بسم الله الرحمن الرحيم

Anti-neoplastic Drugs (partI)

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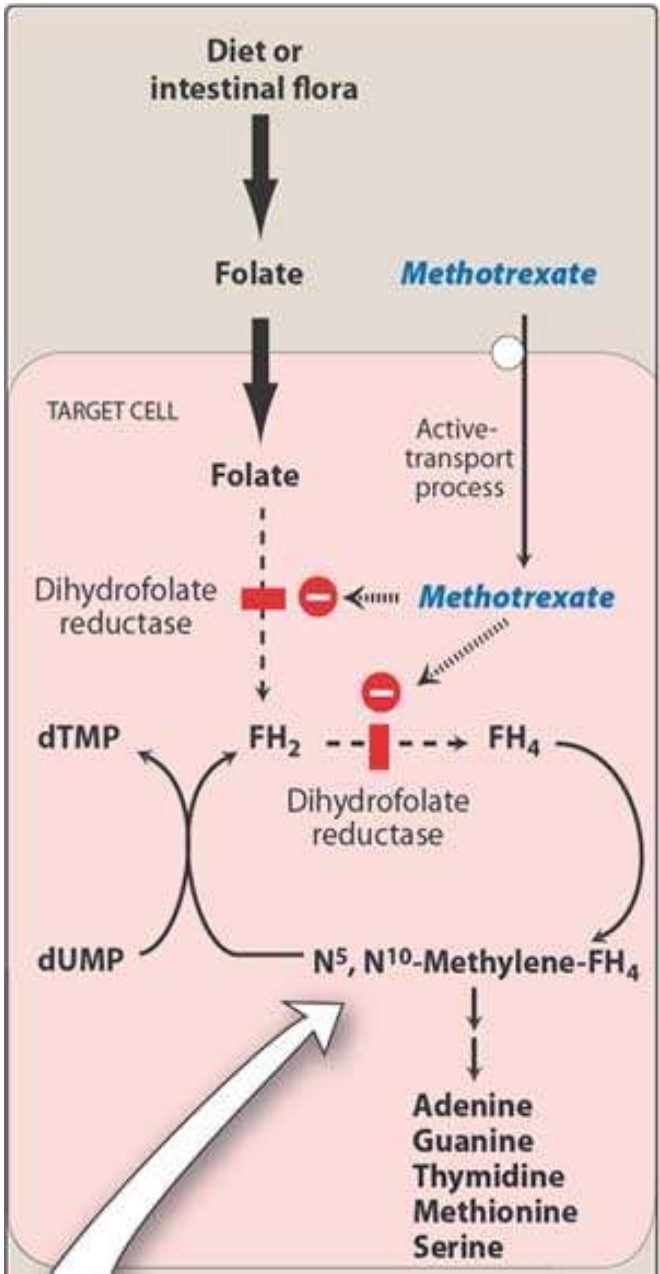
1. Antimetabolites

- 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
- 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:

1. Impaired transport of MTX into the cell
2. production of an altered form of DHFR
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** 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**).

Therapeutic uses

- In combination with other drugs for:
  - Acute **lymphocytic leukemia**
  - **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.

Toxicity of methotrexate

1-Nephrotoxicity (avoided by drinking plenty of water and alkalinization of urine).
2-Bone marrow suppression
3-Mucosal ulcerations of GIT
4- Hepatotoxicity
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)
- 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.**
- 6-TG is used in **treatment of acute non lymphocytic leukemia**

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) :

- 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.

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**

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**

2. Antibiotics

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

A. Dactinomycin:

- It is obtained from streptomyces species.
- It is a powerful protein synthesis inhibitor.
- 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 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.
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**

Adverse effects:

- 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.

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

C. Bleomycin:

Mechanism of action

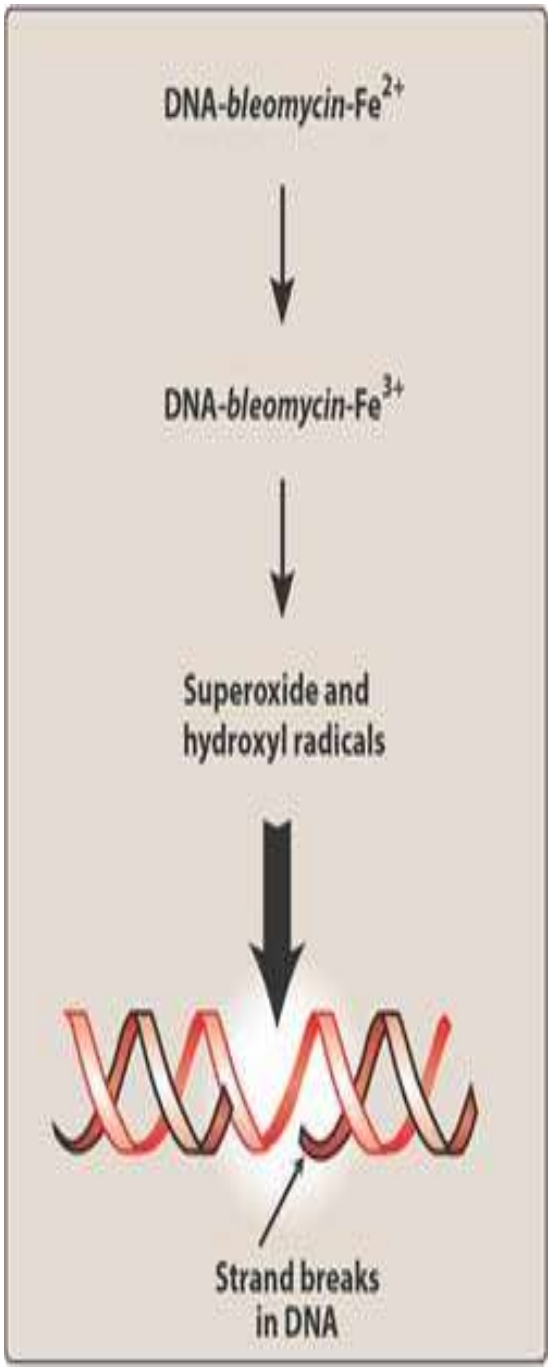
- One end of Bleomycin molecule intercalates DNA while the other end binds to Fe^{+2} , where it is oxidized to Fe^{+3} , thereby generating free radicals that cleave DNA.

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



3. Alkylating agents

- 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 :

- 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.

- **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.**

1. Cyclophosphamide :

- This drug is activated in liver by cytochrome P450 enzyme system into phosphoramide mustard (which has the active anti-cancer alkylating effect) and 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).

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

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

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

3- Streptozocin

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

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)

- 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**

THANK YOU