Done By Mariam

Anticancer Drugs
Part 2

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Pharmacology 3

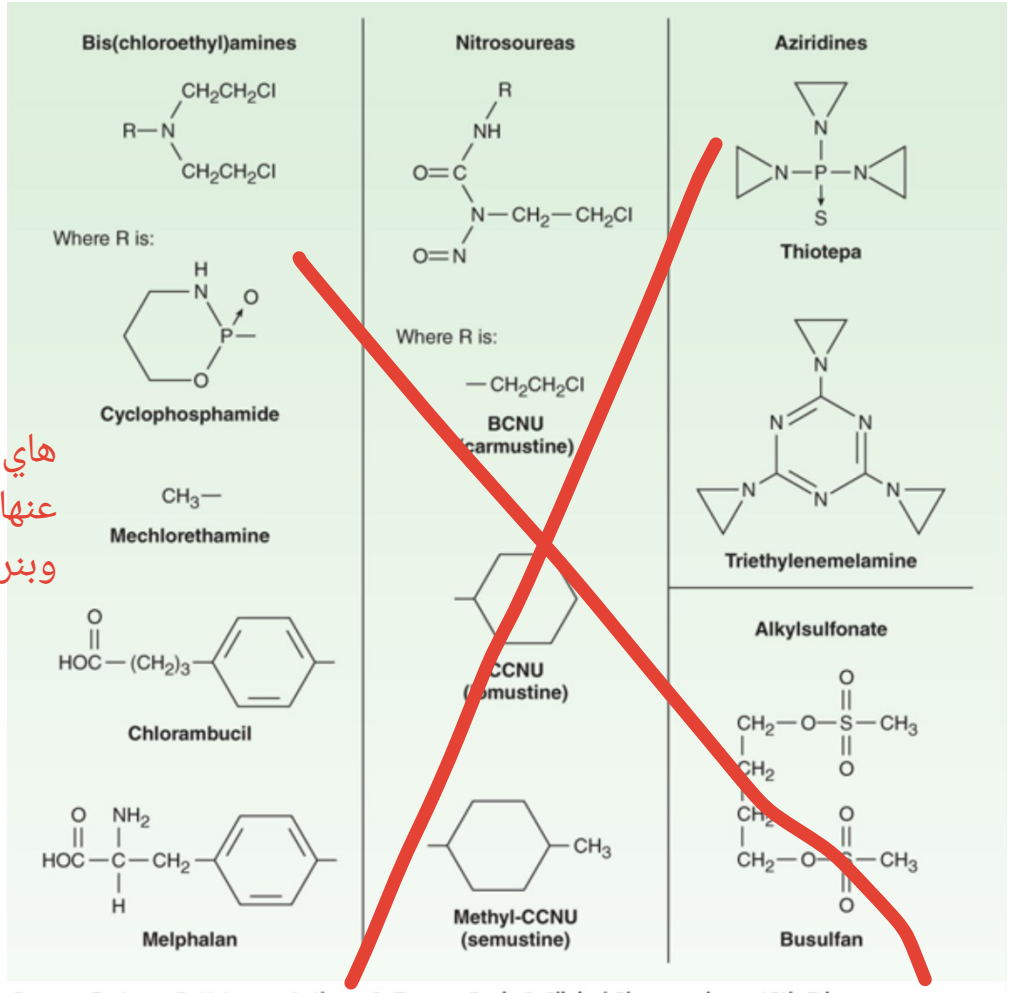
بسم الله نبلش الجزء التاني من الكانسر وإلّي
حيكون بداية مادة السكند ✅
يمكن الشرح مش حيكون كتير بس لإنه كله
أشياء مكررة من الميديسنال

أخدناهم بالميديسنال إنهم بيعملوا alkylation on DNA ف هون ال cytotoxic action هو ال DNA تحديدًا N7-guanin

