The classes of drugs currently used in the cancer clinic are

1. DNA Binding Agents (intercalating and alkylating agents)

2. Mitotic Spindle Inhibitors (modulators of tubulin polymerisation)

3. Antimetabolites (anti-folates, pyrimidine and purine analogues)

4. Hormones and Hormone Antagonists

5. Miscellaneous anticancer drugs
Malignant tissue with numerous mitoses

Cytostatics inhibit cell division

Healthy tissue with few mitoses

Little effect

Wanted effect: inhibition of tumor growth

Damage to hair follicle
Hair loss

Lymph node
Inhibition of lymphocyte multiplication: immune weakness
Lowered resistance to infection

Inhibition of granulo-, thrombocyto-, and erythropoiesis

Inhibition of epithelial renewal
Diarrhea

Unwanted effects

Germinal cell damage

Bone marrow
DNA binding agents

Intercalating agents

• Intercalating agents are flat planar aromatic compounds that insert themselves in between the DNA basepairs.

• They either inhibit RNA polymerase activity but not DNA polymerase or exert their action as cancer drugs by poison the activity of topoisomerase II.

• Clinically used intercalating agents include ANTHRACYCLINES, MITOXANTRONE, ACTINOMYCIN D and Bleomycin
DNA

Damage to template

Alkylation e.g., by mechlorethamine

Cl–CH₂–CH₂

Cl–CH₂–CH₂

Insertion of daunorubicin, doxorubicin, bleomycin, actinomycin D, etc.

Streptomyces bacteria
Anthracyclines

• are the most commonly used anticancer drug,
  ➢ Doxorubicin (adriamycin) having activity against a wide range of solid tumours. (Most common drug)
  ➢ Daunorubicin (daunomycin) being used against acute myeloid leukemia (AML)
  ➢ Idarubicin is a semisynthetic anthracycline that took Daunorubicin place in AML therapy.
  ➢ Epirubicin doxorubicin analogue used in metastatic breast cancer and gastric cancer
Anthracyclines

- DNA strand scission via effects on Top II enzyme (topoisomerase poisons)

- High-affinity binding to DNA through intercalation, resulting in blockade of DNA and RNA synthesis.

- Binding to membranes and altering fluidity

- Generation of the free radical and oxygen radicals
Anthracyclins

• Their main toxicities are
  - Bone marrow depression
  - Total alopecia

• BUT the anthracyclines have a strange dose-limiting irreversible and lethal cardiomyopathy.

• This cardiotoxicity may be a result of the generation of free radicals and lipid peroxidase.

HOW TO REDUCE THIS .................
Mitoxantrone

• Treats pediatric and adult acute myeloid leukemia, non-Hodgkin’s lymphomas, and breast cancer.

• Prostate cancer ???

• poisons the activity of topoisomerase II. And ........

• Myelosuppression is the main side effect.

• Causes cardiac toxicity .

• Blue discoloration of finger nails for 1 – 2 days after treatments.
Actinomycin D

• Actinomycin is a very potent inhibitor of RNA polymerase. Does intercalate in the minor groove of the double helix.

• In the cancer clinic it finds use against special tumours, particularly Wilm’s tumour which is a cancer of the kidney in children (in combination with vincristine).

• It is also combine with methotrexate in the treatment of gestational choriocarcinoma.

• Its toxicities are bone marrow and gut suppression.
Actinomycin-DNA Complex
Bleomycin

bleomycin intercalates DNA, the major cytotoxicity is believed to result from iron catalyzed free radical formation and DNA strand breakage.

• It is useful in Hodgkin’s and non-Hodgkin’s lymphomas, testicular cancer, and several other solid tumors.

Adverse Effects:
• Bleomycin produces very little myelosuppression.
• The most serious toxicities of Bleomycin are pulmonary and mucocutaneous reactions.
Alkylating Agents

- Nitrogen Mustards
  - Cyclophosphamide

- Ethylenimines
  - Thiotepa

- Alkyl Sulfonates
  - Busulfan

- Nitrosoureas
  - Carmustine
ALKYLATING AGENTS

- Alkylating agents bind irreversibly to DNA and function by crosslinking the two Watson-Crick strands, thereby inhibiting strand separation and preventing DNA replication.
Nitrogen mustards

- Cyclophosphamide (oral)
- Ifosfamide
- Melphalan (oral)
- Chlorambucil (oral) least toxic
Nitrogen mustards

cyclophosphamide
1. most commonly used alkylating agent
   used in lymphomas, leukemias, sarcomas, carcinomas of breast or ovary, as well as childhood malignancies.
2. has a special place in the maintenance therapy for breast cancer.
3. It is also a potent immunosuppressant,
   it is used in the management of rheumatoid disorders and autoimmune nephritis.
4. Cystitis (inflammation of the urinary bladder) may result. co-administered with N-acetylcysteine or 2-mercaptopoethanesulfonate (mesna). Both are thiols that neutralized acrolein
Nitrosoureas

• The best known clinical agents are CARMUSTINE and LOMUSTINE (oral).

