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Hormonal Therapy

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Hormone therapy

- one of the major modalities of medical oncology .
- It involves the manipulation of the endocrine system through exogenous or external administration of specific hormones, particularly steroid hormones, or drugs which inhibit the production or activity of such hormones (hormone antagonists).
- Hormonal therapy is used for several types of cancers derived from hormonally responsive tissues, including the breast, prostate, endometrium, and adrenal cortex.
- Hormonal therapy may also be used in the treatment of paraneoplastic syndromes or to ameliorate certain cancer- and chemotherapy-associated symptoms, such as anorexia.

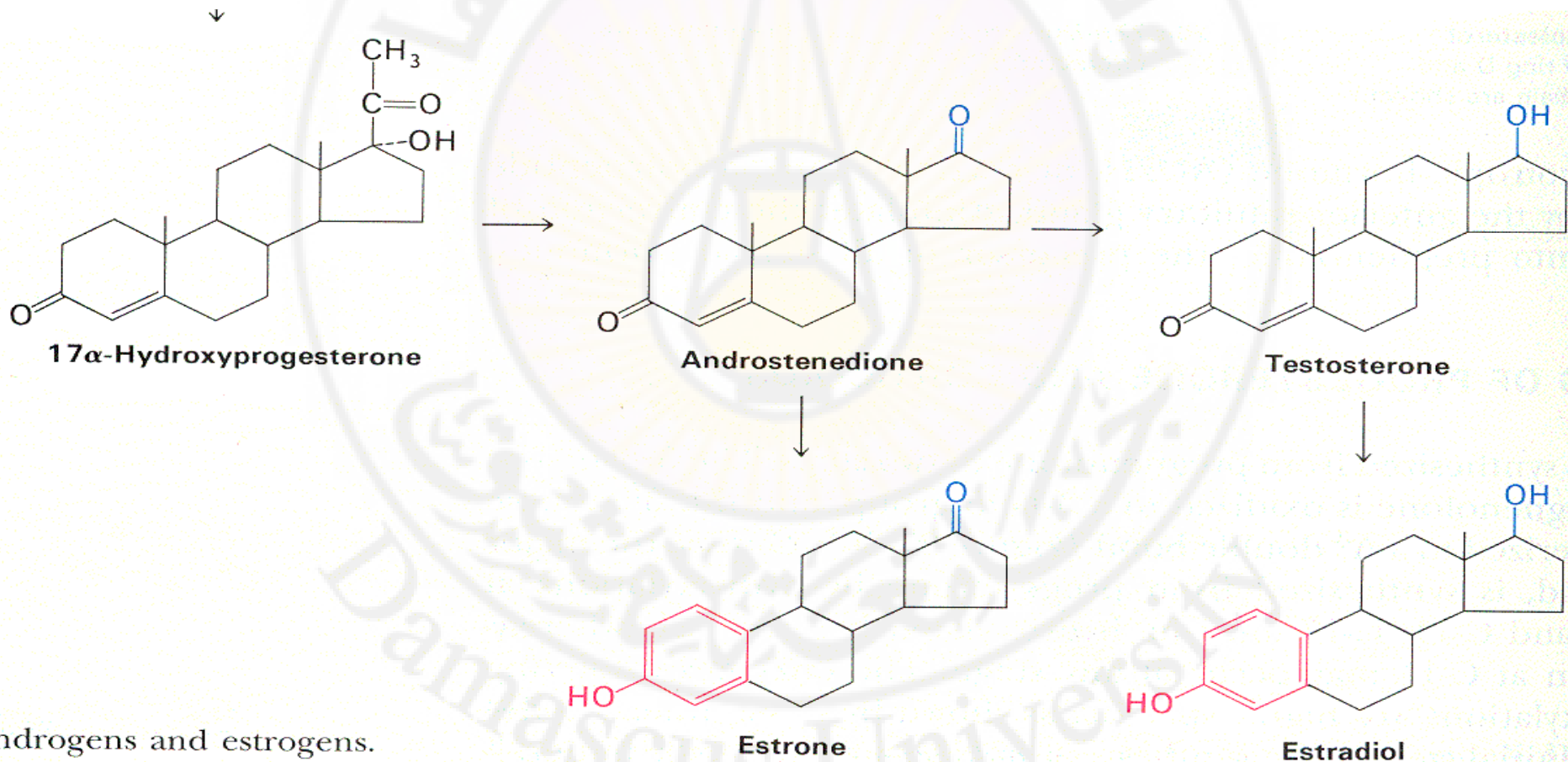
Hormonal therapy

- Hormones are peptide or a steroid which is produced by a tissue and conveyed to the bloodstream to the target organs for maturation
- Hormones are involved in growth and development of an individual
- Breast and Prostate cancers have a common feature in that at some stage in their evolution, they were hormone dependent cancer, and therefore hormonotherapy is an essential therapy approach

Hormones & Hormone Antagonists

- Least toxic of anticancer drugs
- Highly selective
- **Breast**, **Endometrial**, **Prostate** cancers
- **6 Categories**
 - Estrogens
 - Antiestrogens
 - Aromatase inhibitors
 - Androgens – Progestins
 - Antiandrogens
 - Gonadotropin-releasing hormone analogs

Hormone Synthesis

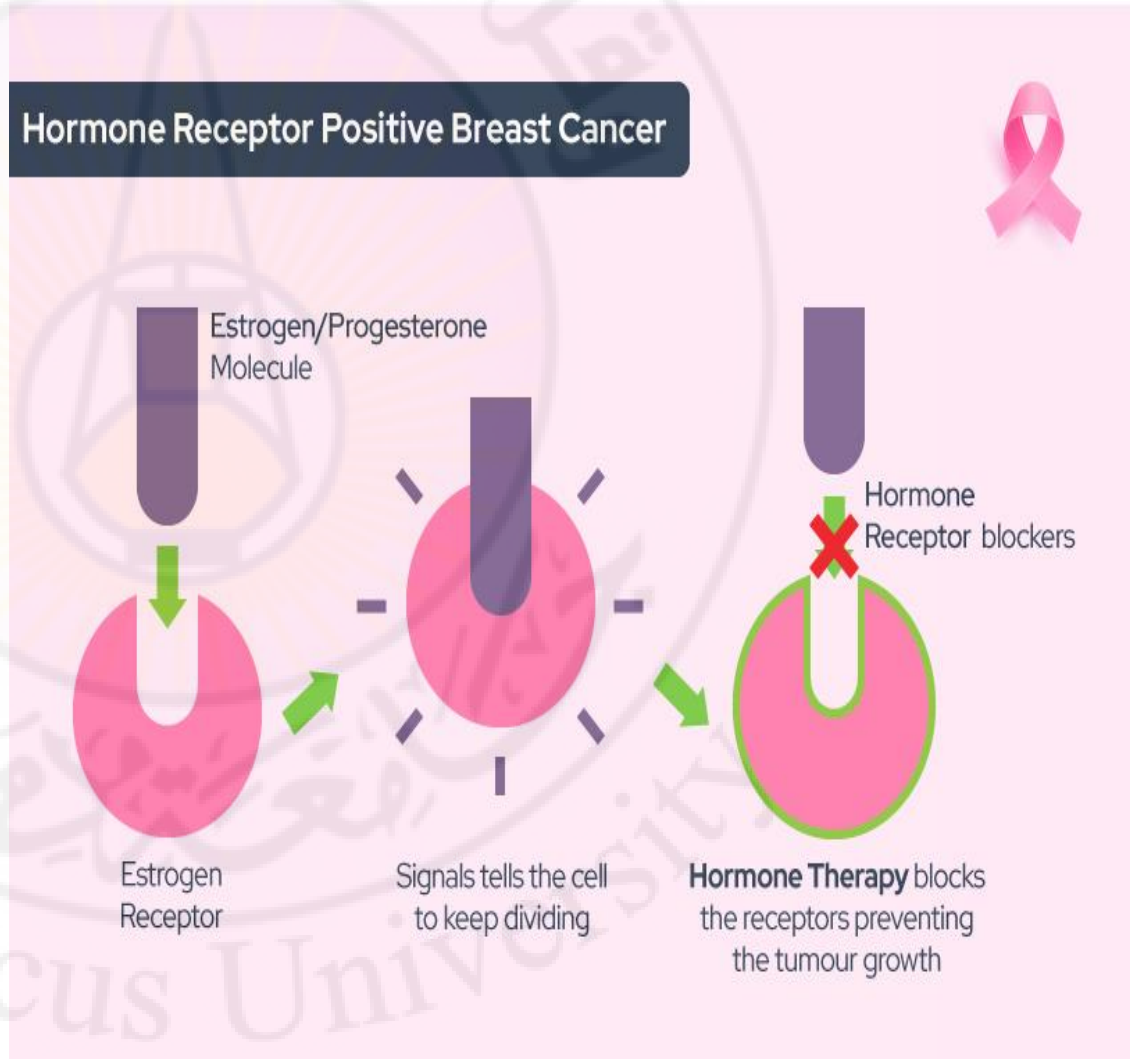


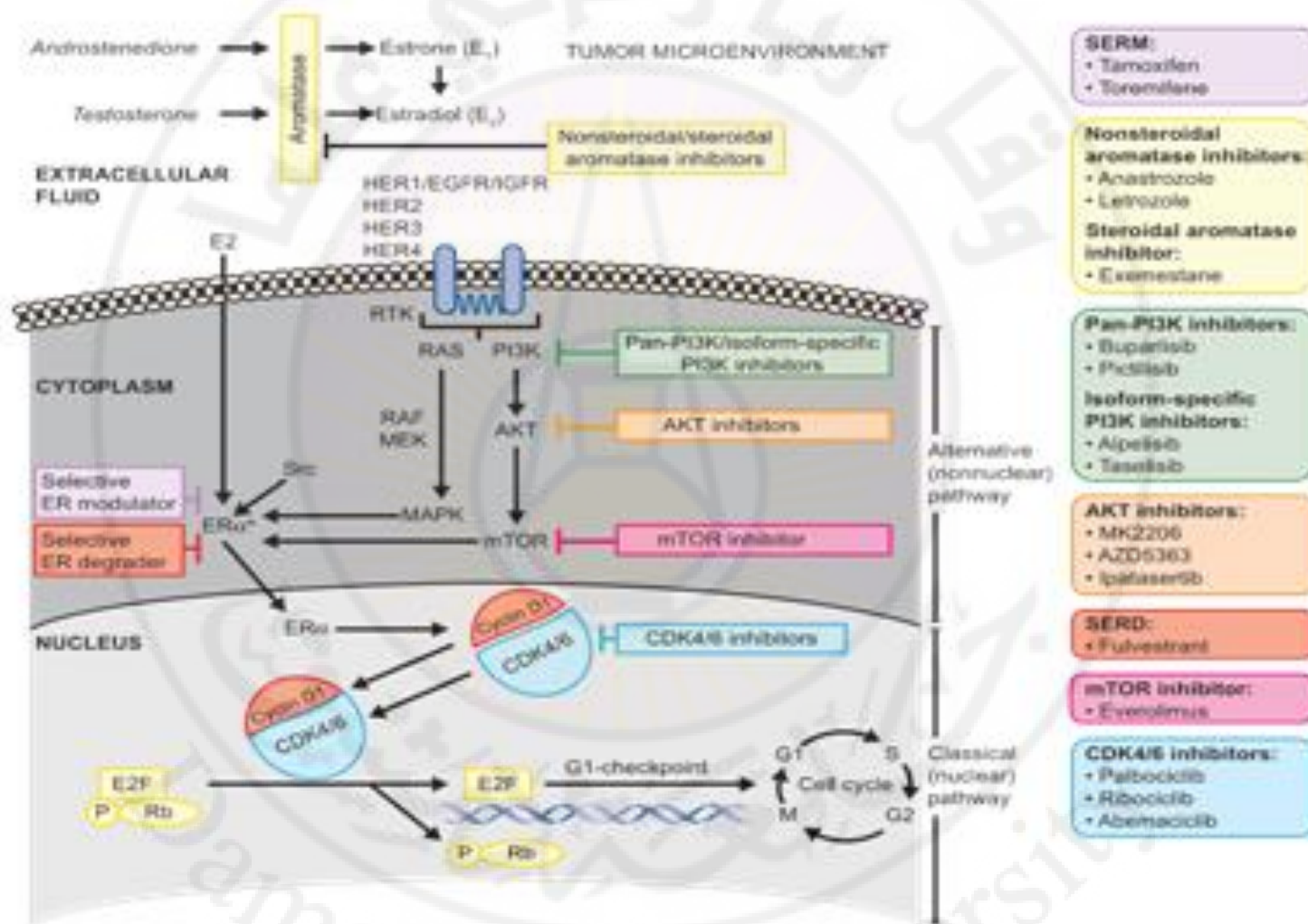
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Breast Cancer & Hormonotherapy

Hormonal therapy

- Hormone therapy can reach cancer cells almost anywhere in the body and not just in the breast.
- It's recommended for women with tumors that are hormone receptor-positive but not hormone receptor-negative)





Antiestrogens

تعتمد المعالجة الهرمونية على إحدى الآليات المبيّنة أدناه والتي تهدف جميعاً إلى إبطال تأثير الإستروجين المحفّز لنمو الخلايا الورمية، وتشمل:

- خفض مستويات هرمون الإستروجين البلازمية عن طريق مثبطات **الأروماتاز (AIs) Inhibitors**
Aromatase
- حجب ارتباط الإستروجين بمستقبلاته ER في نسيج الثدي الورمية من خلال استعمال محوّرات مستقبل الإستروجين الانتقائية (**SERMs**)، مثل: التاموكسيفين Tamoxifen
- التنظيم التّقيصي downregulation لمستقبلات الإستروجين ER α من خلال استعمال Fulvestrant، وهو الدّواء الوحيد الحائز من زمرة المدرّكات الانتقائية لمستقبلات الإستروجين Selective Estrogen Receptor Degraders (**SERDs**) يعمل Fulvestrant بعدّة آليات؛ إذ يرتبط بمستقبل الإستروجين؛ ممّا يعيق تشكّل مثنويات الـ ER؛ ومن ثمّ يمنع انتقال ER من الهيولى إلى النّواة.

