بسم الله الرحمن الرحيم

Anti-neoplastic Drugs (partI)

alkylating agents

MID not final

Dr. Mohammad Salem

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تفاصيل ⊗

! uses

! MOA

! each illness to which drug

1. Antimetabolites

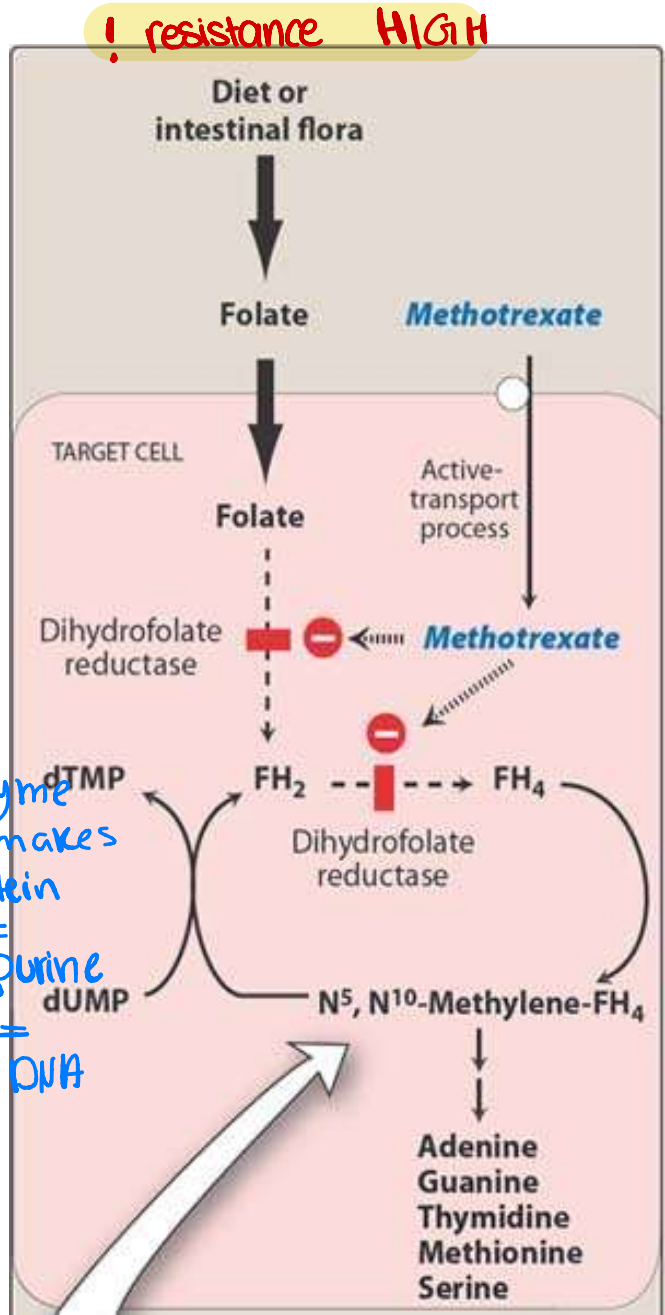
most important

- Compounds bear structural similarity to a naturally occurring substance such as vitamins, nucleoside or amino acid.
- They Interfere with availability of normal purine or pyrimidine nucleotide precursors either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis → since nucleotides changed, ⊗ replication
- Phase specific and act during DNA synthesis (S phase)
- There are three major classes:
  - A. Folic acid analogues
  - B. Purine analogues
  - C. Pyrimidine analogues

A. Folic acid analogues

1. Methotrexate:

- Structurally related to folic acid
- Competitively inhibits dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active tetrahydrofolic acid (FH4)
- In both normal and tumor cells, MTX undergoes conversion into polyglutamates (MTX-PGs) which add inhibitory potency of MTX on thymidylate synthase (TS) enzyme and other enzymes involved in purine synthesis.
- This results in decrease synthesis of DNA, RNA & protein and ultimately cell death



Resistance to MTX:

by cancer cell

1. Impaired transport of MTX into the cell ↗ cancer cells
2. production of an altered form of DHFR ↗ changed binding site
3. increase concentration of DHFR
4. decreased ability to synthesize MTX polyglutamate
5. Increased expression of multidrug resistant protein (MRP) which efflux the drug out of cell.

↑

To overcome resistance, **high dose of MTX** ↗ lethal dose may permit **entry** of the drug into malignant cells.

To avoid toxicity from high dose MTX administration, a fully reduced folate coenzyme called * **leucovorin** (folinic acid) is concomitantly given . It repletes the intracellular pool of FH4 cofactors mainly in normal cells (**leucovorin rescue**) *.