• The nitrosoureas pass the blood-brain barrier and are active against brain tumours.

• These drugs appear to be non-cross-resistant with other alkylating agents.

• Streptozocin (minimal bone marrow toxicity) used to treat insulin-secreting islet cell carcinoma of the pancreas
Platinum analogs

• In the clinic, cisplatin behaves very similarly to the organic alkylating agents and finds widespread use.

• Cisplatin has efficacy against a wide range of neoplasms.

• It is particularly effective in germ cell tumours (testicular cancer and ovarian tumours) and in breast cancer.

• Its use in combination chemotherapy has revolutionised the treatment of testicular and ovarian tumours, frequently leading to complete cure of testicular cancers in young men.
Platinum analogs

• Its main toxicities are to the kidney and to the ear,

• produces relatively little myelosuppression but can cause severe nausea, vomiting.

• Carboplatin is a second generation platinum analog that has less renal toxicity and gastrointestinal toxicity.

• Though Carboplatin has widely replace cisplatin in chemotherapeutic regimen.
Alkylating Agents therapeutic Uses

- *Thiotepa* – ovarian cancer

- *Busulfan* (oral) – chronic myeloid leukemia
  
  *is linked with*
  
  pulmonary fibrosis,
  
  adrenal insufficiency and
  
  skin pigmentation
Resistance to Alkylating agents

• Cells become resistant to alkylating agents by

1. REPAIR OF DNA LESIONS
Alkylating agents and platinum-based agents -resistant cells up-regulate the repair systems.

2. CHEMICAL INACTIVATION OF DRUGS
DNA alkylating and platinating agents are chemically reactive, particularly reactive towards -SH groups and, accordingly, tumour cells can become resistant by up-regulating their thiol content (glutathione).
Antimetabolites

- Folic Acid Analogs
  - Methotrexate

- Purine Analogs
  - Mercaptoguanine

- Pyrimidine Analogs
  - Fluorouracil
Inhibition of nucleotide synthesis

Building blocks

Purines

Thymine Nucleotide

Tetrahydrofolate

Dihydrofolate Reductase

Folic acid

Inhibition by

Aminopterin
Methotrexate

Insertion of incorrect building block

Purine antimetabolite

6-Mercaptopurine instead of Adenine
from Azathioprine

Pyrimidine antimetabolite

5-Fluorouracil instead of Uracil
Cytarabine instead of Desoxyribos
Folate Antagonists

• Folates are essential for the synthesis of both purine nucleotides and thymidylate which are required for DNA synthesis and cell division.

• Folic acid is a coenzyme used in the one-carbon transfer step in these metabolic pathways.

• In order to function as a coenzyme folic acid must be reduced to tetrahydrofolic acid by the enzyme dihydrofolate reductase (DHFR), first to dihydrofolic acid and then to the tetrahydro form.
Folate Antagonists

- Methotrexate is a derivative of folic acid which antagonises DHFR with a high affinity.

- Methotrexate is widely used clinically, usually administered orally. It is used against acute lymphocytic leukemia.

- Main toxicity is myelosuppression

- Rescue method: calcium leucovorin (Folinic acid)
Pyrimidine antagonists

• The best known example is Fluorouracil, 5FU, incorporated into DNA and RNA, finally inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.

• It is widely used in colon cancer.

• 5-FU is effective in palliative management of carcinoma of breast, colon, pancreas, rectum and stomach in patients who can not be cured by surgery or other means.

• Its main toxicities are myelosuppression and gut epithelial damage.
Figure 2. This figure illustrates the effects of MTX and 5-FU on the biochemical pathway for reduced folates.
Pyrimidine antagonists

- Cytosine arabinoside, Cytarabine, is a naturally-occurring analogue of cytidine.

- Their mode of action is due to its rapid conversion into cytosine arabinoside triphosphosphate, which damages DNA when the cell cycle holds in the S phase.

- Main use is in leukaemias and lymphomas.