Antiestrogens

- Block Estrogen receptors
- All estrogen agonist/antagonists
- *Selective Estrogen Receptor Modulators*
 - *SERM's*

Antiestrogens

- Tamoxifen

- The most widely HTx for breast cancer !
- P.O.20 mg daily
- Used to:
 - Treat existing disease
 - Prophylaxis (high risk)
 - Post-surgery adjuvant therapy
 - In metastatic breast cancer without visceral crise.
- Estrogen stimulates tumor growth
- Blocks tumor estrogen receptors
- ***Tumor must be Receptor +(ER/PR+)***

Tamoxifen- AEs

- Receptor deactivation can:
 - Increase bone density
 - **Increase Thromboembolism**
 - Reduce LDL levels – bad lipids
 - Increase HDL levels – good lipids
 - **Increase cancer risk**
 - Endometrial carcinoma**

Antiestrogens

FULVESTRANT

- Intramuscular injection only - once monthly – 500 mg (after loading dose)
- MOA: **Steroidal estrogen antagonist** that competes with estradiol for estrogen receptors in target breast cancer tissues → down regulates the estrogen receptor protein present in human breast cancer cells
- Active against tamoxifen-resistant cell lines
- Metabolism is primary CYP3A4 and some non-CYP450 processes with elimination 90% hepatobiliary

Antiestrogens: FULVESTRANT

INDICATIONS AND USAGE

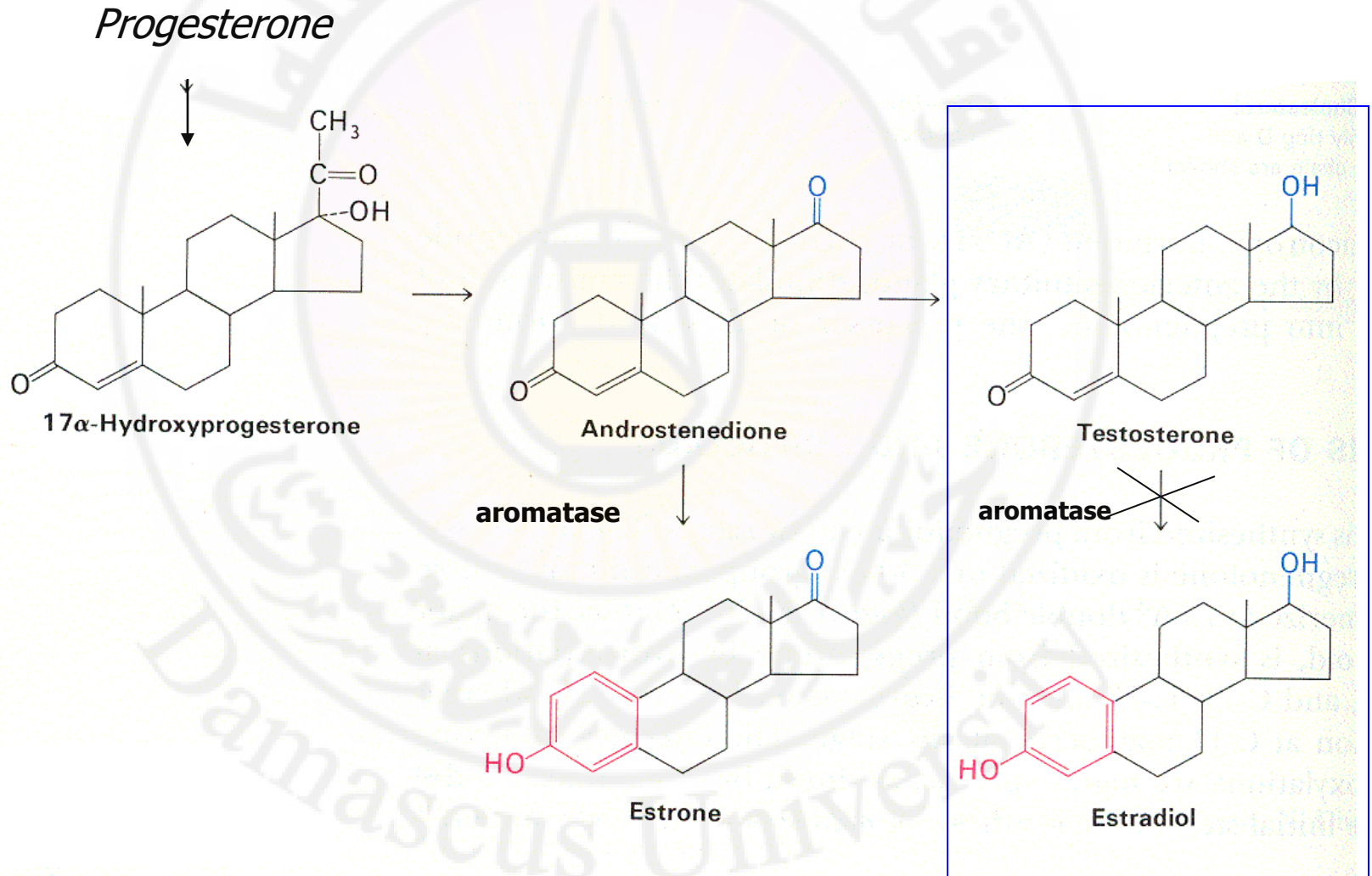
- Treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative **advanced breast cancer** in *postmenopausal* women not previously treated with endocrine therapy. **(1Line)**
- Treatment of HR-positive **advanced breast cancer** in *postmenopausal* women with disease progression following endocrine therapy. **(2line and beyond)**
- Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

Antiestrogens: FULVESTRANT

ADVERSE REACTIONS

- The most common adverse reactions occurring in $\geq 5\%$ of patients receiving Fulvestrant 500 mg :
- injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation.
- Increased hepatic enzymes (ALT, AST, ALP) occurred in $>15\%$ of patients and were not dose-dependent.
- Embryo-Fetal Toxicity.
- Immunoassay Measurement of Serum Estradiol:

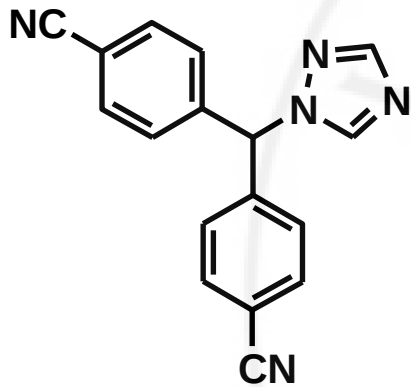
Aromatase Inhibitors



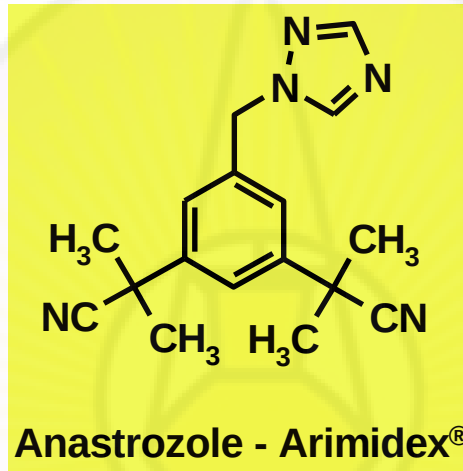
Aromatase Inhibitors

- Target: *post-menopausal women with* **Breast cancer**
- Blocks estrogen production (androgens)
- Does NOT block ovarian production!

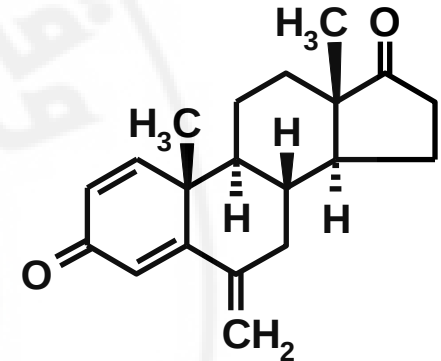
Aromatase Inhibitors



Letrozole - Femara®



Anastrozole - Arimidex®



Exemestane - Aromasin®

MOA: inhibitors of the enzyme “aromatase” that is responsible for the conversion of adrenally produced androstenedione to estradiol - no effect on aldosterone synthesis

- Letrozole and Anastrozole are reversible competitive inhibitors
 - Exemestane is an irreversible inhibitor
- Use caution in patients with hepatic and renal impairment

Aromatase Inhibitors

Indication

- Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer
- Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy
- First and second-line treatment of postmenopausal women with hormone receptor positive metastatic breast cancer

DOSAGE AND ADMINISTRATION-

Recommended dose:

letrozol 2.5.mg once daily

Anastrozol 1mg p.o once daily

Exemestane 25 mg once daily

Aromatase Inhibitors

CONTRAINDICATIONS

Women of premenopausal endocrine status, including pregnant women

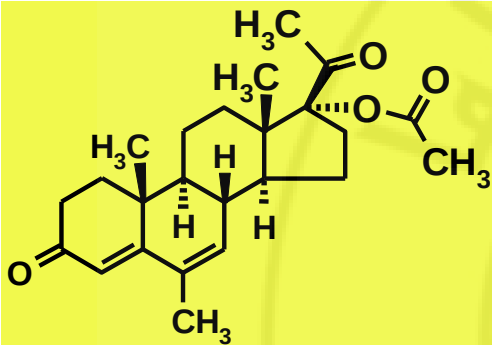
Cautions:

- Decreases in bone mineral density may occur. Consider bone mineral density monitoring
- Increases in total cholesterol may occur. Consider cholesterol monitoring.
- Fatigue, dizziness and somnolence may occur.

ADVERSE REACTIONS(The most common adverse reactions (>20%))

hot flashes,
flushing, asthenia,
edema, arthralgia,
headache, dizziness,
hypercholesterolemia,
sweating increased;
and musculoskeletal

Progestins - *Endometrium*



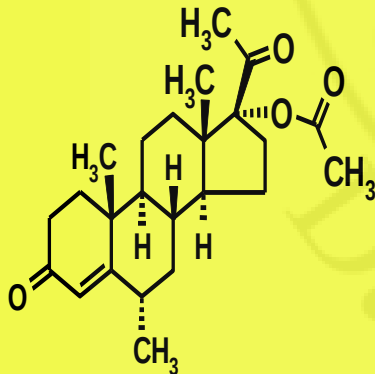
Megesterol acetate - Megace®

Indications: palliative treatment of carcinoma of the breast or ***endometrium***; off-label use: appetite stimulant in HIV

Not recommended during the first 4 months of pregnancy, must use at least 2 months of therapy to determine efficacy

MOA: Anti-leutinizing effect mediated by the pituitary gland and marked changes in progestational agent movement into the endometrium

Marked weight gain, thromboembolisms, USE contraception



Medroxyprogesterone acetate - Depo-Provera®

Indications: **adjuvant and palliative treatment of inoperable metastatic recurrent endometrial cancer**, advanced breast cancer and, Other – long acting contraceptive via IM injection

MOA: inhibits secretion of pituitary gonadotropin which prevents follicular maturation and ovulation, converts proliferative endometrium into secretory endometrium

May cause hepatic failure, avoid use in first 4 months of pregnancy, thromboembolism

Definitions of endocrine resistance in ER + Advanced Breast Cancer (ABC)

Primary endocrine resistance

HR+ Breast Cancer that progresses rapidly on initial endocrine therapy, suggesting that the majority of tumour cells were already resistant before commencement of the therapy

“a relapse

- while on the first 2 years of adjuvant ET
- PD within first 6 months of first-line ET for Metastatic Breast Cancer (MBC), while on ET”

Secondary (acquired) endocrine resistance

HR+ Breast Cancer initially sensitive to the endocrine treatment, but through mutation, altered gene expression or selection pressure, has developed resistance to such therapy

“a relapse

- while on adjuvant ET but after the first 2 years
- within 12 months of completing adjuvant ET
- PD $\geq$ 6 months after initiating ET for MBC, while on ET”

Mechanisms of Endocrine Resistance

- Mechanisms of Endocrine Resistance
 - ✓ Alteration of Oestrogen Receptor
 - ✓ Amplification/overexpression of growth factor receptor pathways
 - ✓ Dysregulation of the PI3K/AKT/mTOR pathway
 - ✓ Dysregulation of the cyclin/CDK pathways

SERM:

- Tamoxifen
- Toremifene

Nonsteroidal aromatase inhibitors:

- Anastrozole
- Letrozole

Steroidal aromatase inhibitor:

- Exemestane

Pan-PI3K inhibitors:

- Buparlisib
- Pictilisib

Isoform-specific PI3K inhibitors:

- Alpelisib
- Taselisib

AKT inhibitors:

- MK2206
- AZD5363
- Ipatasertib

SERD:

- Fulvestrant

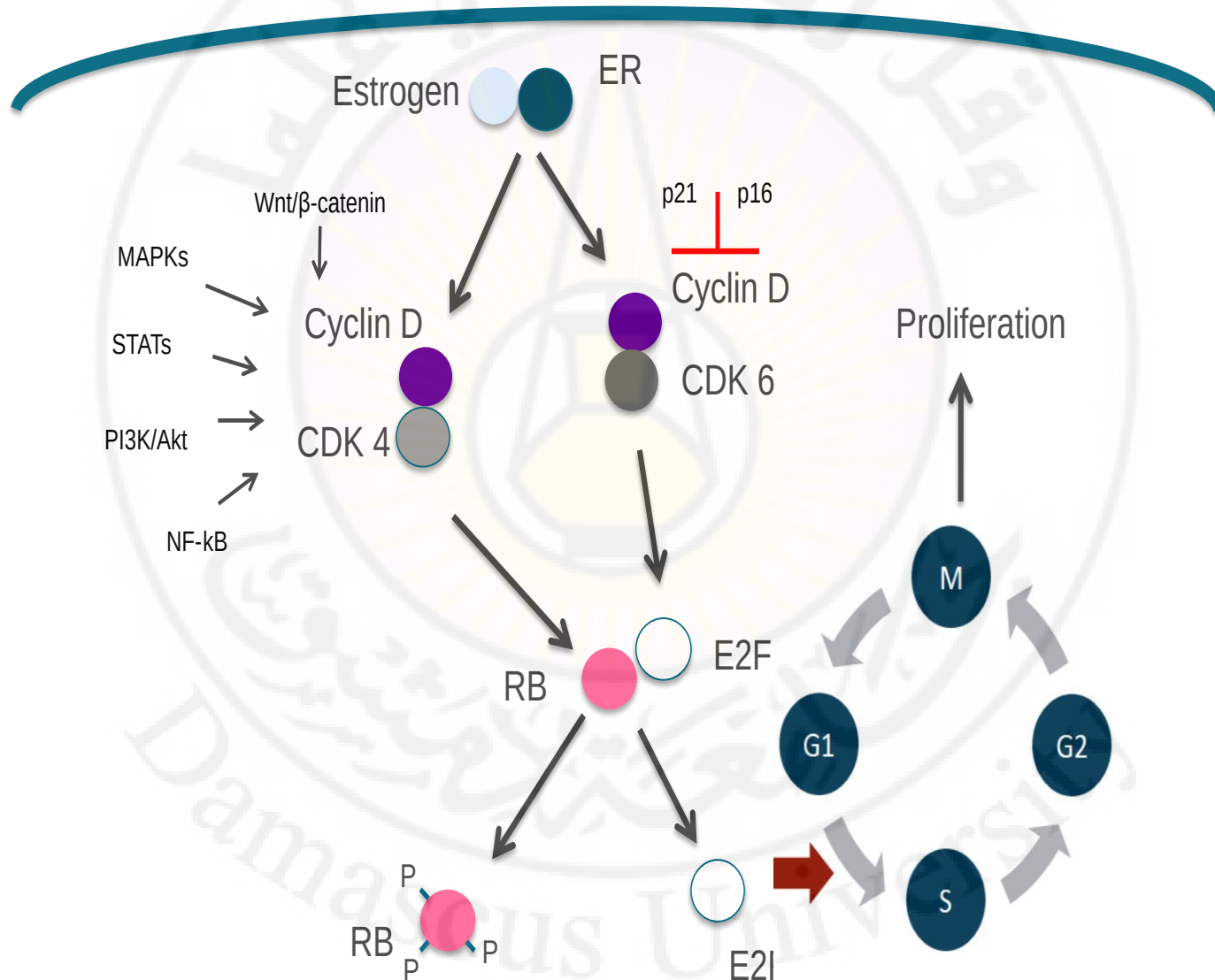
mTOR inhibitor:

- Everolimus

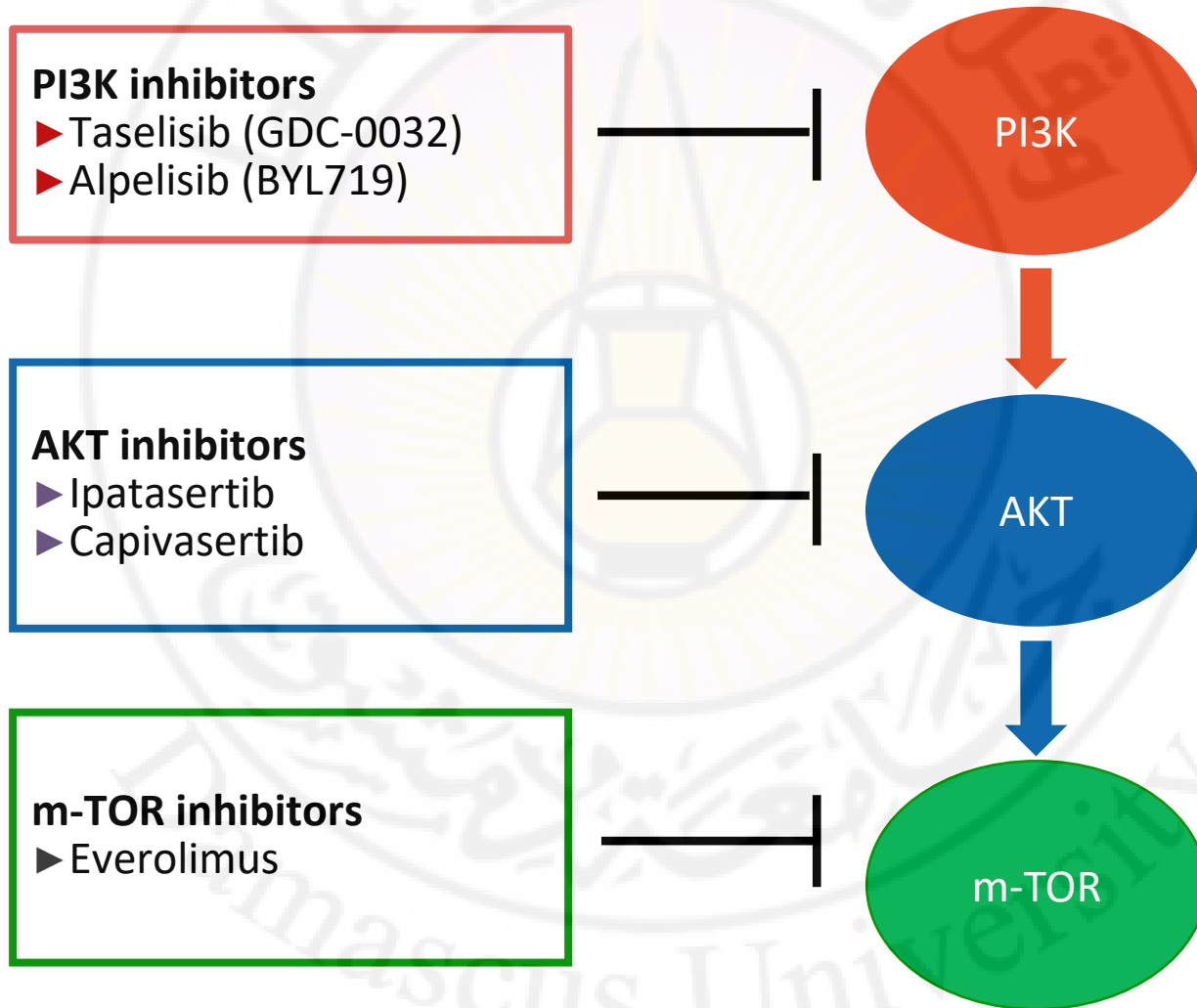
CDK4/6 inhibitors:

- Palbociclib
- Ribociclib
- Abemaciclib

Control of the Cell Cycle: CDKs



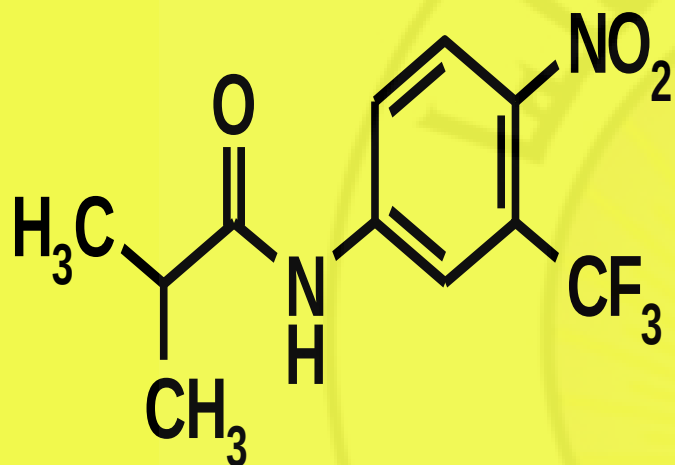
PI3K pathway is a Target for Cancer Therapy



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Prostate Cancer & Hormonotherapy

Anti-Androgens – Prostate cancer



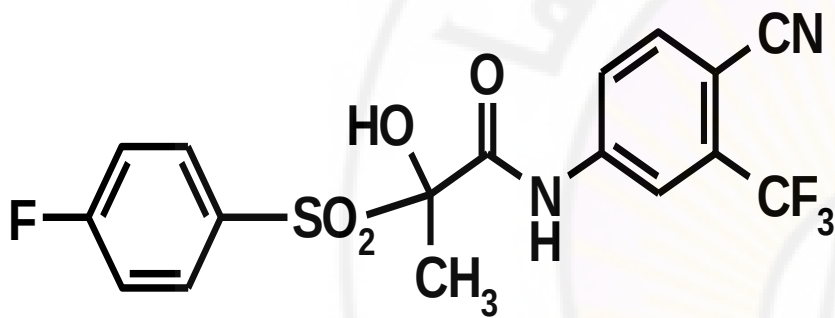
Flutamide - Eulexin®

*Indications: metastatic carcinoma of the prostate

MOA: **non-steroidal anti-androgen** inhibits cellular uptake of androgen steroids and inhibits nuclear binding of androgens to their receptors - adrenal

Used with LHRH (**GnRH**) agonists, photosensitivity, inform patients of urine color changes, hepatic metabolism with renal excretion, 96% protein bound=

Anti-Androgens - *prostate*



Bicalutamide - Casodex®

Indications: Advanced prostate cancer

MOA: **a non-steroidal** competitive inhibitor of the cytosolic androgen receptors - **adrenal**

Prostatic carcinoma is androgen sensitive

Mixture of enantiomers - stereospecific metabolism occurs; R-enantiomer of the drug is predominate serum drug

Drug must be taken in combination with luteinizing-hormone releasing hormone (LHRH) !

GnRH Agonists - prostate

- Gonadotropin-releasing hormone (GnRH)
- GnRH released from the hypothalamus
- Signals pituitary gland
- Agonists
 - Suppress **testicular** androgen production
 - Negative feedback inhibitor
 - *Chemical Castration!*

GnRH Agonists cont...

- **Gosarelin** (Zoladex)
 - SC pellet → upper abdomen
 - Synthetic analog of GnRH
 - Decreased androgen production in testes
 - SC or IM (q month 3.6, q 3 months 10.8)
 - Palliative: Advanced prostate carcinoma
 - **Doesn't decrease adrenal androgens**
 - Add Flutamide!
 - Loss of libido, impotence

Abirateron Acetate

- is a selective and irreversible manner via covalent binding mechanism
- Is a CYP17 inhibitor indicated for treatment of pts with metastatic castration-resistant prostate cancer .
- Recommended dose: 1,000 mg administered orally once daily in
- combination with prednisone 5 mg administered orally twice daily
- Adrenocortical insufficiency!!: Monitor for symptoms and signs of adrenocortical insufficiency

Abirateron Acetate

- أبيراتيرون الأسيتات: هو جزيء صغير يؤخذ عن طريق الفم يتحول في الجسم الحي إلى الأبيراتيرون وهو نوعي غير عكوس عن طريق إنزيم السيتوكروم ١٧ ألفا هيدروكسي ستيرويد ديهيدروجيناز و هو إنزيم يعمل فيزيولوجيا في الخصيتين و قشر الغدة الكظرية في الجسم و نجده مرضيا في النسيج الورمي للبروستات .
- يشارك هذا الإنزيم في تحويل الكولسترول إلى سلائف الأندروجين وتوليد هرمون الستيرويد.
- و بالتالي يمنع أبراتيرون إنتاج الأندروجينات في الورم ، وكذلك في الخصيتين والغدد الكظر

ENZALUTAMIDE

- Enzalutamide is a synthetic AR signaling inhibitor that not only blocks androgen binding to the AR but is also shown to prevent AR nuclear translocation, DNA binding, and co-activator recruitment in prostate cancer cells . inhibits multiple points in the androgen receptor signalling pathway, which is considered an important driver of CRPC.(castration resistant prostate cancer)
- مثبط لعدة نقاط من مستقبلات الأندروجين

Summary – Hormone Drugs

Class	Function & cancer target	Key Examples
Progestins	Decreases secretion of LH and GnRH from the pituitary – endometrial, breast	Megace, Depo-Provera
Androgens	Aromatase inhibitor, testosterone receptor agonist – breast, renal	Teslac
Antiandrogens	Androgen (testosterone) antagonist & uptake inhibitor – prostate	Eulexin, Nilandron, Casodex/ABIRATERONE ENZALUTAMIDE
GnRH Agonists	Decreased androgen production - prostate	Lupron, Zoladex
Estrogens	Estrogen receptor agonist; antagonizes androgens - prostate	Stilphostrol
Antiestrogens	Estrogen receptor antagonist; prevents tumor growth stimulation - breast	Nolvadex, Fareston, Faslodex
Aromatase Inhibitors	Reduces levels of circulating estradiol – Advanced breast cancer	Arimidex