Alkylating agents

- The major clinically useful alkylating agents:
- Bis(chloroethyl)amine
  - Cyclophosphamide
  - Mechlorethamine
  - Melphalan
  - Chlorambucil
  - Ifosfamide
- Ethyleneimine
- Nitrosourea
  - Carmustine (BCNU)
  - Lomustine (CCNU)

هاي الأدوية إلّي ح نحكي عنها اليوم، كالعادة سكيب وبنرجع بالأخر ✅



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Alkylating agents

- **Mechanism of action:**
- As a class, the alkylating agents exert their cytotoxic effects via transfer of their alkyl groups to various cellular constituents. Alkylations of DNA within the nucleus represent the major interactions that lead to cell death.
- These interactions can occur on a single strand or on both strands of DNA through cross-linking, as most major alkylating agents are bifunctional, with two reactive groups, thereby leading to inhibition of DNA synthesis and function.
- Alkylating agents do not discriminate between cycling and resting cells, but they are most toxic for rapidly dividing cells (cell-cycle nonspecific).
- They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers.

الميكانيزم حكينا إنه بيعملوا alkylation on DNA ف بالتالي رح
يتوقف ال DNA synthesis وبتموت الخلية وهاد الحكي ممكن يصير
إنه هاد ال anti cancer agent يكون عنده 2 alkyl group ف بالتالي
يأثر عالسلسلتين لل DNA وممكن ع سلسلة وحدة منه بما يسمى cross
linking ومعظهم من إلّي بيرتبطوا ب 2strands وبنسميهم
bifunctional
تأثير هاي ال agents بكون عالخلايا ال rapidly dividing وبتصير بأي
جزء خلال ال cell cycle يعني ما في جزء محدد ممكن تصير بأي وقت
وممكن نستخدمهم as combination مع أدوية كانسر تانية

Alkylating agents

Monoalkylation

ارتبط ال agent ب strand 1

Crosslinking
(Between strands)

هون ارتبط ب 2strands بس
كل alkyl group عمل
attachment ع وحدة منهم
(inter)

Crosslinking
(Same strand)

هون ارتبط ب 2strands بس
الارتباط ع نفس السلسلة intra

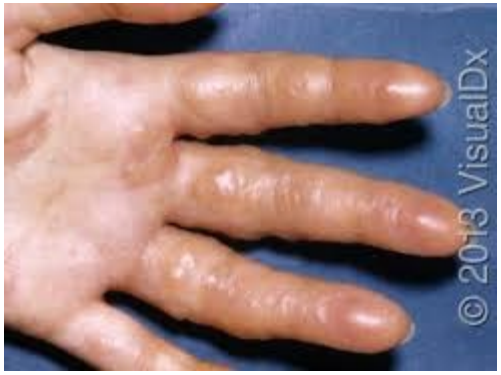
Alkylating agents

- **Adverse Effects**

حكينا أنهم بصيبوا الخلايا إلّي نموها سريع حتى لو كانت normal ف أهم عَرض الهم هو myelosuppressant

- The adverse effects usually associated with alkylating agents are generally dose-related and occur primarily in rapidly growing tissues such as bone marrow (myelosuppression), gastrointestinal tract (diarrhea), and reproductive system.
- In addition, some of them are vesicants and can damage tissues at the site of administration if extravasation occurs.
- As a class, alkylating agents are carcinogenic in nature, and there is an increased risk of secondary malignancies.

بيعملوا vesicants يعني حروق زي الموجود بالصورة نتيجة إنه هي بتنعطى IV ف ممكن يصير extravasation حكينا عنها بالميديسنال
وأهم شي إنه ممكن تؤدي إلى secondary malignancy



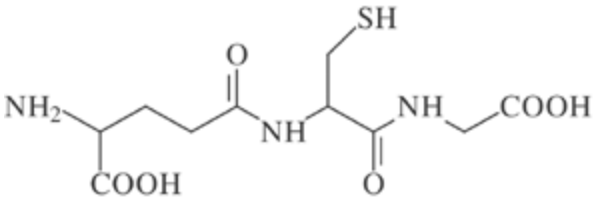
Alkylating agents

الخلية بتقاوم هاد ال agents عن طريق :

- **Resistance:**
- The mechanism of acquired resistance to alkylating agents may involve:

1. Increased capability to repair DNA lesions through increased expression and activity of DNA repair enzymes.
2. Decreased transport of the alkylating drug into the cell
3. Increased expression or activity of glutathione and glutathione-associated proteins, which are needed to conjugate the alkylating agent, or increased glutathione *S*-transferase activity, which catalyzes the conjugation.

