بسم الله الرحمن الرحيم

Anticancer Drugs
Part 3

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Pharmacology 3

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Antitumor Antibiotics

Antitumor antibiotics

هم antibiotics (Ab) لانهم
مستخلصين من بكتيريا ال
streptomycin

- These include:
  1. Anthracyclines
  2. Bleomycin
  3. Dactinomycin (Actinomycin D)
  4. Mitomycin

They are cell cycle nonspecific with bleomycin as an exception.

Anthracyclines

اشهر اشي هذول الثنين واكثر استخدام

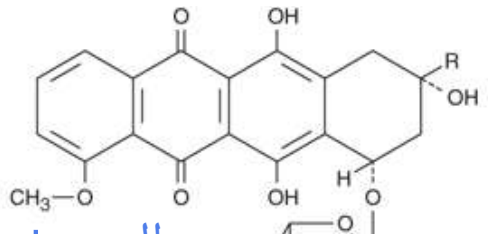
- The anthracycline antibiotics (**doxorubicin** and **daunorubicin**) are among the most widely used cytotoxic anti-cancer drugs.
- Several other anthracycline analogs have entered clinical practice, including **idarubicin**, **epirubicin**, and **mitoxantrone**.
- **Mechanism of action**
- The anthracyclines exert their cytotoxic action through four major mechanisms:

(1) inhibition of topoisomerase II بشبه ال alkylating agent

(2) high-affinity binding to DNA through intercalation, with consequent blockade of the synthesis of DNA and RNA, and DNA strand scission انشقاق او قطع

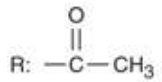
(3) generation of free radicals through an iron-dependent, enzyme-mediated reductive process cytotoxic effect تقريبا هاي اهم

(4) binding to cellular membranes to alter fluidity and ion transport.

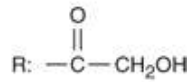


ال structure شبيه ال tetracycline

ال mechanism بتختلف على حسب نوع ال cancer



Daunorubicin



Doxorubicin

Doxorubicin and daunorubicin

Pharmacokinetics:

- IV, because they are inactivated in the GI tract.
- Extravasation is a serious problem that can lead to tissue necrosis.
- Undergo extensive hepatic metabolism. The bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function
- Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and the drugs also impart a red color to the urine

alkylating agent مثل ال

Doxorubicin and daunorubicin

Adverse effects:

- Irreversible, dose-dependent **cardiotoxicity,** apparently a result of the generation of free radicals and lipid peroxidation (heart has low levels of super oxide dismutase).
  - Some success with the iron-chelator dexrazoxane in protecting against the cardiotoxicity of doxorubicin.
  - Also, a new liposomal-encapsulated doxorubicin has been reported to be less cardiotoxic than the usual formulation.
- Others: transient BM suppression, stomatitis, and GI tract disturbances.
- Increased skin pigmentation is also seen.
- Alopecia is usually severe.

ال MOA تاعته انه يعملي free radical وال s.e او ال cytotoxic تاعته انه بأثر عالقلب بسبب ال free radical ، يمكن يعملي مشاكل تكون acute او حتى chronic وبأثر عني على ال ECG ويعملي Arrhythmia، عشان اريح حالي واخلص من كل هاض بعطيه dexrazoxane بيحمي من هاي ال s.e (تكون ال free radical بحتاج iron فبنعطيه iron (chelator

هاض الدواء بكون specific

Bleomycin

بيربط بال DNA من جهة ثانية بال iron(ال ferrous)

- Bleomycin is a small peptide that contains a DNA-binding region and an iron-binding domain at opposite ends of the molecule.
- Cell-cycle specific agent that causes cells to accumulate in the **G_2 phase**.

الادوية الي قبل كانت non-specific

MOA:

ferrous

ال ferrous فقد الكترون وتحول ل ferric

- A DNA-bleomycin-Fe^{2+} complex undergoes oxidation to DNA-bleomycin-Fe^{3+}.

ferric

- The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which in turn attack and destroy the phosphodiester bonds of DNA

الالكترون الي فقدناه بروح عال DNA وبعملي Strand breaks

Clinical uses:

اذا قمنا بإضافة ال cisplatin الاستجابة تقترب الي %100

- Used for testicular cancers in combination with vinblastine or etoposide. Response rates are close to 100 % if cisplatin is added to the regimen.
- Effective for squamous cell carcinomas and lymphomas. فعال لسرطان الخلايا الحرشفية والأورام اللمفاوية.

