells also produce $IFN-\gamma$ and $TNF-\beta$, which can directly activate macrophages and NK cells. T_H17 cells may be induced by IL-1, -6, -23 or $TGF-\beta$ secretion by antigen-presenting cells; T_H17 cells are inflammatory and secrete IL-17 and -22. The humoral response is triggered when B lymphocytes bind antigen via their surface immunoglobulin. They are then induced by T_H2 -derived IL-4 and IL-5 to proliferate and differentiate into memory cells and antibody-secreting plasma cells. Regulatory cytokines such as $IFN-\gamma$ and IL-10 down-regulate T_H2 and T_H1 responses, respectively (dashed arrows).

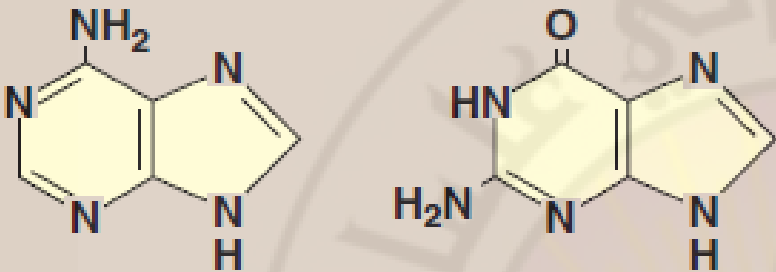
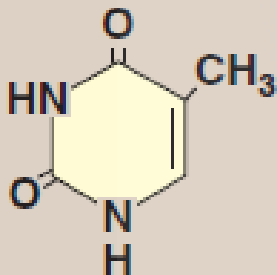
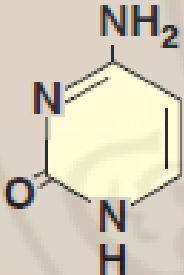
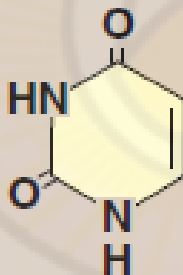
DNA and RNA Purines		
		
Adenine (A)		Guanine (G)
RNA Pyrimidines		
		
Thymine (T)	Cytosine (C)	Uracil (U)
DNA Pyrimidines		

Figure 22.1

Purines and pyrimidines commonly found in DNA and RNA.

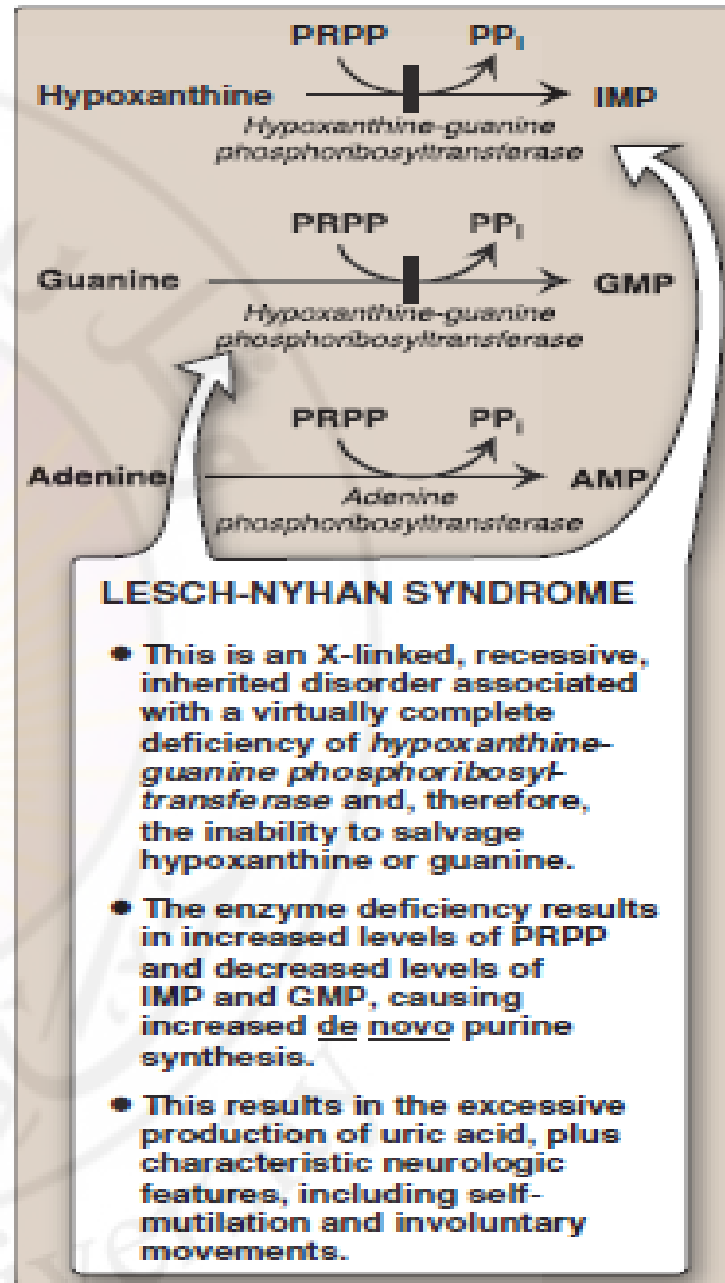


Figure 22.10

Salvage pathways of purine nucleotide synthesis.

Go back to your immunology and remember that your antibodies are just about the most target-specific cells in your body.

- 1-o- : mouse (all mouse)
- 2-xi- : chimeric (part human, part non-human)
- 3-zu- : humanized (mostly human, part non-human)
- 4-u- : human (all human, all the time)

The ending letters (stem) of the generic names are like surnames that tell what family the drug is from and how the drug works to kill cancer cells. **Monoclonal antibodies** end with the stem “-mab” and small molecule inhibitors end with the stem “-ib”.