بتزيد ال DNA repair يعني بتصلّح حالها وكإنه ما ارتبط فيها إشي
٢- بتقلل دخول هاي ال agents لداخل الخلية
٣- بتزيد وجود ال glutathione وهون رح نحكي شوي
هلأ أول شي ال glutathione هو عادي إشي بتنتجه الخلايا الطبيعية وكّونه الخلية
السرطانية هي بالأصل خلية طبيعية ف وظيفتها إنه ترتبط مع أي xenobiotics عن طريق ال
glutathione S transferase وبتعمله neutralization يعني بمعنى آخر ارتبط بالدوا
عشان تمنع ارتباطه بال DNA ، اوكك ؟



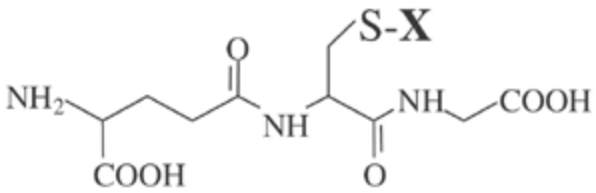
Glutathione

+

Xenobiotic (X)

نفس إلّي حكيناه بالسلايد الماضي ، ف
إنتاج ال glutathione أو ال
glutathione S transferase همة من
الطرق إلّي بتعمل فيها الخلية
resistance تجاه ال alkylating
agent

