Anticancer Drugs 2
**ANTIBIOTICS FOR CANCER THERAPY**

- They’re natural substances that inhibit DNA & RNA synthesis; they behave as both phase specific (Bleomycin) & phase non specific agents they include: Dactinomycin, Daunarubicin, Doxorubicin&( Amsacrine which is similar), Plicamycin & Mitomycin, epirubicin & the related Mitozantrones (Idarubicin & Aclarubicin).

- The antibiotics depress BM, cause GIT upsets & stomatitis, Alopecia, cardiomyopathy (Daunarubicin & Doxorubicin), pulmonary fibrosis & skin rashes (Bleomycin). The effects of some are radiomimetic & the use of radiation causes additive toxicity.

**Dactinomycin (ActinomycinD)**

- **Mechanism of action:** the drug intercalates between guanine cytosine base pairs of the DNA forming a stable drug DNA complex. At high doses may hinder DNA synthesis & may cause strand breaks.

- **Uses:** adjuvant chemotherapy with vincristine & Methotrexate in Rx of Wilm's tumor, also used in choriocarcinoma & soft tissue sarcoma.

- **Kinetics:** metabolized in the liver, the drug & its metabolites are excreted in bile & urine, the drug is given I.V.

- **Side effects:** B.M. (Bone Marrow) depression, extravasations, GIT upsets, alopecia & immunosupression.
Doxorubicin (Adriamycin) & Daunorubicin (Danomycin)

- Classified as Anthracyclin antibiotics, doxorubicin is the hydroxylated form of Daunorubicin.

Site of action (Mechanism of action):

1. Intercalation with DNA, the drug inserts non-specifically between base pairs causing local uncoiling & blocking of DNA & RNA synthesis.
2. Binding to cell membrane altering function of transport process coupled to phosphotidyl inositol activation (IP₃).
3. Generation of O₂ radicals (formation of O₂⁻ & H₂O₂) causing single strand breaks in DNA.

- Tissues with adequate superoxide dismutase & glutathione peroxidase are protected while tissues having low dismutase are more liable for injury.
- Heart & tumor cells have low SOD (superoxide dismutase), the heart also lacks catalase (which is responsible for disposition of H₂O₂), & thus these drugs will affect heart cells as well as tumor cells leading to cardiac toxicity. (cardiomyopathy).

Uses:

1. Doxorubicin is most important & widely used anticancer it is used for: breast CA, lymphomas, sarcomas, lung CA, stomach CA & thyroid CA.
2. Daunorubicin is used for Acute Myeloid Leukemia (AML).
3. Both drugs are given I.V., inactivated in GIT (not given orally) don't penetrate CNS, extensively metabolized & excreted mainly in bile.

Adverse effects: cardiac toxicity (irreversible & dose dependant), alopecia & infertility.
**Bleomycin**

- Cycle specific causes cells to accumulate in G\textsubscript{2} phase; it causes scission of DNA by an oxidation process by forming O\textsuperscript{2} & OH\textsuperscript{+} radicals (superoxide & hydroxyl radicals).

- **Uses:**
  1. Testicular CA together with Vinblastin & cisplastin (etoposide maybe used instead of vinblastin).
  2. Head & neck CA.
  3. Lymphoma.
  5. Cervical CA.


- **Adverse effects:**
  1. Pulmonary toxicity leads to fatal pulmonary fibrosis.
  3. High incidence of fever chills.
  4. B.M. depression (rare & mild).

**Plicamycin (Mithramycin)**

- Acts through restriction of DNA-directed RNA synthesis, it has specific toxicity to osteoclast preventing their resorption & also lowers Ca\textsuperscript{++} concentration in hypercalcemia especially those with bone tumors.

- **Adverse effects:**
  1. Coagulopathy, haemorrhage.
  2. Liver & renal toxicity.
  3. B.M. depression.
ANTIMETABOLITES

- Are phase specific, act during S-phase of cell cycle.
- Are structurally related to normal cellular components, they generally interfere with availability of normal purine & pyrimidine, nucleotide precursors by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.