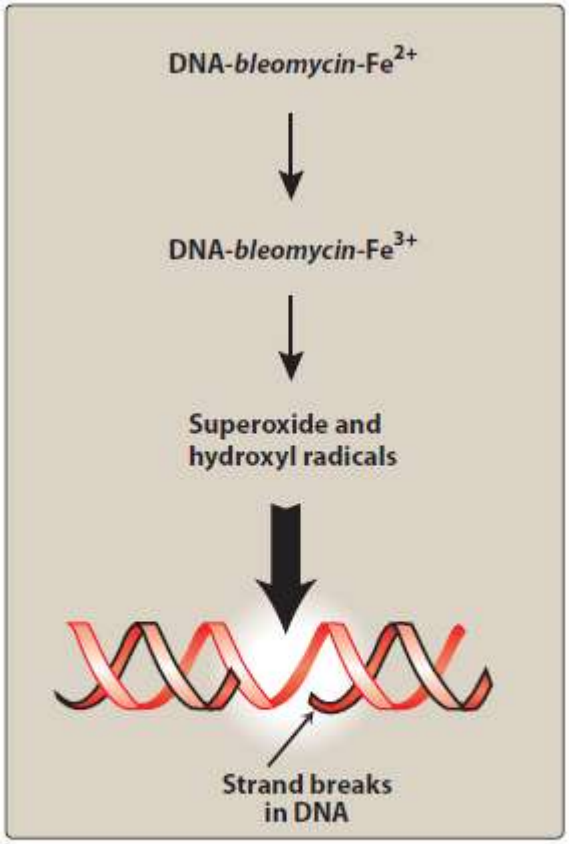


Figure 46.17
Bleomycin causes breaks in DNA by an oxidative process.

Bleomycin

inactivation بيعمل
bleomycin لل

neutralization

Resistance:

- Increased levels of bleomycin hydrolase (or deamidase), glutathione-S-transferase, and possibly, increased efflux of the drug. DNA repair also may contribute.

Pharmacokinetics:

1 2 3 4

- Administered subcutaneous, intramuscular, IV, and intracavitary.
- The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues).

الانسجة بكون عندها Enzy ال hydrolase بشكل
طبيعي واقل tissue عندها هاض الانزايم هم الجلد
والرئة فال toxicity اكثر اشي بتكون عليهم

Adverse effects:

- Pulmonary toxicity is the most serious adverse effect , often referred to it as "bleomycin lung."
- Hypertrophic skin changes and hyperpigmentation of the hands are prevalent.
- Bleomycin is unusual in that myelosuppression is rare.

ميزة اله ما بأثر على ال bone marrow

Natural anticancer

مهمين للانقسام الخلوي

Microtubule Inhibitors

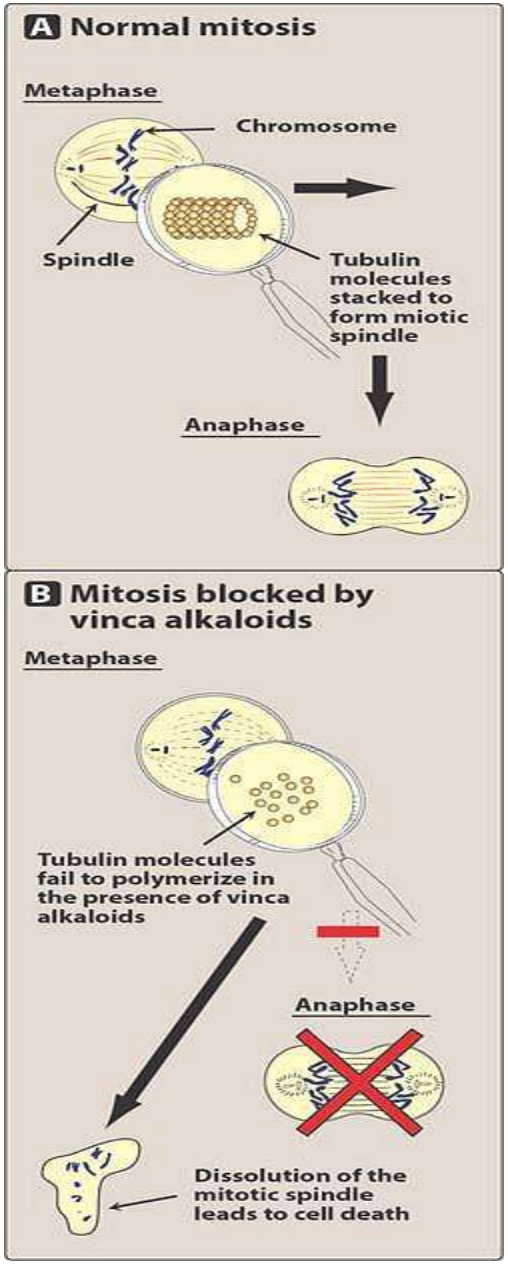
- The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin.
- The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when cell divides.