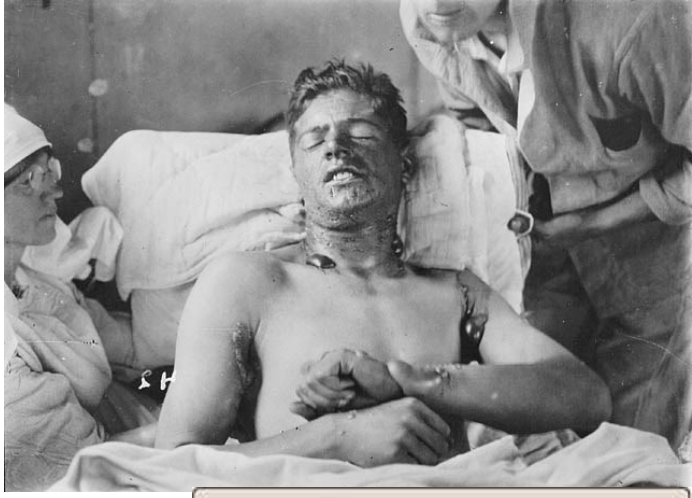
GST



Glutathione-S-Conjugate

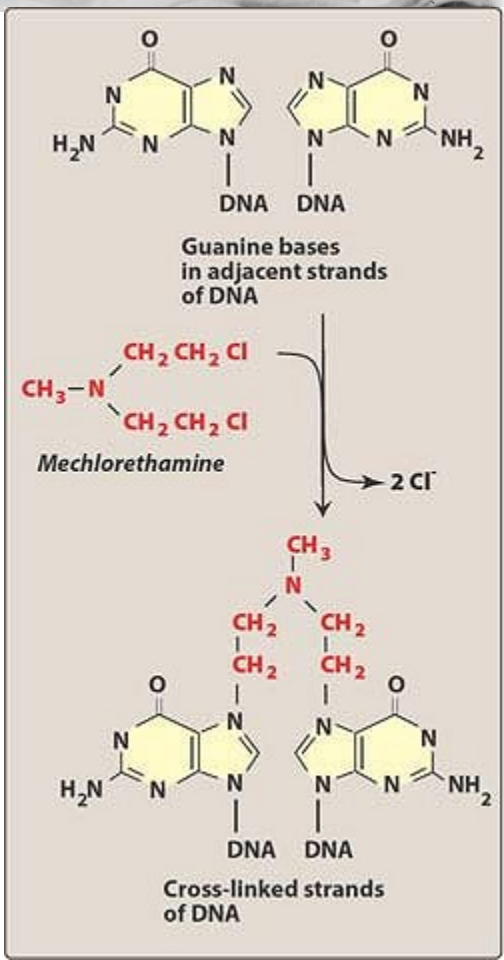
Mechlorethamine

- Mechlorethamine was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers.
- Mechlorethamine was used primarily in the treatment of Hodgkin's disease



Mechanism of action:

- Mechlorethamine is transported into the cell, where the drug forms a reactive intermediate that alkylates the N^7 nitrogen of a guanine residue in one or both strands of a DNA molecule “bifunctional agent.”
- This alkylation leads to cross-linkages between guanine residues in the DNA chains and/or depurination, thus facilitating DNA strand breakage.
- Alkylation can also cause miscoding mutations.



ال mechlorethamine هو أول شي اكتشفوه بهاد الچروب وهو حكينا عنه بالميديسنال كيف قصة اختراعه بالحرب الأولى وبالبداية وجدوا إنه هو بيعمل بالحرب الأولى كان vesicants يعني حروق ، ووجدوا كمان إنه بيعمل lymphocytopenia يعني نقص بال lymphocytes لهيك صاروا يستخدموه بعلاج ال lymphatic cancer

الميكانيزم إنه بدخل لداخل الخلية وبيعمل alkylation عال DNA وكَونه يُعتبر bifunctional ف رح يأثر عال strand 2 وبيعمل cross linking ، هسا ال alkylation تحديدًا بكون على نيتروجينة ٧ من ال guanine
ف بعد ال alkylation حيصير depurination وبعدها break DNA
وكذلك ممكن يعمل ال alkylation هاد شو ؟ miscoding mutation

Mechlorethamine

نفسهم ما في تغيير ، إما الخلية السرطانية بتمنع دخوله ، أو إذا دخل بتربطه مع ال glutathione أو إذا عمل alkylation بتروح بتصلّح ال DNA repair

Resistance:

- Decreased permeability of the drug
- Increased conjugation with thiols such as glutathione
- Increased DNA repair

Pharmacokinetics:

- Mechlorethamine is very unstable, and solutions must be made up just prior to administration.
- Only administered IV. أي rout تانية ممكن تعمل damage of tissue

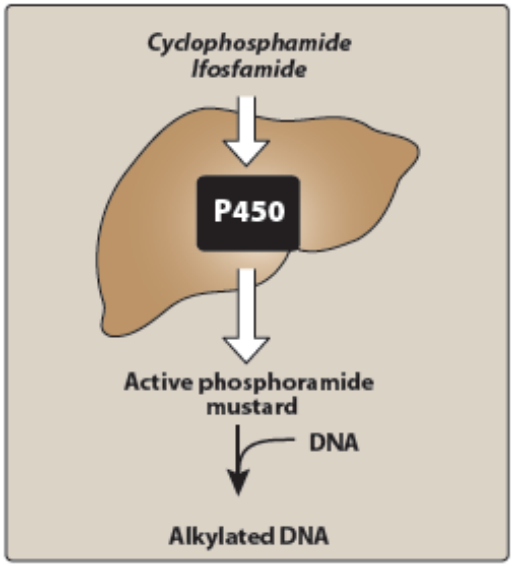
Adverse effects:

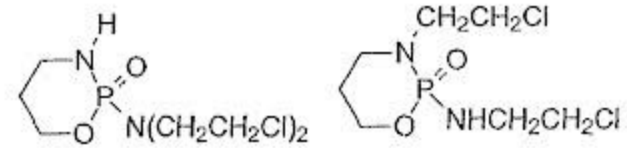
- Severe nausea and vomiting. These effects can be diminished by pretreatment with ondansetron. بنعالجها عن طريق anti emetic زي ال onda
- Severe bone marrow depression limits extensive use.
- Latent viral infections (for example, herpes zoster) may appear because of immunosuppression.
- Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic sodium thiosulfite to inactivate the drug.