مبادئ مقاربة وعلاج المريض الورمي

Nisreen Khazem MD.PhD

Head of Oncology Department

Introduction

- Cancer is a chronic disease, and like any other chronic medical condition, cancer patients have families, jobs, businesses and other commitments.
- Therefore, the oncologist aim is to cure the cancer if possible, and if not curable, then control the symptoms to improve quality of life and prolong the person's life

Malignancy	Curable	Incurable
Lung-non small cell	Up to locally advances	Metastatic
Lung-small cell	Limited stage	Extensive stage
Breast	Up to node positive	Metastatic
Colon	Up to node positive	Metastatic Except solitary liver or lung mets
Cervical	Early and locally advanced	Metastatic
Head and neck	Early and locally advanced	Metastatic
Germ cells/choriocarcinoma	Mostly	
Lymphomas	Mostly	L.G
Sarcomas	Even metastatic Ewings, osteosarcome	
Leukaemia	Mostly	

MDT

- cancer is managed in a multidisciplinary team setting to improve outcome and decrease morbidity of treatment.
- Some centres make decisions at multidisciplinary tumour boards, while some centres have dedicated multidisciplinary clinics

Specialties	Examples of roles
Medical oncologist	Chemotherapy, biological therapy, hormonal therapy
Radiation oncologist	External beam radiotherapy, brachytherapy, systemic radiation
Palliative care	Symptom control, hospice care
Oncological surgeons	Definitive and palliative surgery
Allied health: Dietician, physiotherapy, occupational therapy, social work, pharmacy and psychology	Relevant to each speciality
Cancer nurses	Care coordination, clinical trials, chemotherapy administration

Medical Therapy

- ❑ Medical therapies including chemotherapy, biological therapy (targeted and immune thx) and hormones
- ❑ Medical therapies are offered to patients with the following aims:
 - **Curative** E.g. Leukaemia, lymphoma, germ cell tumours, choriocarcinoma, Ewing sarcoma/osteosarcoma
 - **Adjuvant (to eliminate micro metastatic disease after surgery or radiotherapy)** E.g. Breast, colon, ovarian, sarcoma
 - **Neoadjuvant chemotherapy** (Chemotherapy given before surgery
In Goal is to shrink the tumor for resection to reach to Downstaging)Ex: Breast, rectum, Gastric , bladder
 - **Concurrent with radiation therapy (as radio sensitisers)** E.g. Head and neck, cervical, lung
 - **Palliative** (to improve quality of life and prolong survival) E.g. Metastatic cancers

Types of Chemotherapy Regimens

- **Induction chemotherapy**

- *is the first line treatment of cancer.

- * This type of chemotherapy is used for curative intent.

- **Consolidation chemotherapy**

- *is given after remission in order to prolong the overall disease-free time and improve overall survival.

- *The drug that is administered is the same as the drug that achieved remission.

- **Intensification chemotherapy**

- *is identical to consolidation chemotherapy but a different drug than the induction chemotherapy is used.

- **Maintenance therapy**

- *is a repeated low-dose treatment to prolong remission.

Plus...

- Combination chemotherapy

involves treating a person with a number of different drugs simultaneously.

The drugs differ in their mechanism and side-effects.

The biggest advantage is minimising the chances of resistance developing to any one agent. Also, the drugs can often be used at lower doses, reducing toxicity

- Combined modality chemotherapy is the use of drugs with other cancer treatments, such as surgery, radiation therapy, or hyperthermia therapy

Radiation therapy

*Curative(definitive)

E.g. Head and neck, cervical, lung, prostate, sarcoma

- **Neoadjuvant** : (In Goal is to shrink the tumor for resection to reach to Downstaging) E.g. Rectum,gastric,esophagus,,,
- **Adjuvant** (to eradicate micro metastatic disease after surgery)
E.g. head and neck, breast, brain,gastric,endometrium,,

***Palliative** (to improve symptoms) E.g. Advanced local disease and metastatic cancers

Palliative care

- **Aim of palliative care is to improve quality of life QOL by controlling symptoms**
- If a tumor can be shrunk by chemotherapy or radiotherapy, this would be an efficient option for controlling symptoms.
- In most cases, concurrent use of palliative care services and active anti-cancer therapy are necessary to maintain quality of life.

Palliative care

Examples of symptoms and management are outlined below:

- *Pain*: simple analgesics, narcotics, parenteral narcotics
- *Nausea*: metoclopramide, 5HT3 antagonist, steroids
- *Loss of appetite*: steroids
- *Cough/SOB*: codeine, narcotics, nebulisers.
- *Depression*: control symptoms, correct causes, counselling, antidepressants
family support, aids, home visits, physiotherapy, nutrition, occupational therapy, social work

Surgery

Surgery is performed for:

- cure by removing the primary cancer and lymph nodes
- palliation by removing the mass causing symptoms in selected cases.
- In some cases, removing solitary or limited metastasis could achieve cure.

Overall approach to cancer management

Three main questions to consider are:

- **What is the type of cancer?** In most cases, this requires a tissue diagnosis.

In modern oncology, it is unusual or inappropriate to start treatment based on clinical diagnosis alone without tissue diagnosis. Tissue diagnosis is also important to perform molecular studies to select appropriate targeted therapies.

- **What is the extent of the spread of the cancer?** This is answered by staging scans including CT scans, bone scans and PET scans. **TNM System**
- **Is it curable or not curable?** This depends on the type of cancer and the presence or absence of and the extent of metastasis

Incurable metastatic cancers

- Aim is to prolong survival and improve quality of life
- How does treating with chemotherapy or radiotherapy improve quality of life?
 1. By shrinking the cancer mass
 2. By decreasing the need for the sedative effect of analgesics
 3. By living longer

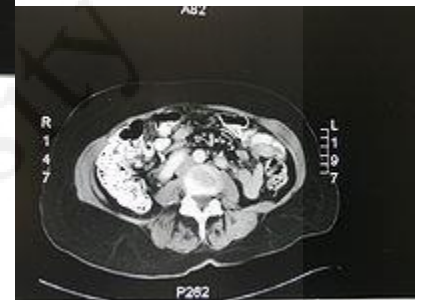
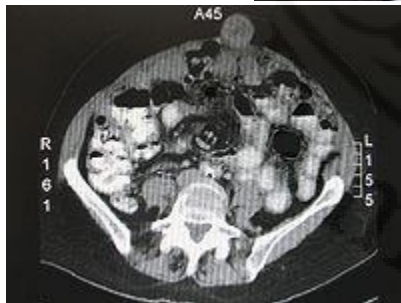
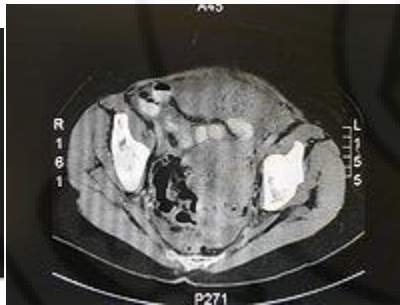
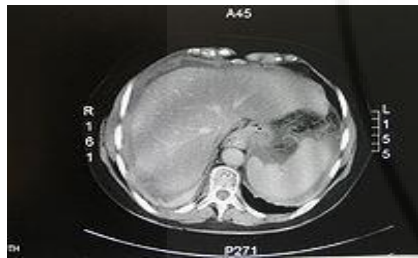
Concept of median survival

- Survival figures are obtained from large data bases.
- Therefore, we can only quote median figures rather than absolute numbers for expected duration of survival.
- The meaning of median survival needs to be clearly explained to patients and families to illustrate uncertainty.

Malignancy	Without treatment	With treatment
Non-small cell lung	6-9 months	9-12 months
Small cell lung	6-8 weeks	12 months
Colon	6-9 months	20 months
Breast	1-2 years	3-4 years

Case study

- A 70-year-old lady presented with abdominal pain, vomiting and bloating. She commenced on morphine which was complicated by confusion and loss of mobility.
- CAT scan show extensive peritoneal deposits and cancer was protruding through umbilicus as well.
- Biopsy of the umbilical mass reveals that the patient has metastatic ovarian cancer.
- She was deemed fit for palliative chemotherapy and underwent 6 cycles of Carboplatin and Paclitaxel +Bevacizumab with complete resolution of masses and symptoms.
- She did not require narcotics anymore. Chemotherapy was well tolerated.
- She lived for 4 years with good quality of life.



Performance Status

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair
5	Dead

Communication skills in oncology

لاشك أن دورنا كأطباء في حياة مرضى السرطان له تأثير كبير عليهم من الناحية المعنوية والنفسية. فقد أوجدت بعض الأبحاث أن أهمية دور الأطباء في الدعم المعنوي لمرضى السرطان بنفس أهمية دعم الأسرة والأقارب بالنسبة للمريض.

وسنستعرض هنا كيفية التعامل معه في الحالات المختلفة.

يُعتبر خبر الإصابة بالسرطان شكلاً من أشكال الأزمة الكبرى التي تُلَمّ بالإنسان، ويكون أثره ابتداءً يُشبه الأثر الذي تتركه الصدمة، حيث يمرّ الإنسان بنفس أطوار الصدمة:

- ✓ طور الإنكار وعدم التصديق (أول أسبوع) **Stage of Denial**:
- ✓ طور الانفعال الشديد والغضب (أسبوعين) **Stage of Anger**: ضدّ الذات أو الآخرين أو الظروف وهنا يتساءل المريض بنفسه لماذا أنا بالذات؟
- ✓ طور المساومة والتّقبّل (شهر) **Stage of Bargaining**: يحاول المريض أن يُقيم نوعاً من التّسوية مع القدر، حيث تتحوّل المشاعر من العموميات إلى المسائل العمليّة من قبيل الورم كبير أو صغير مُنتشر أو لا، ومن قبيل البحث عن إمكانيّة العلاج المتاحة ومن ثمّ تبدأ الخطوات العمليّة.
- ✓ طور الحداد والحسرة والاكتئاب **Stage of Depression**:
- ✓ طور التّقبّل والتّكيّف (شهر.....) **Stage of Acceptance**: يتقبّل الإنسان حالته ومصيره ويُعيد رسم حياته مع مراعاة التّغيّرات الحاصلة على نمط الحياة.

Stages of Grief

1. Denial “This cannot be happening.”
2. Anger “Why is this happening to me?”
3. Bargaining “I’ll do anything to fix this.”
4. Depression “Why should I go on?”
5. Acceptance “I’m going to be okay.”

It is normal for someone to go through these stages in a random order and return to previous stages.

المحاور التي يستند إليها دعم المريض من قبل طبيب الاورام

- **المحور الأول متعلق بتحسّن مسار المرض**، وذلك بسبب التّقدّم الحاصل في وسائل الكشف المبكّر وكذلك العلاج، حيث لم يَعد السّرطان بمثابة حكم الموت وأصبح أمام المرضى سنوات طويلة ليعيشوها أو يتعايشوا مع المرض خلالها.
- **المحور الثّاني** والمتعلّق بسياسة المكاشفة والمصارحة المنبثقة عن ضرورة احترام حقوق المرضى وضرورة المامهم بما يتعلّق بأوضاعهم.
- لا تعني إصابة المريض بالسّرطان أن تتحوّل حياته إلى سلسلة من الأزمات، وإنّما يجب مساعدته على تحسين نوعيّة حياته بكافة مناحيها **QOL**، مثل تحسين الشّهية للأكل، تحسين النّوم، تحسين النّشاط العامّ، التّقليل من الخوف والقلق وشعور عدم الطّمأنينة، التّقليل من مشاعر الحزن واليأس ومعالجة الكآبة، مساعدة المرضى على التّكيّف مع الطّروف الجديدة، وكذلك مساعدتهم على تجاوز العوائق والإعاقات التي يخلقها المرض.
- وبغض النّظر عن المدّة المتاحة للشخص ليحيّاها والتي لا يعرفها لا المريض ولا السّليم، نهدف من تداخلنا أن نجعل هذه الفترة مثمرة وطبيعيّة على أقصى قدر ممكن
- فيما يتعلّق بالأطفال والطّلاب يتمّ مساعدتهم لتجاوز التّأخيرات الدّراسيّة والاضطرابات السلوكيّة التي تنتج عن المرض أو طول فترة العلاج.

أهداف دّعم طبيب الاورام للمريض

١. تحسين نوعيّة حياة المرضى. **QOL**

٢. تحسين النّتيجة العامّة للعلاج. **ORR- OS**

- هنا الأمر يتعلّق بمدة الحياة لا نوعيّتها فقط هو من الأهداف الّتي يحاول طبيب الاورام المساعدة فيها عبر عدّة محاور:

□ تحفيز التّكيّف الإيجابيّ وما يستتبعه من أخذ العلاج وأسباب الشّفاء.

□ إبعاد المريض عن بعض العادات السّلبيّة والمرسّبة للمرض أو لسوء النّتائج مثل التّدخين

دليل عملي لمقاربة المريض الورمي سريريًا – داخل المشفى

- الطَّبيب بحكم عمله سيكون عليه التَّواصل مع مريض السرطان في مختلف المراحل ابتداءً من تبليغ الخبر السيء بالإصابة بالسرطان وما بعد الإخبار وعلى ذلك هناك محوران أساسيان في التَّواصل مع مريض السرطان:
- عند تبليغ خبر الإصابة بالسرطان.
- و بعد معرفته بمرضه.