Vincristine (VX) and vinblastine (vinca alkaloids)

Mechanism of action:

- VX and VBL are both cell-cycle specific because they block mitosis in metaphase (M phase). meta phase
- They bind to the microtubular protein, tubulin, and blocks the ability of tubulin to polymerize to form microtubules.
- The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation

* ال Vincristine and vinblastine بيرتبطوا بال tubulin وال tubul
هذول بدي اياهم عشان ال microtubul الي مهمين لانقسام الخلية بأثر على
ال m phase بال cell cycle



Vincristine (VX) and vinblastine

Resistance:

- Enhanced efflux
- Alterations in tubulin structure may also affect binding of the vinca alkaloids.

Pharmacokinetics :

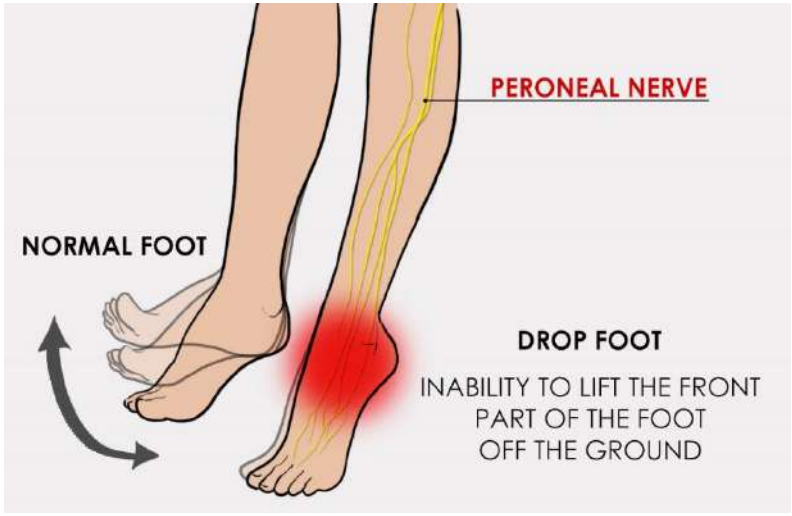
- Intravenous injection leads to rapid cytotoxic effects and cell destruction.
- This in turn can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules, producing uric acid (ameliorated by administration of the xanthine oxidase–inhibitor allopurinol).
- The vinca alkaloids are concentrated and metabolized in the liver by the cytochrome P450 pathway. They are excreted into bile and feces.

dose adjustment في حال في مشكلة بال liver

Vincristine (VX) and vinblastine

Adverse effects:

- Phlebitis or cellulitis, if the drugs extravasate during injection
- Nausea, vomiting, diarrhea, and alopecia. → with VX
- VBL is a more potent myelosuppressant than VX, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with VX.
- These agents should not be administered intrathecally. This potential drug error can result in death.



Paclitaxel

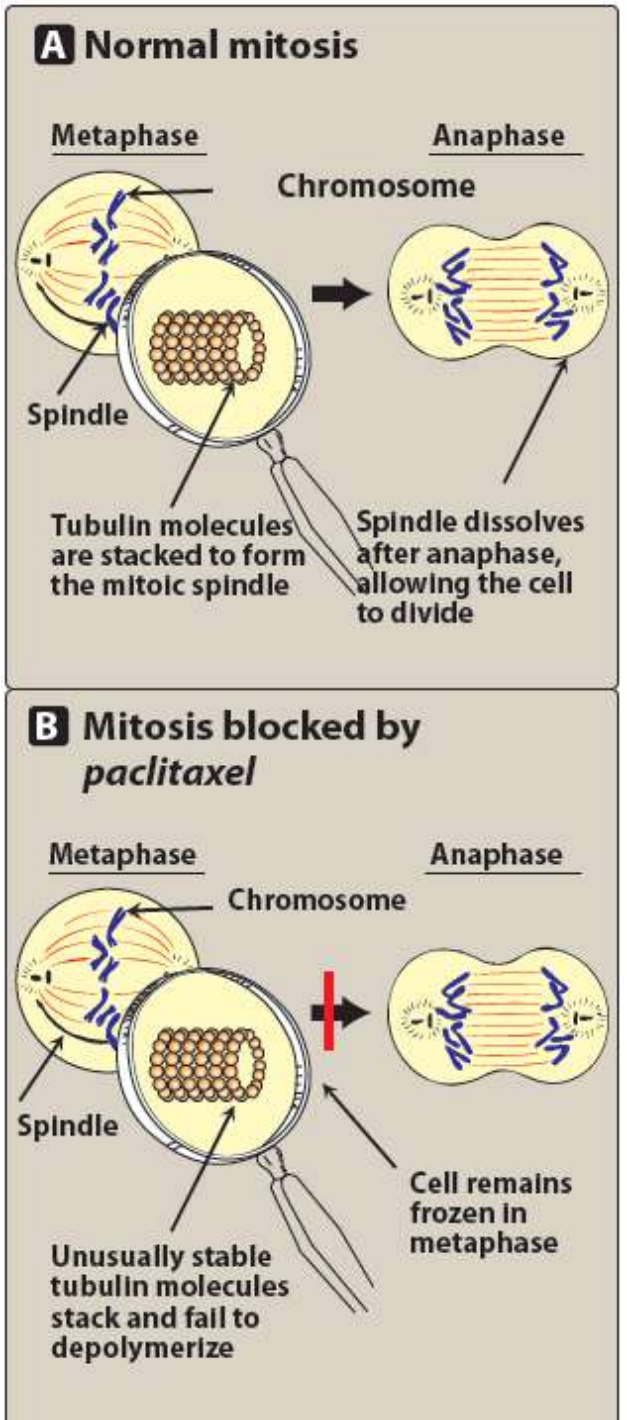
- Better known as Taxol, Paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer.