The suffix اللاحقة "nib" indicates a small-molecule inhibitor ("nib" is verbal shorthand for "inhibit") of kinase enzymes. More specifically, "tinib" is used for tyrosine kinase inhibitors, "anib" for angiogenesis inhibitors, and rafenib for rapidly accelerated fibrosarcoma (RAF) kinase inhibitors.

Monoclonal antibodies are named based on a specific structure developed by the International Nonproprietary Names Working Group, under the direction of the World Health Organization. This structure consists of a prefix, substem A, substem B, and suffix.

Monoclonal antibodies “-mab” and

Chimeric human-mouse—drugs ending in “-ximab” (i.e., rituximab)

Humanized mouse—drugs ending in “-zumab” (i.e., bevacizumab)

Fully human—drugs ending in “-mumab” (i.e., ipilimumab).

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- "anib" for angiogenesis inhibitors, and
- rafenib for rapidly accelerated fibrosarcoma (RAF) kinase inhibitors.

both “-mabs” and “-ibs” contain an additional stem to describe the targeted therapies bullseye.

the “tu” in rituximab indicates the target is the **tumor**,
“ci” in bevacizumab designates the **circulatory** system,
“li” in ipilimumab identifies the **immune system target**.

Some of the intracellular targets for the “-ibs” include:

1. Tyrosine kinase inhibition—sub stem “-tinib” (i.e., imatinib)
2. Proteasome inhibition—“-zomib” (i.e., bortezomib)
3. Cyclin-dependent kinase inhibition—“-ciclib” (i.e., seliciclib)

ib”. The “-mab” family of targeted therapies has three distinct methods for interfering with cancer cell growth.

1. Attach to receptors on the outside of cells to prevent the receptors from interacting with signaling molecules (e.g., growth factor receptors and growth factor interaction)
2. Deliver radioactive molecules or toxins to the inside of the cells through attachment to cellular receptors
3. Activate the body’s natural immune response

The “-mab” family is used when receptor targets are overexpressed on the outside of cancer cells. Conversely, the “-ib” family targets processes within the cell and therefore must be small enough in molecular weight to enter the cell and interfere with proteins on both the inside and outside of the cell. Proteins that code for growth or inhibit growth are some of the targets of these small but powerful family of drugs.

The sub stem of the generic names of the “-mabs” identifies the source where the antibodies were generated or cloned. The three most common sources are

1. Chimeric human-mouse—drugs ending in “-ximab” (i.e., rituximab)
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3. Fully human—drugs ending in “-mumab” (i.e., ipilimumab).

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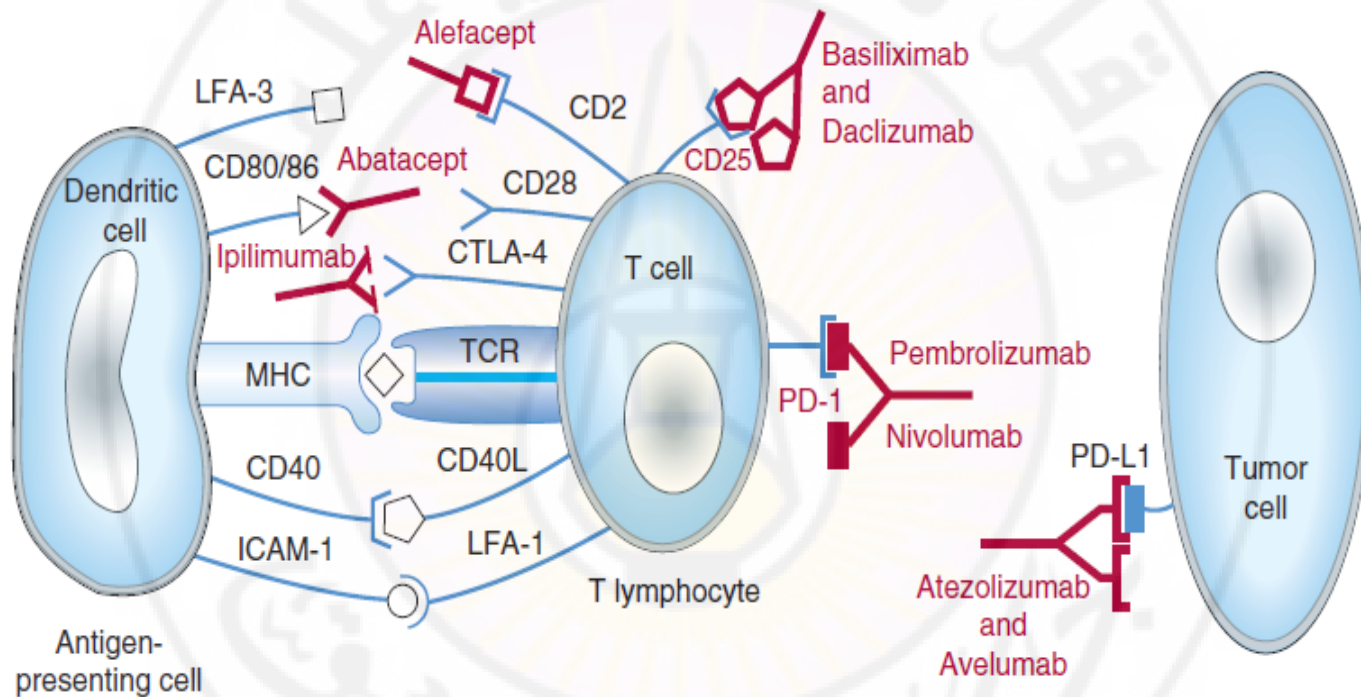


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