مهارات التّواصل مع المريض الورمي

***لفظيّة** بمراعاة نبرة الصّوت واستخدام الألفاظ الواضحة القريبة من لغة المريض، واختيار المكان والزّمان المناسبين، مع منح المريض وقتاً للتفكير عند الحديث.

***غير اللفظيّة** بما فيها التّواصل البصريّ الذي يزيد التّقارب والانسجام (العين مفتوحة كأنّها تنظر لشيء سار أو النّظر لعين المريض، وتجنّب النّظر لجهة أخرى طوال الوقت أو غلق نصف العين)، ولغة الجسد وهي الأكثر تأثيراً لأنّها تؤثر في الحواس (إمالة الرّأس للأمام والجانب عند الاستماع ورفعها باستقامة عند التّحدّث، انحناء بالجسد كامله نحو الآخر مع استخدام إشارات مناسبة وإيماءات مُشجّعة لمتابعة الحديث).

مهارات التواصل المثالية

- ← وجود قاعدة معرفة علمية عند الطبيب تُمكنه من إجابة المريض عن أسئلته بمعلومات بسيطة وكافية.
- ← إعطاء أهمية للمريض ذاته والإصغاء له باهتمام دون مقاطعة
- ← **وذلك بالاستفادة من مهارات التواصل التالية :**
- **أولاً:** تقديم الطبيب لنفسه: وذلك بلفظ اسمه كاملاً وبوضوح، وعليه أن يُكرّر اسم المريض فهذا يُبدي أهمية ويعمل على كسب المودة. ويُفضّل أن يكون بمرافقة هذه الخطوات:
- ✓ إلقاء التحيّة وهي البداية لفتح قنوات التواصل مع المريض، وتُبيّن ردّة فعله تجاه التّعامل مع الطّبيب.
- ✓ الابتسامة وهي أهمّ الخطوات التي تُسهّل بدء الحديث.
- ✓ نظرات العين: خطوة تكشف مكنونات المريض فيما إذا كان مُتقبلاً لإكمال الحديث أم لا.
- ✓ الانحناء وهي أحد وسائل الاحترام خاصّة مع المسنّين والإناث.
- **ثانياً:** تعرّف على طبيعة المريض ودرجة تقبّله لك ولتدخلك ورغبته بالمساعدة. لاحظ وضعه الصّحيّ، استجابته للتحية، تواصله البصريّ، تفاعله واستجابته للأسئلة... وحيد أم لديه زوار.
- **ثالثاً:** في أي حال من الأحوال يجب احترام المساحة الشّخصيّة للمريض والحفاظ عليها وهي المنطقة الخاصّة به وتجاوزها يؤدّي غالباً للانزعاج والنّفور

إخبار المريض عن حقيقة مرضه

- يقول الدكتور جان همبورجه- أحد أساتذة كلية الطب في باريس سابقاً- في كتابه "الطبيب والحياة": يجب عدم قول الحقيقة عندما لا يكون المريض في حالة تؤهله لتقبلها وعندما تضره الحقيقة، ليس من حق الطبيب أن ينشر اليأس، لأنّ اليأس يسبب تدهوراً سريعاً في الحالة الجسميّة" وهذا يعني "أن يتعامل الطبيب مع كلّ حالة على حدة واطّباعاً نصب عينيه مبدأً واحداً، هو إلحاق أقلّ قدر ممكن من التّعاسة بمن يعينهم الأمر، ومنحهم أملاً متلائماً مع الحياة".

إخبار المريض عن حقيقة مرضه

- إعداد المريض وتهيئته نفسياً قبل إخباره:
- طمأنة المريض بأنّ الرّعاية الطّبيّة ستقدّم له في كلّ الأحوال وأنّه لن يُهمَل والطّبيب سيقوم بجهدِهِ لمساعدته بكلّ ما أوتي من إمكانيّات.
- اختيار المكان المناسب لإلقاء الخبر: وهو أمر مهم جداً ويفضّل أن يكون في غرفة المريض بشكل مُفرد، كما ويجتنب نقل مثل هذا الخبر بواسطة الهاتف المحمول فهو أمر غير سليم على الإطلاق.
- اختيار الزّمان المناسب: يفضّل الوقت الذي يكون فيه المريض مستقراً جسديّاً ونفسياً ومُهيئاً لتقبّل الخبر مع تواجد أحد المقربين إليه معه.
- تحرّي مدى تأثير الخبر على المريض: فطبيعة الأشخاص تختلف، هناك من يُصاب بالانهيار لخبر بسيط، وهناك من يتحمّل أقسى الأخبار، أو الاستعانة بالمقربين للمعرفة حول ردّات فعله تجاه تجارب سابقة أليمة.
- تحرّي إلى أي مدى يعرف المريض عن مرضه: إذا كان شاعراً بحقيقة مرضه وفيما إذا كان يريد أن يعرف أو يفضّل تجاهل الموضوع.
- إعطاء وقت كافٍ لإخبار المريض: يجب أن يقدّم الطّبيب الخبر وهو هادئ النّفس، ولا يُشعر المريض أنّه في عجلة من أمره، أو أنّه مشغول بل يتحدّث ببطء ووضوح حتّى يستطيع استيعاب المعلومات الجديدة، كما أنّه لا يجب أن يقوم الطّبيب بتبليغ المريض الخبر وهو يقرأ من التّقرير، فهذا يُعطي انطباع بأنّ الطّبيب لم يأخذ وقتاً كافياً كي يراجع ملفّ المريض، بل من الأفضل أن يقول الطّبيب (راجعت ملفّك والتّقارير المرفقة وتُشير النّتائج إلى اشتباه إصابتك بـ...) أي يكون الطّبيب ملماً بخيارات المريض العلاجيّة وفرصه بالشّفاء.

إخبار المريض عن حقيقة مرضه

- الشرح للمريض عن مرضه بالتدرّج البطيء والتزام الأمانة في عرض المعلومات بعدم إعطاء أمل كاذب، وتصحيح المفاهيم التشاؤميّة الشديدة، والتركيز على النقاط الإيجابية الحقيقيّة عن مآل المرض، ونسبة الذين عاشوا بعد إصابتهم بهذا المرض فترة مُعيّنة، والأولويّة في النقاش لأولويّات المريض واعتباراتِه.
- الشرح للمريض عن البرنامج العلاجيّ المتوقّع بلغة وأسلوب بسيطين، فتوضيح ذلك يبعث على الأمل، كما يجب تقديم أقصى درجات الرّغبة بالمساعدة لطمأنة المريض وتخفيف الصّدمة، وعدم عزل المريض أو تجنّب مقابلته بحجّة أنّه لا يمكن تقديم أكثر ممّا قدّم.
- تذكير المريض بدوره في مُساعدة نفسه للسيطرة على المرض كلّما كان ذلك مُمكنًا، وأنّ بإمكانه السّؤال إذا وجد لديه أيّ استفسار وعدم إنهاء المقابلة قبل السّؤال إن كان لديه أسئلة ينتظر الإجابة عنها. والتّأكيد على ضرورة مراجعة الطّبيب حتّى يشعر المريض بأنّ الطّبيب يستطيع مُساعدته وأنّ هناك شيء يستطيع فعله.
- المتابعة والتّخطيط وتحتاج لضمّ مخاوف المريض مع الرّأي الطّبيّ لتكوين خطّة ثابتة تتناسب مع المريض وشرحها خطوة بخطوة له. وتزويد المريض برقم هاتف يُمكنه الاتّصال به عند حدوث مُستجّدات قبل موعد المقابلة القادمة على ألا يكون رقم خصوصي بالطّبيب. ومراعاة إعطاء وقت كافٍ للمريض لاستيعاب الصّدمة وحده قبل المغادرة.

التواصل مع المريض بعد معرفته بمرضه وأثناء سير المرض

١. حدّد المشاعر الغالبة على المريض، الحزن، القلق، الخوف... ومن ماذا؟ الألم؟ قلة النوم؟
٢. اسأل كيف تشعر اليوم؟ لاحظ أنّه على الأغلب فإنّ أوّل ما ينطق به المريض هو الأكثر أهميّة بالنسبة له
٣. ابحث عن التفاعلات النفسيّة الكامنة خلف هذه المشاعر... انكار المرض، فقدان السيطرة، الاعتماد والنكوص، الخوف من الإهمال، فقدان الهوية والدور، الخوف من الموت، الخوف على الآخرين، هبوط تقدير الذات والثقة بالنفس.
٤. حدّد التفاعل الأكثر وضوحاً وثقلاً على المريض. اسأل مثلاً ما هو اسوأ شيء بالسرطان؟ وما أكثر شيء ضايقك أنت شخصياً؟

مهارات تواصل فعالة للمريض اثناء العلاج

- ابدأ بالاحتياج الجسديّ، ساعد المريض في شرب الماء، الأكل، أو الجلوس في وضع مريح.
- اجلس بجانب المريض حتّى لو كان وقتك قصيراً، أشعر المريض أنّ وقتك له ولست مُستعجلاً.
- ابتسم ولمس المريض، ربّت على كتفه إن كان ذلك مناسباً.
- اسأل ما هو أكثر شيء يُضايقك حالياً؟
- اسأل المريض عن تجربته مع المرض، ما هي طبيعته؟ وما هو العلاج
- ابحث عن فرصه مناسبة للإشادة بقوة المريض وإنجازه وقدرته على التّحمّل، أعطِ للمريض فرصة الحديث الإيجابي عن نفسه، ماذا كنت تعمل؟ ابحث عن النّقاط الإيجابيّة في سيرة حياته، كفاحه، وتعليمه، تربية الأبناء، مهاراته الخاصّة، خبراته المتميّزة، هواياته...
- لا تستعمل مصطلحات طبيّهِ ونفسيّهِ معقّده قد تُشعر المريض بعدم الفهم.
- انتبه للأمور الثقافيّة والاجتماعيّة والدينيّة، وما هي المعتقدات المفيدة للمريض والعلاج.



The background features a large, faint watermark of the Damascus University logo, which is a circular emblem with Arabic calligraphy and a central sunburst. The logo is surrounded by numerous green butterfly silhouettes of various sizes, scattered across the slide.

Cancer-Treatment Chemotherapy

NISREEN KHAZEM MD.PhD

Hematology Oncology

○ Cancer is a complex disease caused by genetic and epigenetic mutations.

○ Simply, it is only unregulated cell division

○ “Traditional” chemotherapy stops mechanisms of mitosis

○ Understanding chemotherapy needs understanding of Biology

Review of Principles

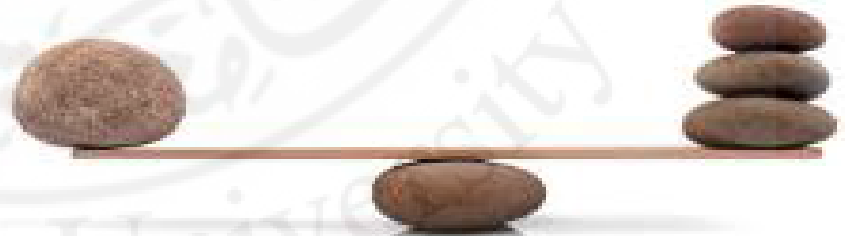
- The tales of the 1940's taught that disruption of cell cycle can effect cancer growth.
- Combination of agents may help prevent resistance and improve outcome
- How the drug reacts in Petri dish is different from in the body
- Chemotherapy can be given at different doses, frequencies and in combination with other modalities

Synopsis

- Agents can be used in a variety of cancers
- Members of the same drug class can have a different side effect profile
- Regimens are combinations of multiple mechanisms of action
 - **Also balancing of side effects
- Drugs administered in different ways can alter their effects in the body
- Drugs respond differently in different patients
 - **Change in toxicity profiles
- Side effects can be dose dependent.

Chemotherapy Regimens

- Agents *obviously* need to be active against a given tumor
- Select agents with different:
 - ☐ MOA
 - ☐ Resistance
 - ☐ Dose-limiting toxicity
- Combinations needed to maximize kill and limit resistance



How is Dose Calculated?