Mechanism of action:

- Active in the G_2/M phase of the cell cycle.
- Binds reversibly to the β-tubulin subunit, but unlike the vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly
- The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.

Adverse effects:

- The dose-limiting toxicity is neutropenia (Patients with fewer than 1500 neutrophils/mm^3 should not be given these agents).
- Treatment with granulocyte colony-stimulating factor can help to reverse neutropenia.
- Peripheral neuropathy can develop.
- Alopecia occurs, but vomiting and diarrhea are uncommon.



Hormonal anticancer

ال cancer الي بتستجيب للهرومون تنقسم الى نوعين
يا اما بقل ال cancer بوجوده او بزيد ال cancer بوجود الهرمون

Steroid Hormones and Their Antagonists

في نوع من ال cancer بيعطوا الهرمون نفسه زي ال prednisolone بيعمل cytotoxic للمفوما

- **Tumors that are steroid hormone–sensitive may be either**
  - Hormone responsive, in which the tumor regresses following treatment with a specific hormone.
    - Only palliative, except in the case of the cytotoxic effect of glucocorticoids at higher doses (ex. prednisone) on lymphomas
  - Hormone dependent, in which removal of a hormonal stimulus causes tumor regression and can be accomplished by
    - Surgery (ex. orchiectomy for patients with advanced prostate cancer) or by
    - Drugs (ex. in breast cancer, for which treatment with the antiestrogen tamoxifen is used to prevent estrogen stimulation of breast cancer cells).

سرطان ال breast بيحتاجوا هرمون عشان يصيرلهم proliferation فانا بعطيه anti hormones

- **For a steroid hormone to influence a cell, that cell must have intracellular receptors that are specific for that hormone.**

Prednisone

- A potent, synthetic, anti-inflammatory corticosteroid.
- Prednisone is employed to induce remission of acute lymphocytic leukemia and in the treatment of both Hodgkin's and non-Hodgkin's lymphomas.

ال active form+ اله ال

Mechanism of action:

anti -cancer effect

- Undergoes 11-β-hydroxylation to prednisolone in the liver. Prednisolone is the active drug.
- This steroid then binds to a receptor that triggers the production of specific proteins that induce apoptosis in certain cells. intracellular

Resistance: Absence of the receptor protein or a mutation that lowers receptor affinity for the hormone.

اي cancer ما عنده steroidal receptor ما رح يتأثر لما تعطيه

Pharmacokinetics:

receptor لل mutation بيعمل cancer ال او بروح !!steroids

- Readily absorbed orally.
- Prednisolone is glucuronidated and excreted into the urine along with the parent compound.

Adverse effects:

- Predispose to infection (immunosuppressant action) and to ulcers and pancreatitis.
- Hyperglycemia, osteoporosis, and change in mood (euphoria or psychosis).

* cushing syndromes

Tyrosine kinase inhibitors

- The tyrosine kinase**s** are a **family of enzymes** that are involved in several important processes within a cell, including signal transduction and cell division.

inhibtion بعمله cells growth اله دخل بال
الهم وبهيك بقلل من السرطان

Tyrosine kinase inhibitors

بعملي Inhibition لل gene نفسه

- **Imatinib**, **dasatinib**, and **nilotinib**
- **Imatinib** inhibits the tyrosine kinase activity of the protein product of the bcr-abl oncogene that is commonly expressed in chronic myelogenous leukemia (CML)

مسؤول عن تكوين بروتين معين ، ال overexpression لهاض
ال gene بيعملي سرطان وهو الي بعملي ال leukemia هاي

- It prevents the phosphorylation of tyrosine on the substrate molecule and, hence, inhibits subsequent steps that lead to cell proliferation.