↗ protect normal cells from lethal dose

! therapeutic drug monitoring

Therapeutic uses

- In combination with other drugs for:
  - Acute **lymphocytic leukemia** 1/3 of children cancers
  - **Choriocarcinoma**
  - Burkitt lymphoma in children
  - Breast cancer
  - Head & neck carcinoma
- Inflammatory diseases: used in small doses as DMARDs for treating sever psoriasis and rheumatoid arthritis.

allowed in pharmacy → still susceptible to adverse effects

Toxicity of methotrexate

1-Nephrotoxicity (avoided by drinking plenty of water and alkalinization of urine). (unexpected)

if vomiting, IV fluids

2-Bone marrow suppression

3-Mucosal ulcerations of GIT

4- Hepatotoxicity → liver fibrosis

5-Teratogenecity

MTX is one of the drugs that need therapeutic drug monitoring (TDM) to avoid toxicity.

B. Purine analogues

1. 6- mercaptopurine (6-MP) & 6- Thioguanine (6-TG):

The sulfur component of these drugs substitutes for the oxygen on C6 of the purine ring creating compounds that **inhibit *de novo* purine synthesis (act on S phase)**

- Intracellular; 6-MP is converted to 6-thioinosinic acid mono phosphate (TIMP), while 6-TG is converted to 6-thioguanine monophosphate (TGMP) → intermediate metabolite
- Both TIMP and TGMP inhibits purine synthesis
- TGMP also incorporated into RNA and DNA leading to non-functional RNA and DNA.
- 6-MP is used in **maintenance of remission in acute lymphoblastic leukemia.** ! دكن عالمرض كتير
- 6-TG is used in **treatment of acute non lymphocytic leukemia**

break down

6-MP has a unique pharmacokinetic style as it is metabolized by xanthine oxidase and thiopurine methyl transferase (TPMT) enzymes. **TPMT enzyme is a substrate for genetic polymorphism** with which low expression of the enzyme is associated with good response, increased drug toxicity (Bone Marrow Supression).

Drug interactions of thiopurines

Allopurinol, a xanthine oxidase inhibitor when given with 6-MP to treat the secondary hyperuricemia produces a prominent increase in 6-MP toxicity. Therefore, dose of 6-MP may be reduced by 50% when concomitantly given with this drug.

C. Pyrimidine analogues

1. 5-Fluorouracil (5-FU) :

uridine tri-phosphate

- 5-FU is converted intra-cellularly into 5-FUTP (which inhibits RNA synthesis) and then 5-FdUTP which inhibits thymidylate synthase, and thus DNA synthesis.
- 5-FU is phase nonspecific, killing cells not only in S phase, but through out the cell cycle.
- Treatment of slowly growing solid tumors (**colorectal**, breast, ovarian, **pancreatic** & **gastric carcinomas**).
- Topical 5-Fu is used for treating vitiligo and for basal cell carcinoma. (skin tumors)

2. ! Cytarabine (Ara-C; cytosine arabinoside):

- Its is activated by intracellular kinases to Ara-CTP (cytosine arabinoside triphosphate) which **inhibits DNA synthesis** leading to cell death. It is an **S-phase-specific agent**
- Major clinical use is acute **non-lymphocytic (myelogenous) leukemia**

3 names

myeloid

adverse effects of anti-metabolites

1. Myelosuppression and aplastic anemia : peak toxicity on blood counts occurs within 1-2 weeks

– **To reduce bone marrow toxicity**

– Pulse courses/3-4 weeks rather than regular daily dosing is indicated. This allows for hematologic recovery between courses.

– Administration of granulocyte colony-stimulating factor (G-CSF) 24-72 h after cytotoxic chemotherapy reduces markedly granulocytopenia.

2. Mucositis of GIT : causing usually stomatitis, but in high doses vomiting and diarrhea occur

3. Liver toxicity : hepatitis and jaundice may occur with 6-MP, and with large doses of methotrexate. Long-term use of methotrexate may cause **hepatic fibrosis** !

psoriasis RA

2. Antibiotics

- Anticancer Antibiotics (obtained from natural sources)
- They are cell cycle nonspecific agents

! MOA ,1
! uses ,2

A. Dactinomycin:

- It is obtained from streptomyces species.
- It is a powerful protein synthesis inhibitor. ①
- It intercalates with DNA , inhibits DNA-dependent RNA polymerase and thus inhibits mRNA synthesis leading to marked inhibition of protein synthesis.
- It is used IV for **Wilm's tumour**; also used for malignant melanoma, neuroblastoma, and for ② sarcomas(Ewing tumour , rhabdomyosarcoma).