- ▶ Fixed Dose: Dose is the same regardless of patient specific factors
 - ▶ Example: Pertuzumab (Perjeta) 840 mg IV x1, then 420 mg thereafter
- ▶ Age Based Dosing
 - ▶ Example: Dosing of chemotherapy in infants
- ▶ Weight Based Dosing: Dosing based on body weight in kg (TBW/IBW/ABW?)
 - ▶ Example: Bevacizumab 5 mg/kg IV every 2 weeks
- ▶ Body Surface Area: Most common
 - ▶
$$\sqrt{\frac{\text{weight (kg)} \times \text{height (in)}}{3600}}$$
 - ▶ Cisplatin 75 mg/m² IV every 3 weeks
- ▶ Others:
 - ▶ Calvert Equation for Carboplatin: Based on AUC and renal function

Adverse Effects of Chemotherapy

AEs

- Immunosuppression and myelosuppression
- Neutropenic enterocolitis
- Gastrointestinal distress
- Fatigue
- Nausea and vomiting
- Alopecia

Adverse Effects of Chemotherapy

AEs

- Secondary neoplasm
- Infertility
- Teratogenicity
- Peripheral neuropathy
- Organdamage:
(Cardiotoxicity, Hepatotoxicity, Nephrotoxicity)|
- Ototoxicity
- Vesicant

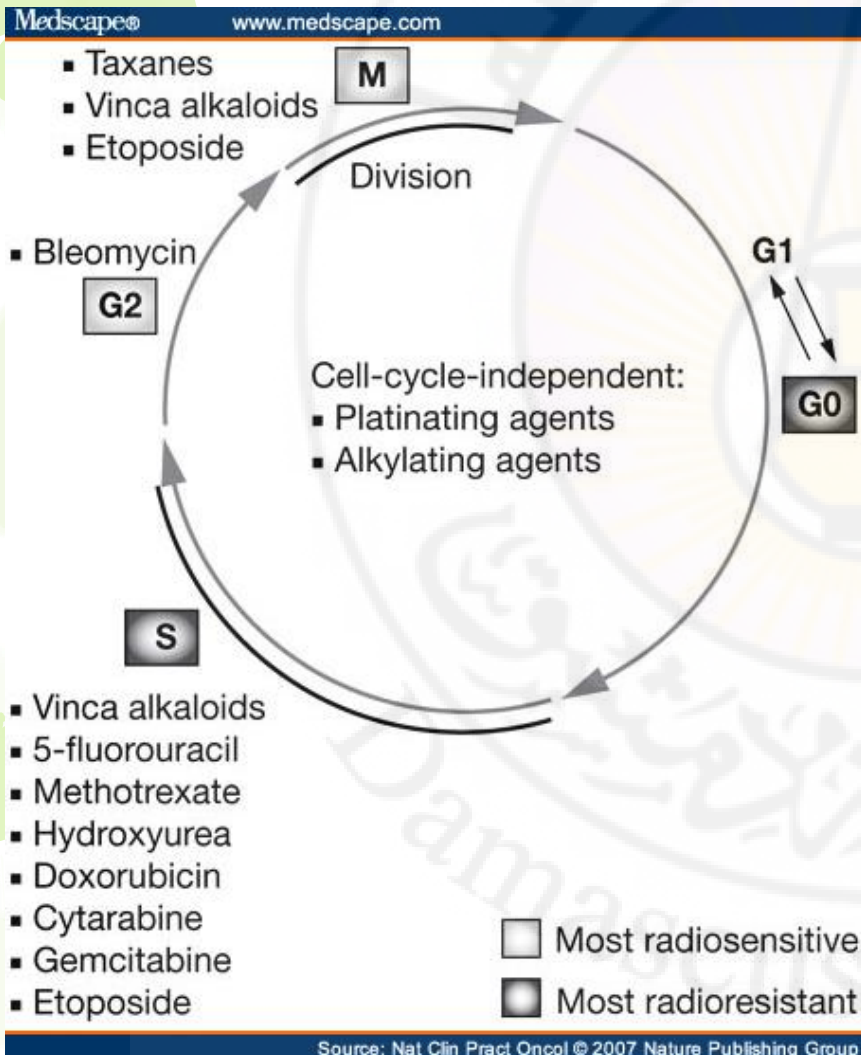
Eastern Cooperative Oncology Group (ECOG) Performance Status

- ▶ Assuming an equivalent BSA and same type/stage of cancer, is a 30 year old athlete going to tolerate the same therapy the same as a 70 year old chronic smoker on dialysis who cannot work?
- ▶ ECOG Performance Status (PS)
 - ▶ Standard to measure the impact of disease on daily living
 - ▶ Used extensively in clinical trials
- ▶ Changes of PS are one reason why doses and therapies change
 - ▶ Consider changes in PK/PD
- ▶ 70 year patient might start with lower dose or different therapy all together

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Adapted from Gliss, et al. 1982
ECOG = Eastern Cooperative Oncology Group

Cell Cycle and Chemotherapy



◆ Cell cycle specific drugs:

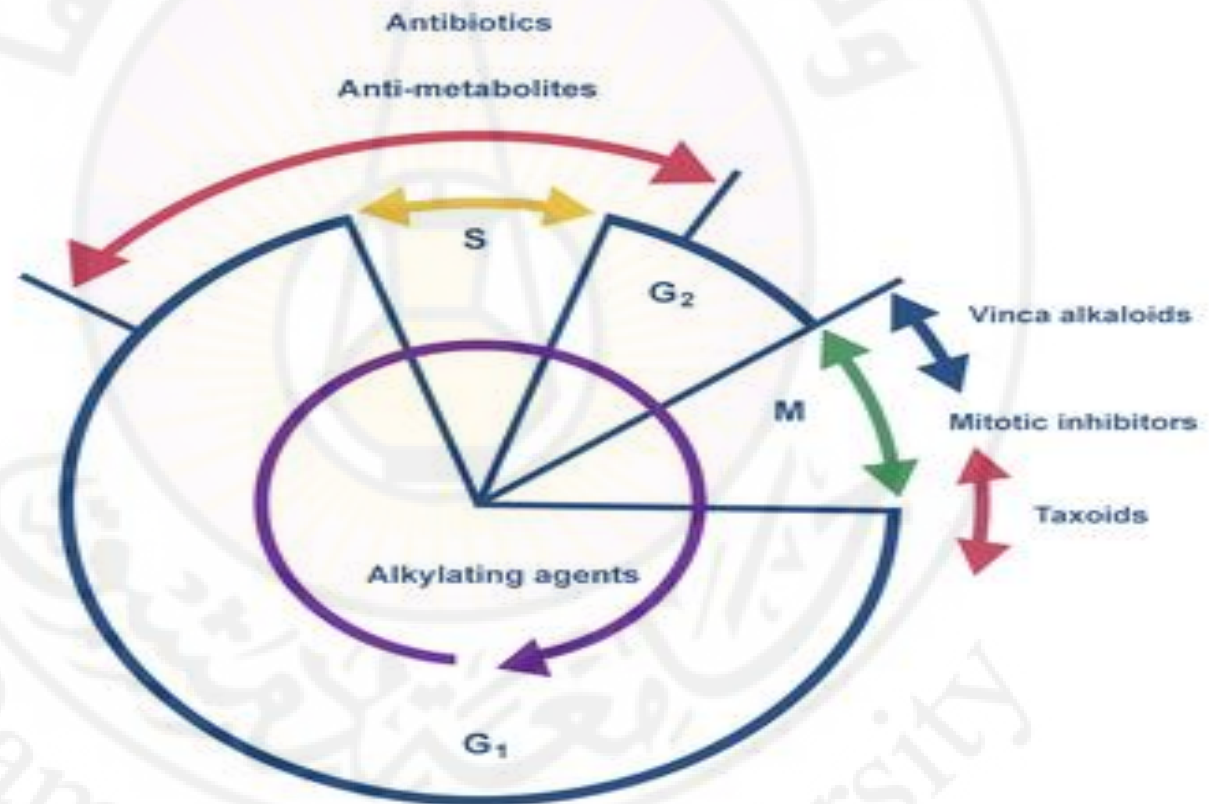
- Drugs interfere with faster growing cells
- S-phase (**DNA synthesis**) and M-phase (mitosis) are particularly important

◆ Cell cycle non-specific drugs:

- Drugs that can interfere for more slow growing cells
- Inflict damage whenever DNA is needed
- Not just mitosis
- ◆ usually regimens contain both types of agents

How does Chemotherapy work?

Cell phase where chemo agents work



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 'Damascus University' at the bottom. In the center is a stylized lamp or torch with radiating lines. The slide also has a decorative border of green leaves and butterflies on the right and bottom edges.

ALKYLATING AGENTS AND PLATINUM COMPOUNDS

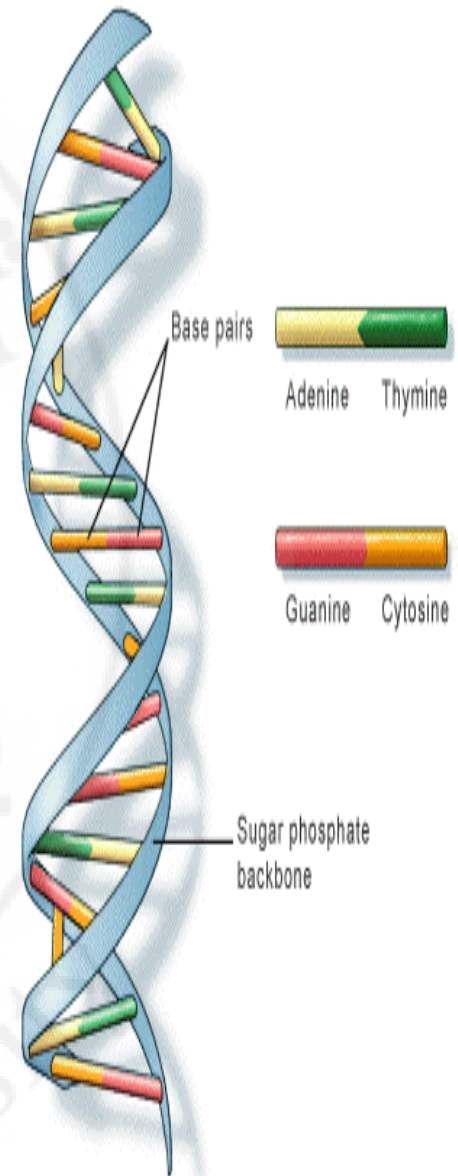
Nisreen.Khazem MD.PhD

Alkylating Agents

- the ability to bind covalently to DNA via their alkyl group is the primary cause for their anti-cancer effects.
- Heterogenous group of loosely related compounds:
 - ☐ Nitrogen mustards (Mechlorethamine, cyclophosphamide, ifosfamide)
 - ☐ Ethyleneimines (thiotepa, altretamine)
 - ☐ Alkyl sulfonates (Busulfan)
 - ☐ Nitrosureas (Carmustine)
 - ☐ Triazenes (Dacarbazine)

Alkylating Agents

- DNA is made of two strands....
- If the cell tries to replicate crosslinked DNA during cell division, or tries to repair it, the DNA strands can break. This leads to apoptosis.
- **Alkylating agents will work at any point in the cell cycle and thus are known as cell cycle-independent drugs.**
- For this reason the effect on the cell is dose dependent; the fraction of cells that die is directly proportional to the dose of drug.



Alkylating Agents in practice

- Uses: extensive

- ☐ Solid Tumors: Breast cancers, prostate cancers, sarcomas, etc

- ☐ Hemematologic malignancies: leukemias, lymphomas, myeloma

- ☐ Non-malignant conditions: rheumatic diseases

- Commonly used with cell cycle dependent agents

Toxicities of Alkylating-Agents

- ▶ Bone Marrow Suppression (Mostly dose-limiting): affects dose density
 - ▶ Class effect but to varying degrees
 - ▶ Can lower platelets (thrombocytopenia), white blood cells (neutropenia) and red blood cells (anemia)
 - ▶ Can be used advantageously for bone marrow transplants
 - ▶ Acute myelosuppression: nadir of 7-10 days and recovery in 14-21 days
 - ▶ Cyclophosphamide, ifosfamide
 - ▶ Delayed myelosuppression: nadir in 4 – 6 weeks with gradual recovery
 - ▶ Carmustine
 - ▶ Why the concern:
 - ▶ Thrombocytopenia: bleeding complications
 - ▶ Neutropenia: Opportunistic infections
 - ▶ Anemia: Fatigue, QOL, SOB

- ▶ GI Toxicity:
 - ▶ Mucosal ulceration
 - ▶ Chemotherapy Induced Nausea and Vomiting (CINV):
 - ▶ Caused by various stimuli in the body and sent via redundant pathways
 - ▶ Varies depending on agent to varying degrees
 - ▶ Divided into 4 categories: High, Moderate, Mild, Minimal
 - ▶ Treatment is based on rating
 - ▶ Can start in hours (acute) and last for days (delayed)
 - ▶ Complications: GI bleeds, dehydration/malnutrition, kidney failure, esophageal tears
 - ▶ Constipation
 - ▶ Diarrhea

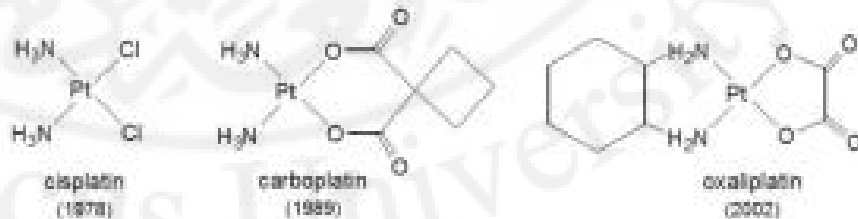
Platinum Complexes

- Cisplatin
- Carboplatin
- Oxaliplatin



Platinum Complexes

- Behave similar to alkylating agents without alkylation!!
- MOA: forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules
- ◆ Cis/carboplatin share similar activity and are somewhat interchangeable
- ◆ cross-Resistance:
 - Cis/carboplatin share cross-resistance, while oxaliplatin does not



Platinum Complexes

Spectrum of activity:

- ◆ Cis/carboplatin: Solid tumor primarily
(SCLC, NSCLC, Head and Neck, Bladder, Testicular)
- ◆ Oxaliplatin: GI tract cancers (Gastric, Pancreatic, CRC)



Platinum Complexes

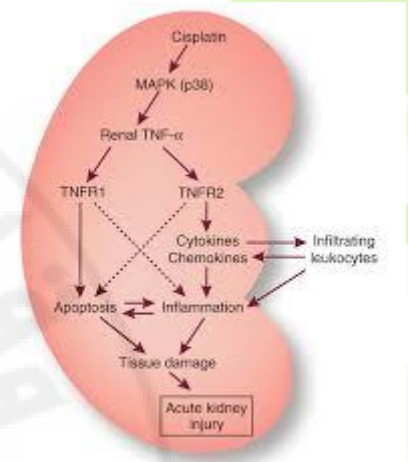
○ Toxicities:

◆ Cis/carboplatin:

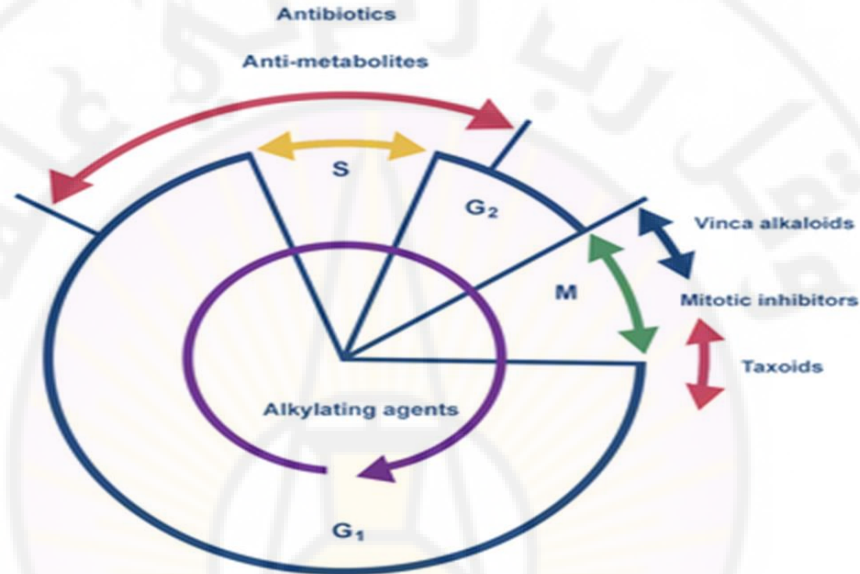
- * N/V: Cisplatin more so
- * Renal toxicity: Cisplatin more so
- * Myelosuppression: carboplatin more so (thrombocytopenia)

◆ Oxaliplatin:

- * Peripheral Neurotoxicity
- * Myelosuppression: thrombocytopenia



Cell phase where chemo agents work

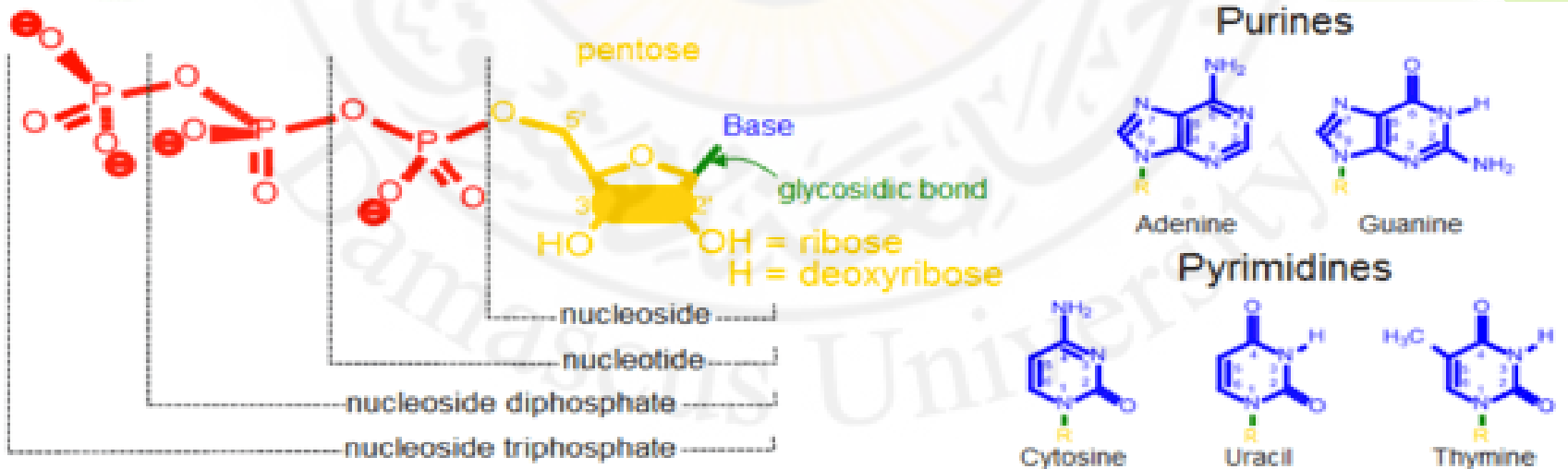


S-Phase: Antimetabolites

FOLIC ACID ANALOGS,
PYRIMIDINE ANALOGS,
PURINE ANALOGS

Antimetabolites

- A group of molecules that impede DNA and RNA synthesis.
- The building blocks are nucleotides(=nucleobase +sugar + phosphate).
- The nucleobases are divided into purines (guanine and adenine) and pyrimidines (cytosine, thymine and uracil).
- Anti-metabolites resemble either nucleobases or nucleosides (a nucleotide without the phosphate group), but have altered chemical groups.



Antimetabolites

- blocking the enzymes required for DNA synthesis.
- → So they prevent mitosis
- they only work during S-phase (the DNA synthesis phase). **For this reason, at a certain dose, the effect plateaus and proportionally no more cell death occurs with increased doses.**

Anti-folates- Methotrexate

- include methotrexate and pemetrexed.
- Methotrexate inhibits enzyme dihydrofolate reductase (DHFR) so the cellular levels of folate coenzymes diminish.
- These are required for thymidylate and purine production, which are both essential for DNA synthesis and cell division

Methotrexate Uses

- **Used in all types of cancers** and include autoimmune conditions as well
 - Control graft-versus-host disease
- Doses can be given orally, intravenously or intrathecally
- **High-Dose Methotrexate** ($> 1 \text{ g/m}^2/\text{dose}$)
 - Requires therapeutic blood monitoring
 - Use of leucovorin “rescue”
 - Requires urine alkalinization
 - Penetrates CNS

Antifolates (Methotrexate)

○ Side Effects

- ◆ Myelosuppression
- ◆ Mucositis and intestinal inflammation
- ◆ Nephrotoxicity !!!
- ◆ Neurotoxicity

****Leucovorin, an antidote can be used in poisonings and to high-dose MTX rescue**

Anti-folates-Pemetrexed

- Pemetrexed is another anti-metabolite that affects purine and pyrimidine production, and therefore inhibits DNA synthesis.
- It primarily inhibits the enzyme thymidylate synthase, but also has effects on DHFR

Anti-folates-Pemetrexed

Use:

Mesothelioma

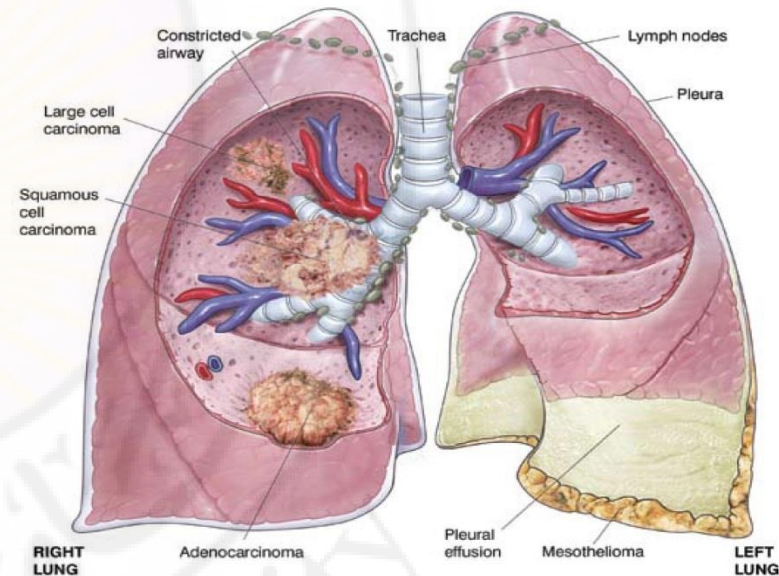
Lung Adenocarcinoma.

● B12 supplement 1week before

Pemetrexed and every 3 week for 12 w.

B9 daily for 12 week is very necessary

Lung Cancer and Mesothelioma



PYRIMIDINE ANALOGS/fluoropyrimidines:

- include fluorouracil (5FU) and capecitabine (Cap)
- Fluorouracil is a nucleobase analogue that is metabolised in cells to form at least two active products; 5-fluorouridine monophosphate (FUMP) and 5-fluoro-2'-deoxyuridine 5'-phosphate (fdUMP).
- FUMP becomes incorporated into RNA and fdUMP inhibits the **enzyme thymidylate synthase; both of which lead to cell death**

Dihydropyrimidine dehydrogenase (DPD) deficiency:

- ☐ DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines.
- ☐ 5% of population have partial DPD deficiency & 0.05% have complete DPD deficiency.
- ☐ **Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity.**
- ☐ Complete DPD deficiency → Contraindicate to use 5-FU & Capecitabine products.
- ☐ Partial DPD deficiency → Reduced starting dose

How do you find out how much DPD deficiency is?

☐ By DPD genotype or phenotype (assessed by dosing uracilemia)

“preferred”, where:

- o Uracilemia ≥ 150 ng/ml → Complete DPD deficiency.
- o Uracilemia (16 – 150) ng/ml → Partial DPD deficiency.
- o Uracilemia ≤ 16 ng/ml → No DPD deficiency.

5-Fluorouracil: Pyrimidine Analog

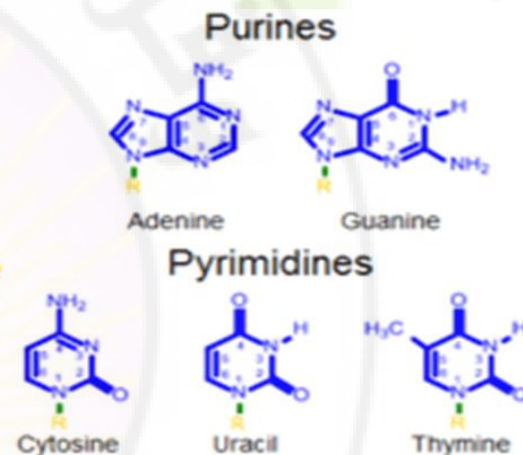
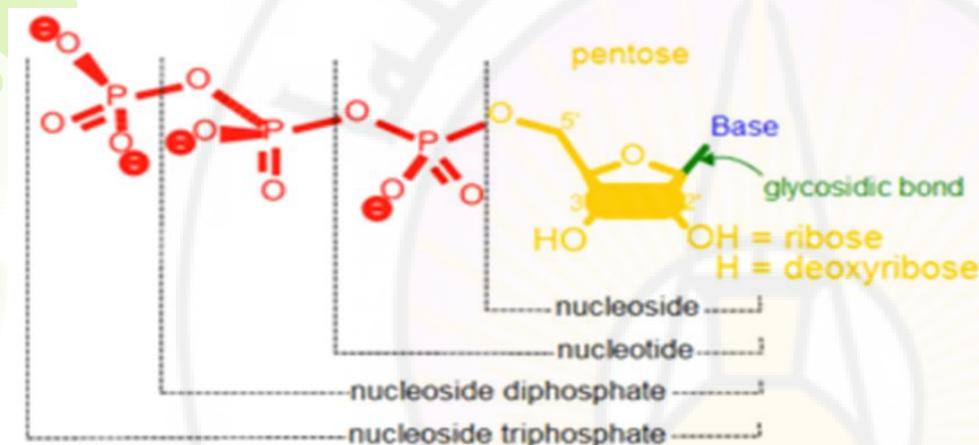
- **Continuous infusion: inhibition of thymidylate synthase leading to thymidine deficiency
- ☐Leucovorin is administered prior to starting to stabilize 5FU-TS complex
- **Bolus: False base integration into RNA and DNA
- ☐Pharmacogenomics: Clearance is mediated through dihydropyrimidine dehydrogenase (DPD)
 - ☐Polymorphic
- Resistance:
 - ☐Reduced conversion to active metabolite
 - ☐Amplification of TS or alteration of TS binding site
 - ☐Amplification of degradative enzymes

5-Fluorouracil in Practice

- Colon cancer: FOLFOX regimen (developed at RPCI):
 - ☐ Oxaliplatin X mg/m² IV on day 1
 - ☐ Leucovorin Y mg/m² IV given with oxaliplatin on day 1, followed by
 - ☐ 5-FU 400 mg/m² IV Bolus, then
 - ☐ 5-FU 2.4 g/m² IV given continuously over 46 hours
- **Side effects:**
 - ☐ Bolus: myelosuppression, angina
 - ☐ i: N/V, diarrhea, mucositis, hand-foot syndrome
- Antidote: uridine triacetate



PYRIMIDINEANALOGS /fluoropyrimidines:-



- **Capecitabine** is a prodrug of 5-fluorouracil that is broken down in tumor-cells to produce the active drug.
- The deoxynucleoside analogues include **cytarabine**, **gemcitabine**, **azacitidine**, **fludarabine**, **cladribine**, and pentostatin.
- The thiopurines include thioguanine and **mercaptopurine**.