بنعطي anti dote وهو ال sodium thiosulfite

Cyclophosphamide and ifosfamide

- Related to the mustard agents and share most of the same primary mechanisms and toxicities.
- Used either singly or as part of a regimen in the treatment of Burkitt's lymphoma and breast cancer.
- MOA: Both cyclophosphamide and ifosfamide are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system.
- The hydroxylated intermediates then undergo breakdown to form the active compounds, **phosphoramide mustard** and **acrolein**.
- Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.
- The parent drug and its metabolites are primarily excreted in urine.





Cyclophosphamide (CPA) Ifosfamide (Ifos)

بنقدر نعتبرهم as prodrug ح يدخلوا للجسم ويصيرلهم أول شي hydroxylation in the liver by CYP450 وبعدها رح يصيرلهم breakdown ويعطونا ال active form منهم.
هسا بس يتكسروا ح يعطونا مركّبين وهمة phosphoramide mustard وكمان acrolin إلّي حترتبط ببروتينات ال bladder وتعمل hemorrhagic cystitis
هلأ بيجي ال phosphoramide mustard وبرتبط بال DNA وبيعمل كمان cytotoxic effects
بالنهاية الدوا الأساسي وكلشي نتج منه حيصيرلهم excretion in the urine

Cyclophosphamide and ifosfamide

مش حفتح صفحة جديدة لأنه كله مكرر، بس
ركزولي عال mesna

Adverse effects:

1. Bone marrow depression and hemorrhagic cystitis, which can lead to fibrosis of the bladder
   - hemorrhagic cystitis has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to toxic metabolites of *ifosfamid*e. [Note: Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.] mesna is anti dote

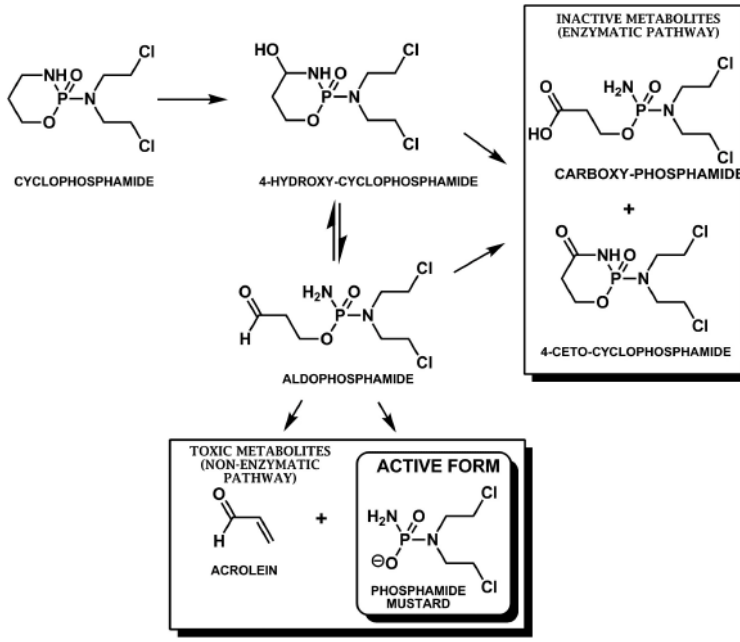
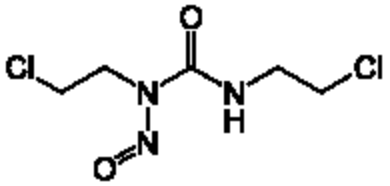


FIGURE 13 - Diagram of cyclophosphamide bioactivation.

