بسم الله الرحمن الرحيم

Anticancer drugs (part 2)

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Alkylating agents and platinum complexes

Alkylating agents include **Nitrogen mustards**, **ethyleneimines**, **alkylsulfonates**, **nitrosourea**, **triazenes** & **DNA-methylating drugs**, including procarbazine and dacarbazine.

Mechanism of action

These drugs are converted to **highly reactive ethyleneimine** intermediate that transfer alkyl groups to various cellular components particularly the **N^7** position of **guanine** base of DNA. Alkylation of N^7 of guanine leads to any of the following reactions that end by cell death.

- **Mispairing** with **thymine** instead of **cytosine** during DNA synthesis.
- **Depurination** of the DNA by excision of the alkylated guanine residue
- **Cross linking** of two nucleic acid chains, or the linking of a nucleic acid to a protein that disrupts the nucleic acid function.

- 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.
- All alkylating agents are CCNS drugs and can kill cells at any phase of the cell cycle (they have broad spectrum activity and are used in treatment of several cancers).

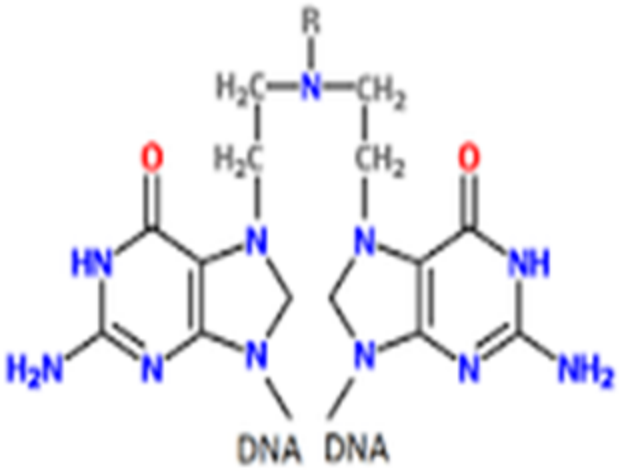
Common sites of alkylation

1-N7 of guanine

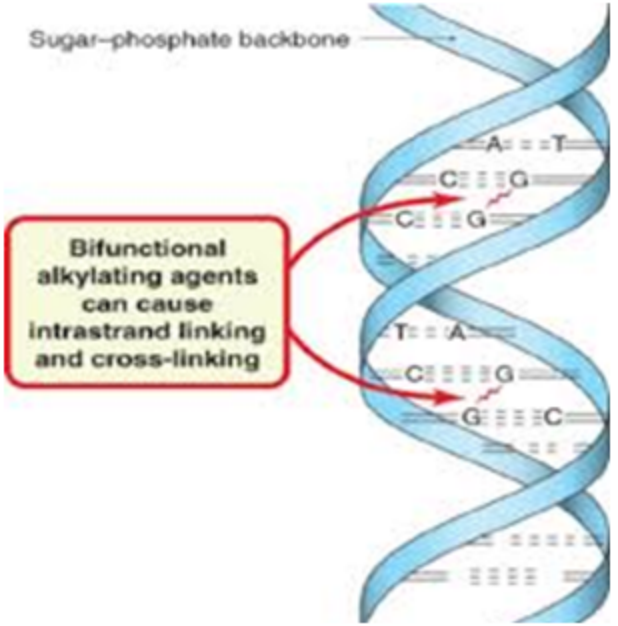
2-N3 of cytosine

3-O6 of guanine

4-N1 & N3 of adenine



N7 interstrand crosslinked DNA



Cyclophosphamide

- It is a Nitrogen Mustard (bi-functional alkylator) prodrug.
- It is activated in the liver by CYP450 into **hydroxy-cyclophosphamide** & **aldo-phosphamide** to produce the **cytotoxic effect.**
- Further metabolism leads to formation of **toxic metabolites** (**acrolein**) that may cause **hemorrhagic cystitis**.
- It is used for **chronic lymphocytic leukemia**, **breast cancer, neuroblastoma** and **lymphomas.**
- Used in **rheumatoid arthritis & nephritic syndrome.**

Adverse effects of cyclophosphamide:

1- Bone marrow suppression (BMS)

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

Busulfan

- It is specific in treatment of chronic myelogenous leukemia.
- It may cause hepatic veno-occlusive disease as a side effect.

Carmustine and lomustine :

- They are highly **lipophilic Nitrosoureas** and easily cross the blood brain barrier, an important property in the treatment of **brain tumors**.
- The profound and delayed **myelosuppression** limit its use.

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.

Dacarbazine

- It is used in malignant melanoma and Hodgkin's disease.
- Nausea and vomiting are induced by the drug in >90% of patients.

Procarbazine:

- It is used in treatment of Hodgkin's disease.