B. Anthracyclines:

- Doxorubicin and daunorubicin
- These are also obtained from streptomyces species

Mechanism of action

1. Intercalation of DNA: bind to the backbone of DNA leading to **local uncoiling of DNA** and thus blocks DNA and RNA synthesis.
   - ⊗ replication
   - ⊗ transcription
2. Generation of free oxygen radicals: like superoxide ions & hydrogen peroxide, which cause single-strand breaks in DNA

Uses:

- Daunorubicin is used for acute leukemias

- Doxorubicin has wide spectrum of activity in leukemia, lymphomas , myeloma, and also for carcinomas of breast, lung, thyroid, stomach, ovary, and for sarcomas . It is used **IV**

very broad spectrum

Adverse effects:

very specific

- Irreversible, dose-dependent cardiotoxicity (resulting from generation of free radical & lipid peroxidation).
- Cardiac toxicity may progress to congestive heart failure. The use of the cardioprotective iron-chelating agent; **dexrazoxane** may reduce the incidence of cardiac toxicity.

"anti-oxidant" ← anti-dote of anthracyclin

- Transient bone marrow suppression, stomatitis, increased skin pigmentation & alopecia

non-specific

C. Bleomycin:

iron : very toxic

Mechanism of action

- One end of Bleomycin molecule intercalates DNA while the other end binds to Fe^{+2} , where it is oxidized to Fe^{+3}, thereby generating free radicals that cleave DNA.

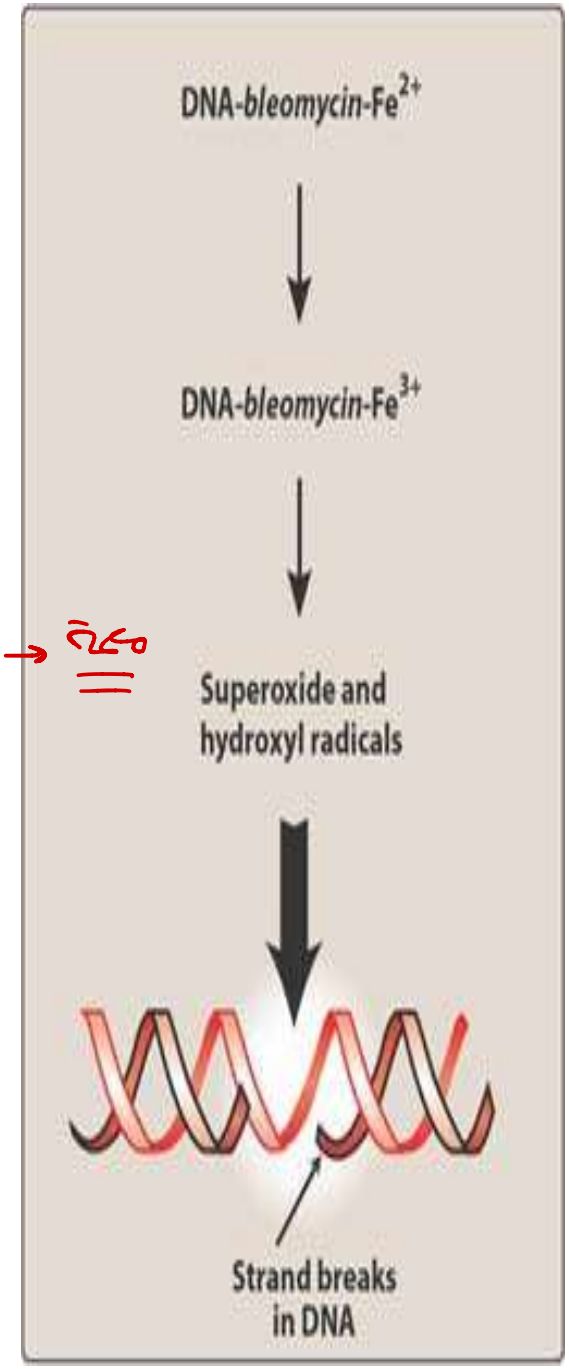
Uses:

- It is used in drug combinations in **head & neck cancer**, lymphoma, and **testicular cancer**.

!!!

Adverse effects:

- Pulmonary toxicity (most serious) !
- Mucocutaneous reactions & alopecia
- Skin changes & hyperpigmentation of hands
- Fever & chills



بيشيل اشياء عشوائية = خربطة

3. Alkylating agents

2 active sites – RNA – DNA – amino acid

- Alkaylation of DNA (addition of alkyl groups to DNA) is responsible for cytotoxic activity of these drugs.
- Most common binding site for alkylating agents is the **7-nitrogen group of guanine**.
- Alkylators exert their action by the following:

1. Cross-linking between two DNA strands leading to inhibition of DNA replication
2. Mispairing of bases leading to defective proteins
3. Deprurination of DNA: alkylation causes cleavage of purine ring leading to weak backbone of DNA and thus strand breakage

- They are cell **cycle nonspecific agents**

A. Nitrogen mustards :

المجموعة مش مهمة
بس إلي إسم النوا

- They are bifunctional Alkylators

General mechanism of action

- These drugs form **ethyleneimonium ion** which reacts with DNA causing alkylation of purine or pyrimidine bases esp. N7-guanine forming cross links between DNA strands and thus leads to inhibition of DNA replication which is lethal to cancer cells.

why?