**These include:**

1. **A folic acid antagonist**: Methotrexate (MTX).
2. **Purine antagonist**: mercaptopurine 6-MP, Azathiopurine and thioguanine, Fludarabine, cladribine.
3. **Pyrimidine antagonist**: capecitabine, Fluorouracil (5FU), cytarabine, & Gemcitabine.

Fludarabine: used in low grade non Hodgkin and CLL.

Cladribine: used as Fludarabine and in hairy cell leukemia

**Adverse effect:**

1. GIT upset (ulceration, mucositis).
2. B.M. depression.
3. Renal impairment potentiates their toxicity.

**Methotrexate (very important)**

- **Mechanism of action**: structurally related to folic acid, it acts as folic acid antagonist by inhibiting (dihydrofolate reductase) which is responsible for conversion of folic acid into active form (tetrahydrofolic acid) which is important in synthesis of amino acids & nucleic acids.
Methotrexate enters cells by active transport process; it has strong affinity to FH$_2$ reductase. This inhibitory step by MTX can be bypassed by giving FOLinic acid (leucovorin) & this is called "leucovorin rescue" which means B.M. rescue.

- The consequences of ↓ FH$_4$ leads to ↓ biosynthesis of thymidilic acid, amino acids (meth. & serine) & purines (adenine & guanine) → ↓ DNA, RNA synthesis, ↓ protein synthesis → cell death.

- Uses: in combination with other drugs, MTX is effective in:
  1. Acute lymphoid leukemia.
  2. Lymphoma.
  3. Osteogenic sarcoma & choriocarcinoma, here MTX is curative, high doses of MTX followed by leucovorin to rescue B.M.
  4. Head & neck carcinoma.
  5. Breast carcinoma.
  6. Gastric & bladder CA.
  7. Carcinomatous meningitis (low dose).
  8. As immunosuppressive agent as a single agent for Rheumatoid arthritis & psoriasis (also low dose).
Kinetics:
1. Rapidly absorbed from gut.
2. Given I.M., I.V., intrathecally because it poorly penetrates CSF.
3. It's metabolized inside the cells to polyglutamate derivatives; they inhibit FH$_2$ reductase & remain in cells even in the absence of the extracellular drug (i.e. the effect of MTX lasts for long time after it's been given).
4. MTX also undergoes hydroxylation (7-OH metabolites) both (MTX+ metabolites) are excreted in urine.
5. 7-OH metabolite has ↓ water solubility → crystal urea, therefore, good hydroxylation & alkylinization of urine is important to avoid renal toxicity.

Adverse effects: most frequently are stomatitis, B.M. suppression, alopecia, N & V (Nausea & Vomiting), diarrhea, erythema, rash & urticaria. Some of these can be prevented or ↓ by leucovorin (but dose should be minimal to avoid interference with antitumor action of MTX). Leucovorin is taken by normal cells more readily than cancer cells.

Other toxicities: Renal, hepatic, pulmonary & neurologic toxicity (often intrathecally → meningitis-like picture).

Contraindications (CI): pregnancy because it causes abortion & it's teratogenic.

6-Mercaptopurine (6-MP)
- It's a thiol analog of hypoxanthine. Azothioprine (an Immunosupp.) exerts its effects after conversion to 6-MP.

Mechanism of action (site of action): it penetrates target cells & is converted to the corresponding nucleotide (6-MP ribose phosphate also known as Thio-IMP) this process is catalyzed by HGPRT (Hypoxanthine Guanine Phospho Ribosyl Transferase).
This Thio-IMP can feed back to inhibit the 1$^{st}$ step of de-novo purine synthesis. In addition, there'll be dysfunction of DNA & RNA resulting from the incorporation of guanylate analogs generated from the unnatural nucleotide.
**Uses:** for maintenance of remission in ALL (Acute Lymphoid Leukemia), absorption by the oral route is erratic, doesn't penetrate the CNS. Metabolized in the liver to thio uric acid by (Xanthine oxidase). Allopurinol therefore; ↑ toxicity of 6-MP. The metabolite & the drug are excreted in urine.