في كثير انواع من ال growth factor وال receptor الهم هو ال tyrosine kinase

ال tyrosine kinase اله شغل بال cell growth فلما اعمل inhibtion اله بهيك ساعتها انا ممكن اعمل suppression of cancer growth

كل بروتين في gene معين مسؤول عن تكوينه

اول دوا معنا هو imatinib هاض بيعمل inhibtion لل bcr-abl oncogene فالبتالي ما رح يتكون البروتين بتاعه ولا حتى كمان السرطان وبكده بنكون رتبنا المعلومات

tyrosine من ال other type ل inhibtion بيعملوا Dasatinib and nilotinib ال
kinase (non spicific)

Tyrosine kinase inhibitors

- **Dasatinib** is an oral inhibitor of several tyrosine kinases, including Bcr-Abl, Src, c-kit, and PDGFR-α.
- It differs from imatinib in that it binds to the active and inactive conformations of the Abl kinase domain and overcomes imatinib resistance resulting from mutations in the Bcr-Abl kinase.

يعني مستخدم كثير في حالات صار عندي resistance لل imatinib

- It is approved for use in CML and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL) with resistance or intolerance to imatinib therapy.
- **Nilotinib** inhibits Bcr-Abl, c-kit, and PDGFR-β tyrosine kinases.
- It has a higher binding affinity (up to 20- to 50-fold) for the Abl kinase when compared with imatinib, and it overcomes imatinib resistance resulting from Bcr-Abl mutations.
- Recently approved as first-line therapy of chronic phase CML.

هذول هم الجينات المسؤولين عن تصنيع البروتيان وال
overexpression الهم بعملي سرطان

Tyrosine kinase inhibitors

هاي الادوية كثير بصيريلها drug-drug interaction ،فلازم
يراجعوا كل الادوية للنريض ويزبطوها ، خاصة الي بصيرلها
metabolism بال cyp3A4

- **Pharmacokinetics**
- **Imatinib**, **dasatinib**, and **nilotinib** are all available in oral formulations, and are metabolized in the liver, mainly by the CYP3A4 liver microsomal enzyme.
- A large fraction of each drug is eliminated in feces via the hepatobiliary route.
- It is important to review the patient's current list of prescription and nonprescription drugs because these agents have potential drug/drug interactions, especially with those that are also metabolized by the CYP3A4 system.
- In addition, patients should avoid grapefruit products and the use of St. John's wort, as they may alter their metabolism.
- **Adverse effects:**
- Fluid retention and QT prolongation

هدول باثروا على ال metabolism
لهاي الادوية فلازم المريض ما ياخذهم

Tyrosine kinase inhibitors

- **Other ones:**
- **Gefitinib & Erlotinib**
- Gefitinib and erlotinib are small molecule inhibitors of the tyrosine kinase domain associated with the EGFR, and both are used in the treatment of non-small cell lung cancer that is refractory to at least one prior chemotherapy regimen.
- **Bevacizumab, Sorafenib, Sunitinib, & Pazopanib**
- VEGF inhibitors
- The vascular endothelial growth factor (VEGF) is one of the most important angiogenic growth factors. The growth of both primary and metastatic tumors requires an intact vasculature. As a result, the VEGF-signaling pathway represents an attractive target for chemotherapy.

Growth factor receptor inhibitors

في منهم بربطوا بال receptor وفي منهم بربطوا بال growth factor نفسه
وفي منهم بعمل inhibtion لل tyrosine kinase activity الموجودة اصلا
بال gf-receptor

- **Cetuximab & Panitumumab**
- The epidermal growth factor receptor (EGFR) is overexpressed in a number of solid tumors, including colorectal cancer, head and neck cancer, non-small cell lung cancer, and pancreatic cancer.
- Activation of the EGFR signaling pathway results in downstream activation of several key cellular events involved in cellular growth and proliferation, invasion and metastasis, and angiogenesis.

كل هاي الاشياء بتزيد عندي من السرطان فبدي اعمل inhibition to EGFR

- **Cetuximab** is a chimeric monoclonal antibody directed against the extracellular domain of the EGFR.
- Cetuximab is well tolerated, with the main adverse effects being an acneiform skin rash, hypersensitivity infusion reaction, and hypomagnesemia.

زي ال حب acne الشباب

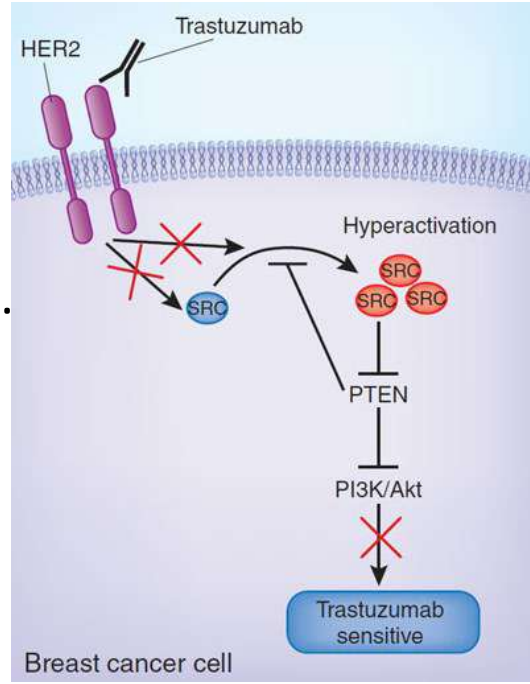
فكرة ال chimeric (اعتقد مني انا انهم جابوها من مصطلح ال chimera😂
المهم بستخدموه بال monoclonal AB [لانه ال mab يا بكونوا جايبينه من حيوان او انسان/ او انسان ومعدلين عليه شوي او بكونوا جابوه من الحيوان والانسان]😂)
فال chimeric هاض بكون جزء Human وجزء animal
عشان اعرفه من الاسم بكون قبل ال mab دي ال xi