2. Effects on the germ cells, resulting in amenorrhea, testicular atrophy, aspermia, and sterility. تأثيره عال reproductive system

3. Secondary malignancies may appear years after therapy. متل ال mechlorethamine

Nitrosoureas



- **Carmustine** and **lomustine** are closely related nitrosoureas.
- Penetrate into the CNS and used for treatment of brain tumors.
- **Streptozocin** is another nitrosourea that is specifically toxic to the β cells of the islets of Langerhans, hence its use in the treatment of insulinomas.

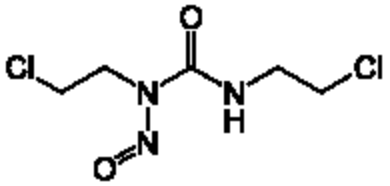
Mechanism of action:

تأثيره تحديدًا عال B cell بالبنكرياس

- Alkylation of the DNA that inhibits replication and, eventually, RNA and protein synthesis.
- Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing (Cell-cycle non-specific agents).
- Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.

Resistance: results from DNA repair and reaction of the drugs with thiols.

Nitrosoureas



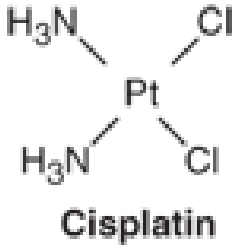
Pharmacokinetics:

- In spite of the similarities in their structures, carmustine is administered IV, whereas lomustine is given orally. واحد اورال وواحد iv
- Because of their lipophilicity, they distribute widely in the body to many tissues including CNS.
- The drugs undergo extensive metabolism.
- The kidney is the major excretory route for the nitrosoureas.

Adverse effects:

- These include delayed hematopoietic depression
- An aplastic marrow may develop on prolonged use نقص بال RBCs
- Streptozotocin is also diabetogenic. بصير معتمد عالإنسولين

Platinium analogs



Cisplatin

- Three platinum analogs are currently used in clinical practice: **cisplatin, carboplatin**, and **oxaliplatin**.
- Although the precise mechanism of action of the platinum analogs is unclear, they are thought to exert their cytotoxic effects in the same manner as alkylating agents.
- They have broad-spectrum activity against a wide range of solid tumors.
- Cisplatin and the other platinum analogs are extensively cleared by the kidneys and excreted in the urine. As a result, dose modification is required in patients with renal dysfunction.
- **Cisplatin** causes nephrotoxicity (can be decreased by I.V hydration) and neurotoxicity (manifested by a peripheral sensory neuropathy).
- **Carboplatin** exhibits significantly less renal toxicity and gastrointestinal toxicity. Its main dose-limiting toxicity is myelosuppression.
- Since vigorous intravenous hydration is not required for carboplatin therapy, carboplatin is viewed as an easier agent to administer to patients, and as such, it has replaced cisplatin in various combination chemotherapy regimens.
- Neurotoxicity is the main dose-limiting toxicity for **oxaliplatin** but it is more readily reversible than that observed with cisplatin-induced neurotoxicity.

الچروب الأخير مش معروف كتير ال mechanism الهم بس still لساتنا بال alkylation والهم broad spectrum وبرضو بيطلعوا عن طريق ال kidney ف بالتالي أكيد لازم اعمل dose adjustment بحالة ال renal dysfunction وللعلم كذا دوا بال alkylating agent بتطلع عن طريق ال kidney وكلهم بختلفوا بالسايد ايفيكت بس

Questions??

ف ال cisplatin بيعمل nephrotoxicity وبخففها عن طريق ال IV hydration وبيعمل كمان neuropathy
أما ال carboplatin ف هو بيعتمد عالدوز بس أقل toxicity عال gi+renal ف بس بيعمل myelosuppressant
آخر شي ال oxaliplatin برضو معتمد عالدوز وبيعمل neuropathy بس بنسبة أقل من ال cisplatin وحتى بكون بشكل reversible