**Adverse effects:** N & V, diarrhoea, B.M. depression, (the chief toxicity) hepatotoxicity.

**6-Thioguanine (6-TG)**
- Another purine analog, used primarily in Rx of Acute Non Lymphocytic Leukemia in combination with daunorubicine & cytarabine. Like 6-MP it must be converted to the corresponding nucleotide from which will inhibit purine synthesis.

- 6-TG can also be incorporated in the NA & RNA. Very little of 6-TG is metabolized to Thio uric acid (therefore Allopurinol doesn't potentiate the toxicity of 6-TG). Other toxicities are similar to 6-MP.

**5-Fluorouracil (5-FU)**
- It's a pyrimidine analog. To be cytotoxic 5 FU is converted to the corresponding deoxynucleotide (5-F dump) which competes with dump for thymidylate synthetase (T.S.).

- 5-F dump acts as pseudosubstrate entrapped with the enzyme that can't proceed to products. DNA synthesis ↓ because of thymidine lack. 5 FU is also incorporated in the RNA.

- **Uses:** solid tumors, colorectal CA, breast & ovarian CA, pancreatic & gastric CA. Adjuvant therapy with Levamisole improves survival of colon CA.
Anticancer Drugs 2

- **Adverse effects:** severe toxicity to GIT if given orally, so taken I.V. Penetrates well to the CSF. Metabolized in the liver to CO$_2$. Toxicity includes beside the GIT, BM depression & hand foot dermopathy.

- **Cytarabin (Ara-C)**
  - A pyrimidine antagonist, it has to be converted to corresponding nucleotide (Ara-CTP) in order to be cytotoxic. It is S phase specific & it's also incorporated into DNA & can terminate chain elongation.

  - **Uses:** AML (Acute Myeloid Leukemia) in combination with 6-TG & Daunorubicin. Ara-C is ineffective orally, is given I.V., doesn't penetrate to the CSF (can be injected intrathecally).

  - **Adverse effects:** N & V, diarrhea, severe B.M., suppression (primarily granulocytopenia) & hepatotoxicity.

- **Capecitabine:**
  - prodrug, extensively metabolized in the liver to many intermediates that is finally hydrolyzed by thymidine phosphorylase to fluorouracil (5-FU) in the tumor cell
  - **Uses:** metastatic breast cancer either as a single agent or in combination with other taxans (docetaxel). Recently approved for use in treatment of metastatic colo-rectal cancer (combination with oxaliplatin & irinotecan)
  - **Toxicity:** mylosuppression

- **Gemcitabine:**
  - Approved for pancreatic cancer, non small cell lung cancer, bladder cancer
  - **Main toxicity:** mylosuppression
  - Phosphorylated to triphosphate form, the end result is inhibition of DNA synthesis.
**Fludarabine**
- It's un-natural purine nucleotide, its triphosphate incorporated in both DNA & RNA decreasing their synthesis & function.
- **Uses:** CLL (chronic Lymphoid Leukemia) may replace chlorambucil. Hairy cell leukemia. It's given I.V., causes Myelosuppression (dose-limited toxicity).

**Procarbazine**
- Inhibits DNA & RNA synthesis. It's part of the MOPP for Hodgkin's disease. It is given orally & parenterally, penetrates the CSF, excreted in urine together with its metabolite.
- **Adverse effects:** BM depression (Major toxicity), GIT & neurotoxicity. It inhibits MAO (contraindicated with Tyramine contained food) it induces Disulfiram reaction with Alcohol. It's both mutagenic & teratogenic (cause non-Lymphocytic leukemia).

**L-Asparaginase**
- It's derived from bacteria, it catalyses the deamination of Asparagine → Aspartic acid & ammonia. Neoplastic cells require an extra source of asparagine to support growth & function. The drug will hydrolyze blood Asparagine thus deprives the tumor cells of their nutrient required for protein synthesis.
- **Uses:** for ALL in combination with vincristine & prodinsolone. It is given I.V. or I.M. not given orally (destroyed by gastric acidity).
- **Toxicity:** hypersensitivity reactions → ↓ clotting factors & liver abnormalities, also Pancreatitis, coma, seizures due to ammonia toxicity.