عشان تتذكروا هعمل اشي زي نقطة حفظ

البت دي اسمها نينا ومعاها الكلب بتاعها اسمه اليكساندر
كان ابوها رجل مجنون وكان بده يوصل لاشي اسمه الكيميرا الناطق، وصلت فيه المرحلة لدرجة انه عمل تجارب عالبشر والحيوانات وقام بدمج بنته مع الكلب واعطانا هذا الشيء الي اسمه"كيميرا" وبس😂

Growth factor receptor inhibitors

Trastuzumab



- In patients with metastatic breast cancer, overexpression of transmembrane human epidermal growth factor–receptor protein 2 (HER2) is seen in 25 to 30 % of patients.
- Trastuzumab a humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor in breast cancer tissue and inhibits the proliferation of cells that overexpress the HER2 protein, thereby decreasing the number of cells in the S phase.
- Pharmacokinetics: Trastuzumab is administered IV.

Adverse effects:

- congestive heart failure
- infusion-related fever and chills
- headache, dizziness, nausea, vomiting.

* 25-30% من ال patients الي عندهم breast cancer بكون عندهم ال HER2 ، فا في Test بعملوها ، اذا هاض ال patient عنده overexpression لهاض الجين معناها ال "trastuzumab" بكون كثير فعال و effective اله ، اما اذا ما كان عندهم فالدواء هاض مش effective الهم

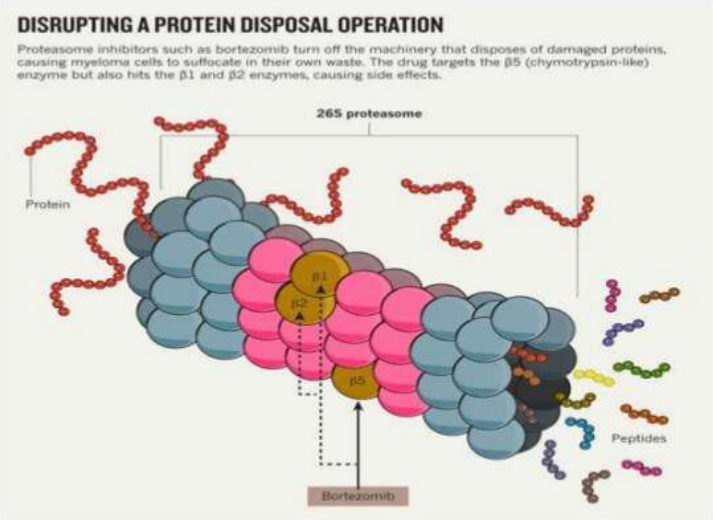
ال side effect (s.e) الي بالاحمر هاي واردة تصير مع ال biological drugs الي اخرهم mab, لانه ببساطة الجسم بشوفهم كجسم غريب عنه فبعمل immune reaction وكل ما كانوا او عملوهم بشبهوا ال human اكثر بتقل ال s.e والي بيجوا من الحيوان بكون احتمال ال s.e هاض انه يصير اكثر واكثر

Proteosome inhibitors

programmed cell death

- Proteasomes are cellular complexes that break down proteins.
- Proteasome inhibition prevent degradation of pro-apoptotic factors such as the p53 protein, permitting activation of programmed cell death in neoplastic cells.
- The first proteasome inhibitor was **bortezomib.** Others are **carfilzomib** and **ixazomib.**
- Approved for use in multiple myeloma.