- **The P53 gene products senses DNA damage and initiate apoptosis in response to DNA alkylation.**
- **Mutations of P53 in tumor cells lead to resistance to alkylating agents.**

if :

1. Cyclophosphamide :

into 2 metabolites

- This drug is activated in liver by cytochrome P450 enzyme system into ① phosphoramide mustard (which has the active anti-cancer alkylating effect) and ② acrolein (which is excreted into urine and may cause hemorrhagic cystitis) ✱

Uses:

- It is used orally or IV for lymphomas, multiple myeloma, leukemias , and with drugs for solid cancers e.g., breast and neuroblastoma.
- It is used for treating autoimmune diseases (like rheumatoid arthritis, nephritic syndrome, etc.)

Adverse effects:

1- Bone marrow suppression (BMS)

2- Hemorrhagic cystitis (Mesna ✱ is used to trap acrolein and prevent cystitis).

Stops it from destroying bladder mucosa

2. Melphalan

- The drug of choice for multiple myeloma;
- Adverse effects include myelosuppression, nausea, vomiting and alopecia.

3. Chlorambucil:

- This is slowest acting.
- It is first choice drug for CLL (**chronic lymphocytic leukemia)**
- It can be given oral and IV.
- Adverse effects include mild myelosuppression, alopecia, and rarely vomiting

B. Nitrosoureas :

1. **Carmustine:** given IV
2. **Lomustine:** oral

✓ BBB !

Mechanism of action:

- These drugs spontaneously form ions that alkylates DNA strands or cause protein carbamoylation.
- These drugs are highly lipid soluble , and easily enter CNS

- They are primarily used for brain tumours ← CNS.

Adverse effects: myelosuppression , vomiting & **liver toxicity.**

3- Streptozocin !

induces diabetes

- It has high affinity for cells of islets of Langerhans and is used in **pancreatic islet cell carcinoma** and carcinoid syndrome. It is nephrotoxic.

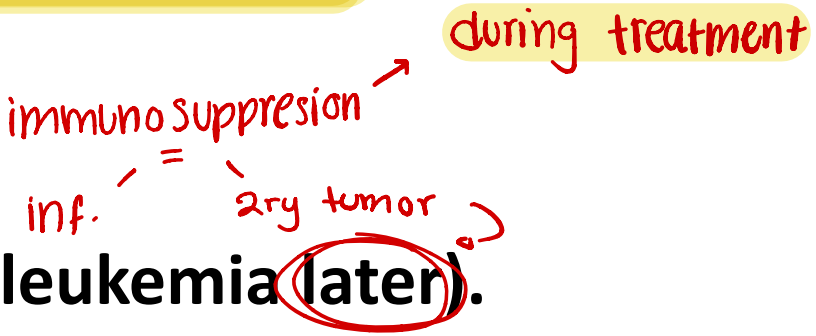
B-cell of : ↑ insulin

Q.

C. Triazenes

1. Procarbazine

- It is used in treatment of Hodgkin's disease.
- **Adverse effects**
- **It causes BMS**
- **It is leukemogenic (may cause leukemia later).**
- **It causes lung injury and pneumonitis.**



2. Dacarbazine

- It is biotransformed in liver to active metabolite that can methylate DNA and RNA and thus inhibits DNA, RNA and protein synthesis
- It is **used IV mainly for the treatment of melanoma**
- Adverse effects include nausea, vomiting and myelosuppression

3. Temozolomide

- Mechanism like dacarbaine
- Unlike dacarbazine, temozolamide can penetrate blood brain barrier
- Temozolamide is used orally in treatment of resistant brain tumors (gliomas & anaplastic astrocytomas)
- Adverse effects include nausea, vomiting and myelosuppression

D- Alkyl sulfonates (e.g. Busulfan)

specific

- It is specific in treatment of chronic myeloid leukemia.
- It may cause pulmonary toxicity include acute lung injury, chronic interstitial fibrosis, and alveolar hemorrhage as a side effect.

Platinum compounds

- Examples are **Cisplatin and carboplatin**.
- Cisplatin binds to the N7 of purine residues and causes cross linkage of DNA strands leading to DNA damage in cancer cells.
- They are used for treatment of testicular, ovarian, bladder, esophagus, and lung cancers.

Toxicity of cisplatin

1. **Cisplatin is nephrotoxic (Avoided by amifostine).**
2. **Cisplatin is neurotoxic (deafness may occur).**
3. **bone marrow suppression is minimal**