- Main toxicity is to bone marrow and gut damage.
Purine antagonists

1) 6-Mercaptocaptopurine (6-MP)

- Purine
- Hypoxanthine
- 6-Mercaptocaptopurine

2) 6-Thioguanine (6-TG)

- Guanine
- Thioguanine
Purine antagonist

• They inhibit various steps in *de novo* purine synthesis and antagonise the enzyme Ribonucleotide Reductase.

• Ribonucleotide reductase is a key enzyme in DNA synthesis.

• Both 6-MP and 6-TG are administered orally and used for treating acute leukemia.

• their main toxicity is to the bone marrow and gut.

• allpuranoL
MITOTIC SPINDLE INHIBITORS

Inhibition of formation
Vinca alkaloids

Microtubules of mitotic spindle

Inhibition of degradation
Paclitaxel

Vinca rosea
Western yew tree
INHIBITORS OF TUBULIN POLYMERISATION

• The vinca alkaloids Vincristin and Vinblastin are natural products isolated from the periwinkle plant.

• They act by binding to tubulin and inhibit its polymerisation into microtubules,

• thereby preventing spindle formation during mitosis. This causes dividing cells to arrest at metaphase.

• They are widely used in the treatment of solid carcinomas and leukaemias and lymphomas.
INHIBITORS OF TUBULIN POLYMERISATION

- Vinblastine therapeutic Uses include Systemic Hodgkin’s disease Lymphomas

- Vincristine is used against lymphomas, breast cancer, sarcomas, and the various childhood neoplasms.

- Vincristine used With prednisone for remission of Acute Leukemia
Toxicity of the Vinca alkaloids

• Vinblastine main toxicity is Nausea & Vomiting, Bone Marrow depression, and Alopecia

• While Vincristine is relatively non-toxic, generally having mild myelosuppressive activity but cause they cause sensory changes and neuromuscular abnormalities fairly frequently.
INHIBITORS OF TUBULIN DE-POLYMERISATION

- The TAXANES, of which Taxol is the best known example, are isolated from the yew tree.
- They also bind to tubulin but have the opposite effect to the Vinca alkaloids and stabilise microtubules to de-polymerisation. (mitotic spindle poison)

- The taxanes are generally more toxic than the Vinca alkaloids and side-effects include myelosuppression and Peripheral neuropathy.

- Taxol has proven beneficial in late-stage drug-resistant ovarian and breast cancers, prolonging life by about 6 months.

- Dec pica ad more
Hydroxyurea

- It interferes with DNA synthesis by inhibiting ribonucleotide reductase, and this action results in decreased levels of deoxyribonucleotides.

- Hydroxyurea may interfere with the function of the enzyme by chelating with its ferrous iron cofactor.

- (can be given orally) It is active against melanoma, chronic myelocytic leukemia, and metastatic ovarian carcinoma.

- Has the typical side effects.
Asparaginase

- Asparaginase (L-asparagine amidohydrolase) is an enzyme that is isolated from various bacteria for clinical use.
- The drug is used to treat childhood acute lymphocytic leukemia.

- It hydrolyze circulating L-asparagine to aspartic acid and ammonia. Because tumor cells lack asparagine synthetase, they require an exogenous source of L-asparagine.

- Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. (normal cells can synthesize L-Asparagine)

- The main side effect of this agent is a hypersensitivity reaction manifested by fever, chills, nausea and vomiting, skin rash, and urticaria.
HORMONE ANTAGONISTS

- Tumours derived from hormone-sensitive tissues may be hormone-dependent.

- Their growth can be inhibited by
  1. hormones with opposing actions,
  2. hormone antagonists
  3. inhibit hormone synthesis.
Tamoxifen

• Selective estrogen receptor modulator (SERM), have both estrogenic and antiestrogenic effects on various tissues

• Patients with estrogen-receptor (ER) positive tumors are more likely to respond to tamoxifen therapy, while the use of tamoxifen in women with ER negative tumors is still investigational

• When used prophylactically, tamoxifen has been shown to decrease the incidence of breast cancer in women who are at high risk for developing the disease

• It is active orally and is therefore particularly useful in maintenance therapy.
• Hot flashes, Fluid retention, nausea.
HORMONE ANTAGONISTS

• ANTIANDROGENS such as Flutamide bind to androgen receptors and are effective in the treatment of prostate cancer.

• Aromatase inhibitors decrease the production of estrogens. Aminoglutethimide is an example that inhibit hydrocortisone synthesis.

Anastrozole is the newer agent that have less problem