Bortezomib



ال proteosome هاض بيعمل break down للبروتينات، ال MOA لل pro-inhibitor هي inhibtion لل proteosome الي اله activity على ال protien الي كان بيعمل اييييه؟ كان بيعمل كشري هههء بمزح كان بعمل suppresion لل cancer... يعني بمعنى اخر بيزيد ال tumor suppressive protien

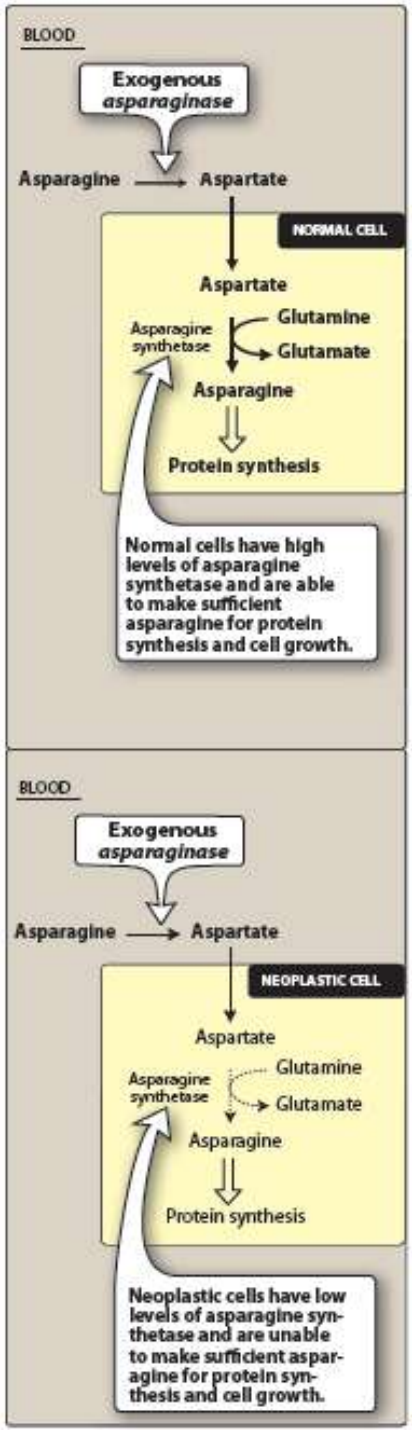
* يعني هاض ال proteosome كان يعمل تكسير لل p43 الي اصلا اصلا بعمل apoptosis فهيك ال p53 ما رح يتكسر فرح يصير عند المريض "programmed cell death"

Asparaginase هاض Enzyme

ال asparaginase بيعمل تكسير ال asparagine ويحوله ل aspartic acid (aspartate) فما رح تستفيد منه ال cancer cell.....ال asparagine مهم لتصنيع البروتينات

- **Asparaginase** (L-asparagine amidohydrolase) is an enzyme occasionally used to treat childhood acute lymphoblastic leukemia (ALL).
- It hydrolyzes circulating L-asparagine to aspartic acid and ammonia. Because tumor cells in ALL lack asparagine synthetase, they require an exogenous source of L-asparagine for protein synthesis. Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. In contrast, normal cells can synthesize L-asparagine and thus are less susceptible to the cytotoxic action of asparaginase.
- must be administered either IV or IM, because it is destroyed by gastric enzymes.
- The main adverse effect of this agent is a hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, and urticaria

من ال cancer cell زي ال leukemia لازم توخذ ال asparagine زي ما هو جاهز اذا مافي asparagine ما رح تصنع البروتينات فما رح يصير proliferation وال growth بيخرب ويوقف