Natural Products

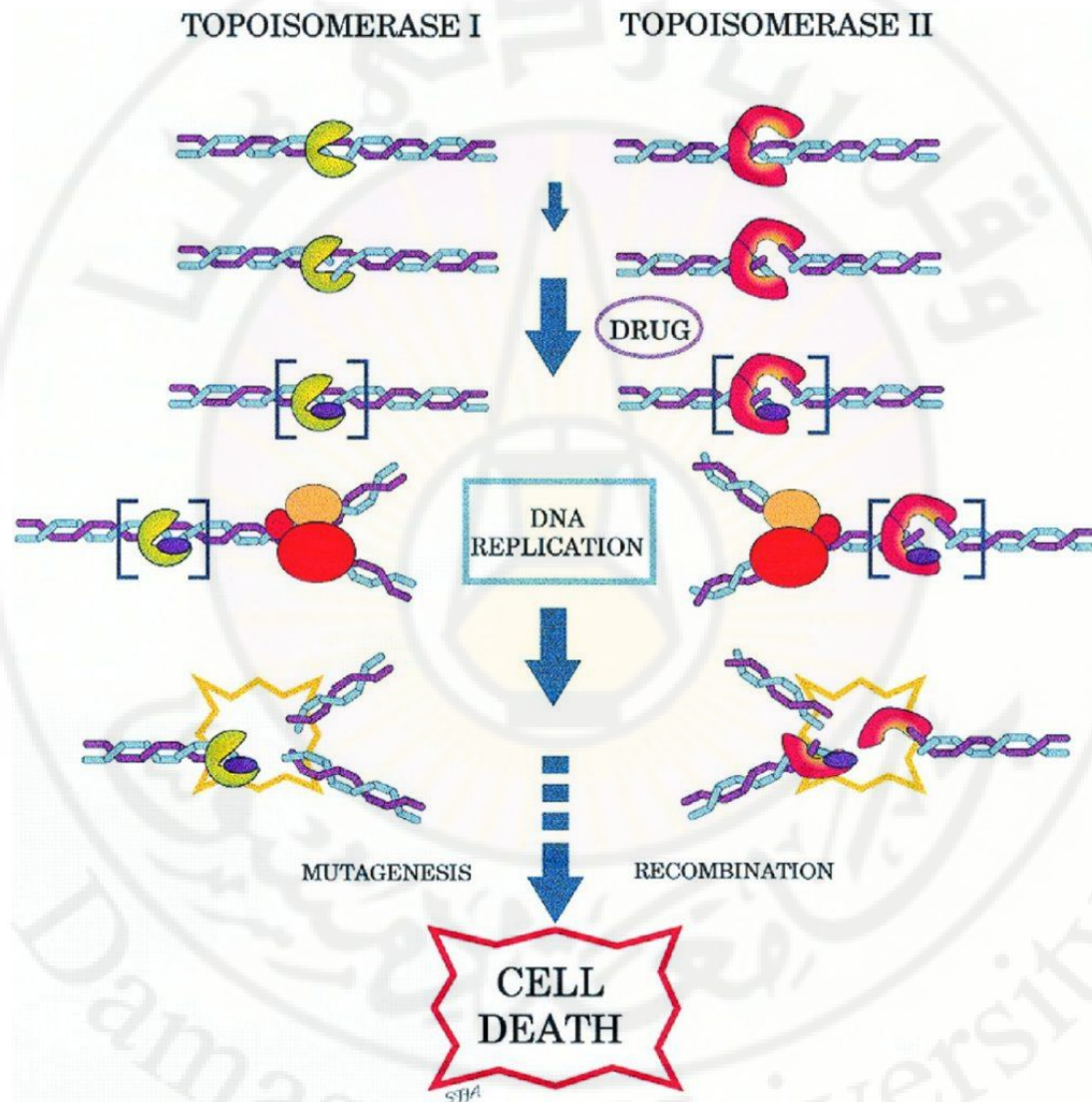
EPIPODOPHYLLOTOXINS,

TAXANES,

VINCA ALKALOIDS

CAMPTOTHECANS





Topoisomerase inhibitors

❑ Topoisomerase I inhibitors, **irinotecan** and **topotecan**,

****are semi-synthetically derived from camptothecin, (obtained from the Chinese ornamental tree).**



Irinotecan (CAMPTO)*

- ▶ MOA: Prodrug, Topoisomerase I inhibition
 - ▶ Active metabolite is SN-38
 - ▶ SN-38 is inactivated via UGT1A1
- ▶ Side effects:
 - ▶ DIARRHEA
 - ▶ Alopecia
 - ▶ Myelosuppression

Topoisomerase II inhibitors

- ❑ The topoisomerase II poisons cause increased levels enzymes bound to DNA. This prevents DNA replication and transcription, causes DNA strand breaks, and leads to (apoptosis).

***These agents include **Etoposide, Doxorubicin, Mitoxantrone** and Teniposide.

Anthracycline: Doxorubicin

□ anti-tumor antibiotics,
isolated from *S. peucetius*



□ Class includes: daunorubicin, epirubicin, idarubicin

□ MOA: Prodrug (doxorubicinol)

*Major: Topo II inhibition- prevents re-ligation of DNA

*Minor: prevention of free radical formation

Anthracycline: Doxorubicin

□ Side Effects:

*Cardiotoxicity (-Accumulation dose 450mg/m²-Lifetime dosing limits)

*Myelosuppression

*Alopecia

*Mucositis/ N/V

*Vesicant

*Red discoloration of: urine, tears, CSF

*Extravasation



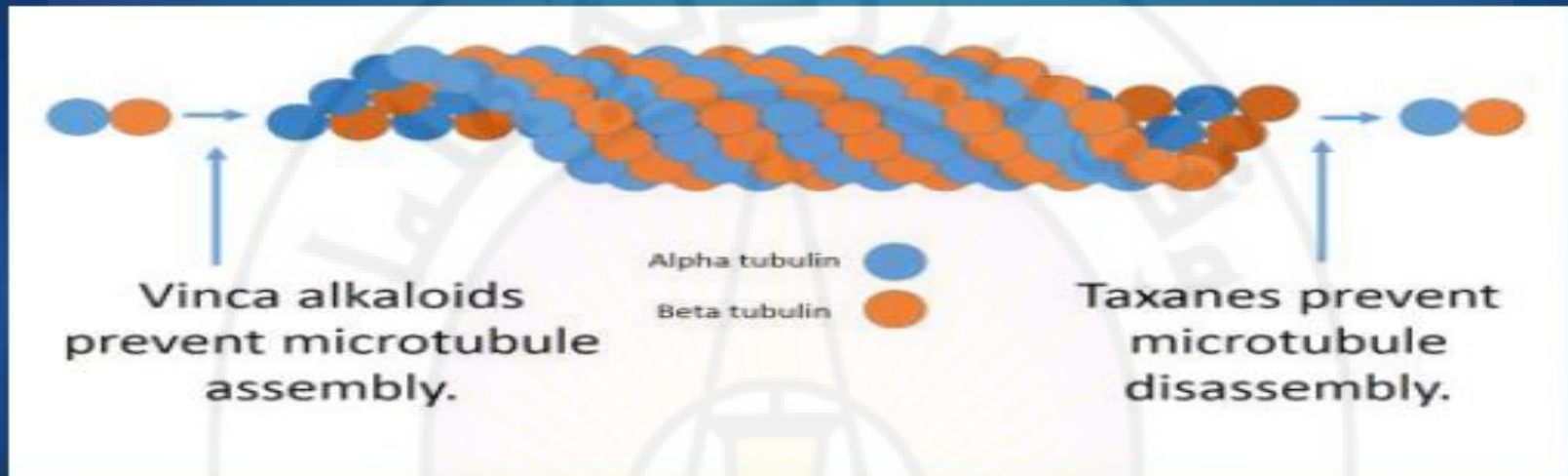
Etoposide

- ▶ Extract from roots of *Podophyllum peltatum* (mandrake plant)
- ▶ MOA: Topoisomerase II inhibitor via stabilization of TOP2 complex
 - ▶ Accumulation of cells in S phase (G_2 Phase as well)
 - ▶ Leads to apoptosis
- ▶ Side Effects:
 - ▶ Myelosuppression
 - ▶ Alopecia

Anti-microtubule Agents

- plant-derived chemicals that block cell division by preventing microtubule function.
- Microtubules are an important cellular structure composed of two proteins; α -tubulin and β -tubulin. They are hollow rod shaped structures that are required for cell division, among other cellular functions.
- Vinca alkaloids and taxanes (the two main groups) they both cause microtubule dysfunction, **but their mechanisms of action are completely opposite.**

Taxanes vs Vincas

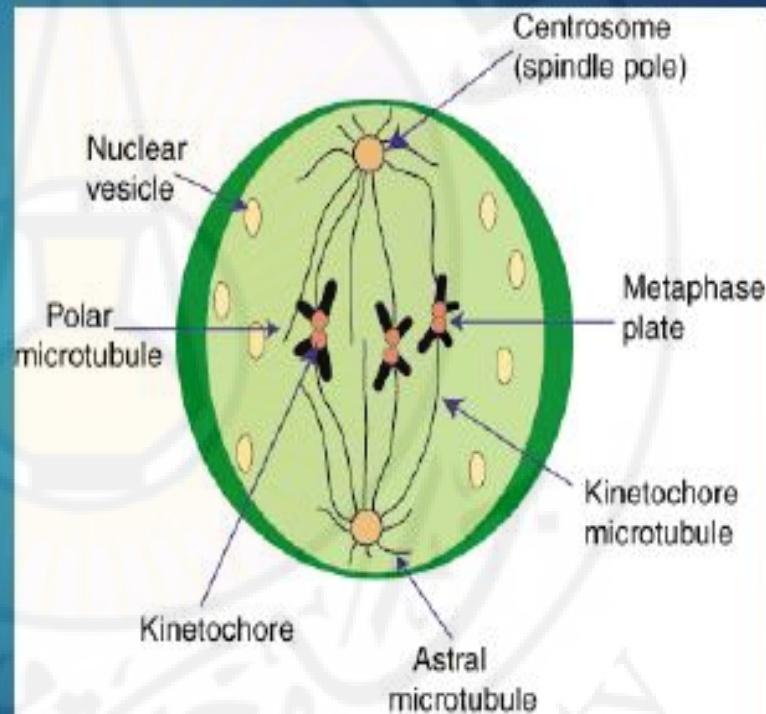


- **The vinca alkaloids prevent the formation of the microtubules**(They bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules)
- **the taxanes prevent the microtubule disassembly.** By doing so, they prevent the cancer cells from completing mitosis. Following this, cell cycle arrest occurs, which induces (apoptosis)

Antimitotic Agents

55

- ▶ Building blocks of microtubules consist of two subunits, an α and a β
- ▶ Microtubules grow from the spindle pole towards the metaphase plate
 - ▶ Repetitive assembly of both subunits
- ▶ Microtubules bind to kinetochore and then disassemble back to the spindle pole
- ▶ Drugs that target mitosis target microtubules
 - ▶ Assembly
 - ▶ Disassembly



Taxanes: Polymerizing agents

- Discovered from *Taxus brevifolia* (Pacific Yew Tree)
- MOA: Inhibit depolarization by binding to β -tubulin, causing mitotic arrest
- **Paclitaxel** prevents the cell cycle at the boundary of **G2-M**, whereas **docetaxel** exerts its effect during **S-phase**.
- Paclitaxel, docetaxel, cabazitaxel, nab-paclitaxel



Taxanes: Polymerizing agents

- Drugs are **extremely hydrophobic**, use castor oil for dissolution (that causes anaphylactic reactions)
- Side Effects:
 - ☐ Myelosuppression
 - ☐ Alopecia: full body
 - ☐ Neuropathy -PNP
 - ☒ Myalgias !!!
 - ☐ Edema



Vinca Alkaloids: Depolymerization

- Isolates from *Catharanthus roseus* (Madagascar periwinkle)
- MOA: Inhibition of polymerization by binding to β - tubulin and stabilizing it.
- Vincristine, vinblastine(natural products)
vinuflunin(semi-synthetic)
- Fatal if given intrathecally
(No vines in the spine!)



Vinca Alkaloids: in practice

Use:

**Hematologic malignancies, Sarcomas,
Breast, bladder**

Side Effects:

- ☐ **Vesicant (vinorelbine)**
- ☐ **Neurotoxicity: Vincristine**
- ☐ **Peripheral neuropathy**
- ☐ **GI: constipation**
- ☐ **Myelosuppression**



Cytotoxic Antibiotics

- a varied group of drugs that have various mechanisms of action.
- The common MOA (interruption cell division).
- The most important subgroup is the **Anthracyclines** and the **bleomycins**; other prominent examples include **mitomycin C**, **mitoxantrone**, and **actinomycin**.

Cytotoxic antibiotics

- Actinomycin is a complex molecule that intercalates DNA and prevents RNA synthesis.
- Bleomycin, a glycopeptide isolated from *Streptomyces verticillus*, also intercalates DNA, but produces free radicals that damage DNA.
- Mitomycin is a cytotoxic antibiotic with the ability to alkylate DNA

Putting it all together... A regimen

- ▶ Regimen known as CHOP is a cure for lymphomas even in stage IV
- ▶ C: Cyclophosphamide: alkylation of DNA (non-specific)
 - ▶ Myelosuppression, NV, Renal dysfunction, alopecia
- ▶ H: Doxorubicin: Topoisomerase II inhibitor (S-phase)
 - ▶ Cardiotoxicity, NV, myelosuppression, mucositis
- ▶ O: Vincristine: Antimitotic agent (M-Phase)
 - ▶ Neuropathy
- ▶ P: Prednisone: Not covered but immunosuppression
 - ▶ Increased appetite, hyperglycemia, hypertension
- ▶ Note the mechanisms of actions of the agents
 - ▶ Note the toxicities as well

وحبة من ترابك بكنوز الدني.....





SYRIA IN OUR HEARTS