Melphalan

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

Chlorambucil

- This is slowest acting agent
- It is used for CLL (**chronic lymphocytic leukemia)**
- Adverse effects include mild myelosuppression, alopecia, & rarely vomiting

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**

Natural products

1. Antimitotic and microtubule inhibitors

1-Vinca alkaloids: example: vincristine and vinblastine

- **Mechanism of action:** They are cell cycle specific and block cells in mitosis through an action on microtubules of mitotic spindle.
- One important clinical use of **vinblastine** is in combination in the curative therapy of **metastatic testicular tumors**.
- **Vincristine** used together with glucocorticoids as **treatment of choice to induce remission in childhood leukemia.**

2-Taxanes: example: paclitaxel

- bind to microtubules stabilizing them in the polymerized state (arrest of mitosis)
- Paclitaxel clearance is nonlinear and decreases with increasing dose.
- **Used in advanced cancer of the ovaries, breast, non-small cell lung cancer, and Kaposi sarcoma.**

2- Topoisomerase inhibitors

The topoisomerases are nuclear enzymes that reduce torsional stress in supercoiled DNA allowing selected regions of DNA to become sufficiently relaxed to permit replication, repair and transcription. Two classes of topoisomerase (I and II) mediate DNA strand breakage and resealing, and both have become the target of cancer chemotherapy.

1-Inhibitors of topoisomerase I e.g. **topotecan and irinotecan** cause DNA damage and cell death. Irinotecan has been shown to be effective in the treatment of colon cancer, and topotecan has been shown to be effective in the treatment of ovarian and small cell lung cancers.

2-Inhibitors of topoisomerase II e.g. **etoposide and tenoposide** inhibit the re-ligation of the broken double strand DNA leading to apoptosis. in small cell lung cancer, acute lymphoblastic leukemia (ALL), lymphoma and testicular germ cell cancer.

3- Antibiotics

1-Actinomycin-D or **dactinomycin** acts by **intercalation between adjacent guanine-cytosine base pairs** of the DNA leading to blocking of the transcription of DNA by RNA polymerase. The most important clinical use of dactinomycin is in the treatment of **Ewing's sarcoma, rhabdomyosarcoma and Wilms tumor.**

2-Anthracyclines (**doxorubicin & daunorubicin**)They **intercalate** between base pairs in DNA, **inhibit topoisomerase II** and **generate superoxide free radicals** which attack DNA and oxidize DNA bases. These drugs are used in leukemias, AIDS-associated Kaposi's Sarcoma and metastatic cancers.
Cardiotoxicity is the most important long-term toxicity with **anthracyclines** (It is dose related and progresses to congestive heart failure). Generation of free oxygen radicals by these drugs is related to the cardiac lesion. The use of the cardioprotective iron-chelating agent; **dexrazoxane** may reduce the incidence of cardiac toxicity.

3-Bleomycin:

It **produces oxidative damage to the deoxyribose of thymidylate** and other nucleotides leading to single-double-stranded breaks in DNA. It is highly effective in **germ cell tumors of the testis and ovary and uterine cancer**.

Because bleomycin causes **little myelosuppression as a side effect**, it has significant advantages in combination with other cytotoxic drugs.

4- Enzymes

L-asparaginase

Most normal tissues can synthesize L-asparagine in amounts sufficient for protein synthesis, but **lymphocytic leukemias** lack adequate amounts of asparagine synthetase and derive the amino acid asparagine required for protein synthesis from plasma.

When L-asparaginase is given, it hydrolyzes circulating asparagine into aspartic acid and ammonia and thus reduces the extracellular level of asparagine and deprives the malignant cells of the amino acid.

Hormones & their modulators

- **Glucocorticoids:** they induce antiproliferative and apoptotic responses in sensitive cells. Because of their lympholytic effects and their ability to suppress mitosis in lymphocytes, glucocorticoids are used as cytotoxic agents in the treatment of **acute leukemia in children** and **malignant lymphoma in children and adults.**
- **Progestins**: They are used as second line hormonal therapy for **metastatic hormone-dependent breast cancer** and in the management of **endometrial carcinoma** previously treated by surgery and radiotherapy. Progestins induce apoptosis in these malignant cells.
- **Estrogen receptor modulators e.g., tamoxifen** is used in **breast cancer** which are estrogen receptor positive **(ER+)** or progestin receptor positive (PR+) but not breast cancer with ER negative or PR negative.

- **Aromatase inhibitors**: They block conversion of androgen into estrogen induced by aromatase enzyme. Examples are type I inhibitors like **androstenedione** which binds irreversibly to aromatase enzyme, and type II like **letrozole** which binds reversibly to the enzyme. They are used as adjuvant therapy in postmenopausal women with hormone receptor positive breast cancer.

- **Prostatic cancer:** Androgens stimulate the growth of normal and cancerous prostate cells. Localized prostate cancer is curable with surgery or radiation therapy. But, with distant metastases, hormone therapy is the primary treatment. It is the androgen deprivation therapy (ADT) which is considered palliative, not curative, alleviates cancer symptoms. (**Using** gonadotropin-releasing hormone agonists or antagonists and flutamide). Flutamide **and** bicalutamide **are antiandrogen** drugs


Thank you!