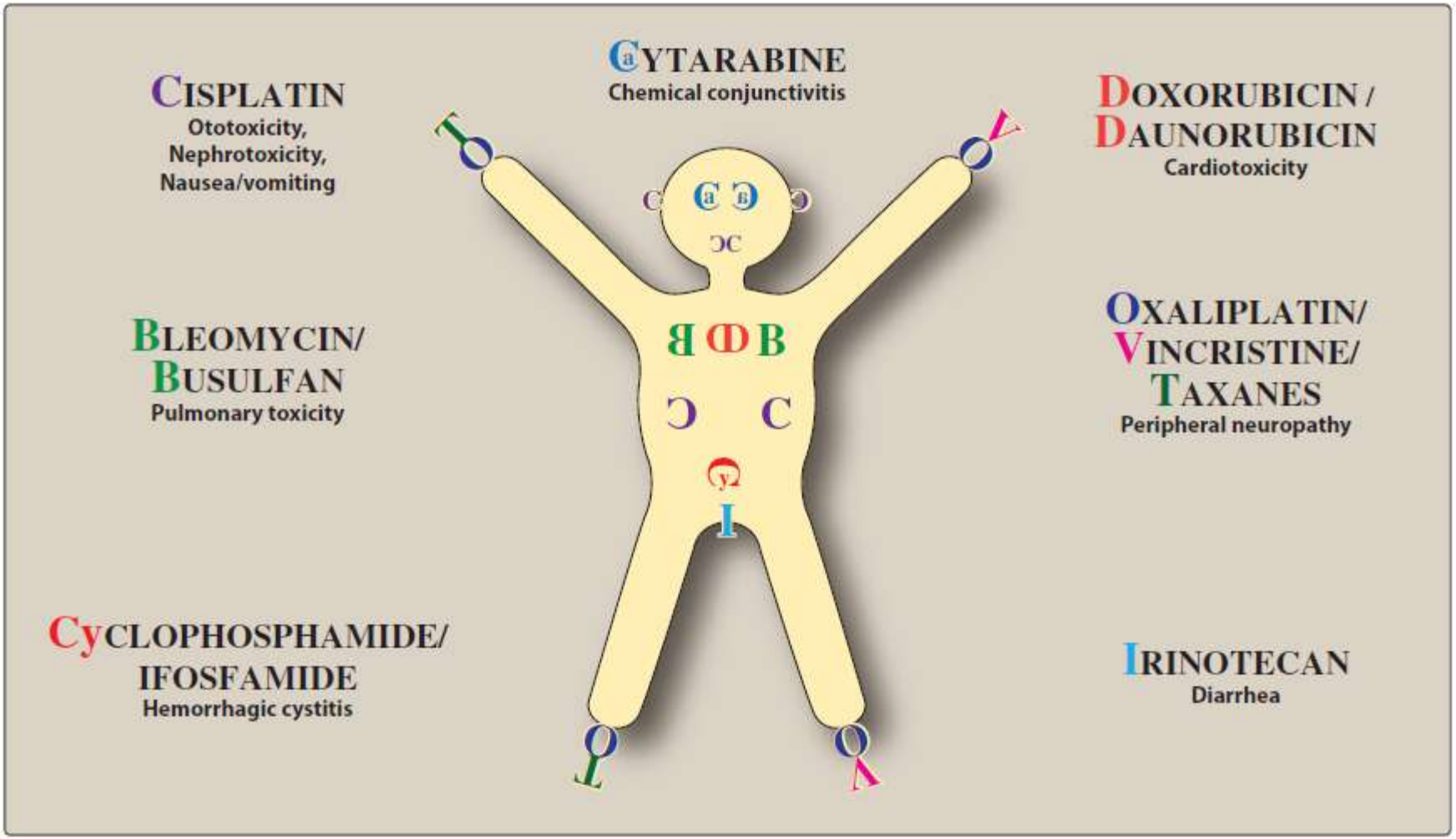


Figure 46.35
Chemo Man—a summary of toxicity of chemotherapeutic agents.

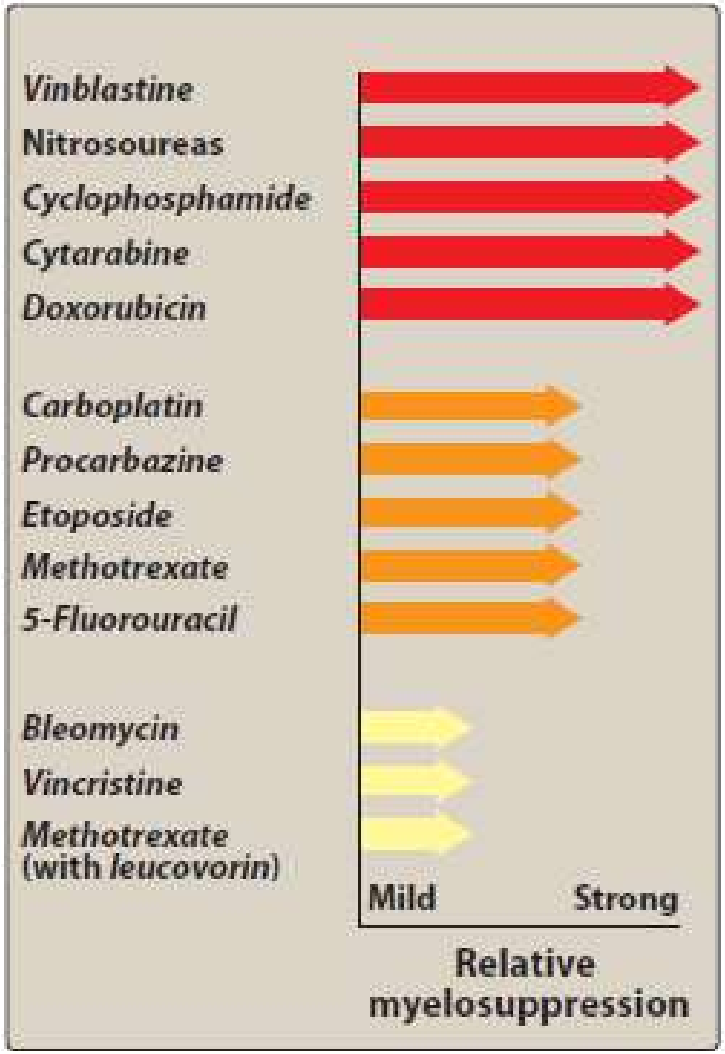


Figure 46.7
Comparison of myelosuppressive potential of chemotherapeutic drugs.

The End