

3. ANTINEOPLASTIC – ANTICANCER DRUGS

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3. ANTINEOPLASTIC/ANTICANCER DRUGS

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3. ANTINEOPLASTIC – ANTICANCER DRUGS

ANTINEOPLASTIC

CANCER: It is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues.

CLASSIFICATION OF CANCER:

1. Behaviouristic classification:

- According to types and size of tumors.

A. Benign tumors:

- Benign tumors are tumors that cannot spread by invasion or metastasis; hence, they only grow locally.

B. Malignant tumors:

- Malignant tumors are tumors that are capable of spreading by invasion and metastasis.

Characteristic	Benign	Malignant
Differentiation	Tumor cells resemble the original mature cells	Tumor cells might not resemble the original mature cells
Growth Rate	Slow; might stop or regress	Rapid, autonomous; usually does not stop or regress
Type of Growth	Expand and displace	Invalidate, destroy, and replace
Metastasis	No	Yes
Health Effect	Usually does not cause death	May cause death if not diagnosed and treated

2. Histogenic classification:

- According to the tissues or cells from which it arises.
 - **Carcinoma:** Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged, and include nearly all those developing in the breast, prostate, lung, pancreas, and colon.
 - **Sarcoma:** Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchymal cells outside the bone marrow.
 - **Lymphoma and leukemia:** These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukemia is the most common type of cancer in children accounting for about 30%.
 - **Germ cell tumor:** Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

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- **Blastoma:** Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults.

CLASSIFICATION OF ANTICANCER DRUGS ACCORDING TO CHEMICAL STRUCTURE:

1. Alkylating agents:

A. Mustards (Nitrogen Mustards):

Eg.: Cyclophosphamide, Chlorambucil, Melphalan, Ifosfamide, Uracil mustard, Mechlorethamine.

B. Nitrosoureas:

Eg.: Streptozotocin, Lomustine, Carmustine, Semustine

C. Ethylenimines:

Eg.: Triethylenemelamine, Triethylenethiophosphoramide (Thiotepa), Hexamethylinemelamine

D. Alkylsulphonates:

Eg.: Methanesulphonates (Busulphan)

E. Trazenes:

Eg.: Dacarbazine

2. Antimetabolites:

A. Folic acid analogues:

Eg.: Methotrexate

B. Pyrimidine analogues:

Eg.: Fluorouracil, Cytarabine, Gemcitabine, Azaserine, Floxuridine

C. Purine analogues:

Eg.: Mercaptopurine, Thioguanine, Fludarabine, cladribine, Pentostatine

3. Natural Products:

A. Plant Products

- Vinca Alkaloids: Vincristine, Vinblastine, Vindesine, Navelbine.
- Taxanes: Paclitaxel, Docetaxel
- Epipodophyllotoxins: Etoposide
- Camptothecins: Irinotecan

B. Microorganism Products

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- Antibiotics: Doxorubicin, Doxorubicin, Bleomycin, Mithramycin, Mitomycine, Actinomycin-D,
- Enzymes: L-Asparaginase, Crisantapase

4. Hormones:

- Esrogens: Diethylstilbestrol, Ethinyl estradiol
- Progestins: Hydroxyprogesterone, Medroxyprogesterone acetate, Megestrol
- Androgens: Testosterone, propionate, Fluoxymesterone
- Antiestrogens: Tamoxifen
- Antiandrogens: Flutamide, Cyproterone

5. Radiosotopes:

Eg.: Radioiodine, Radiogold, Radiophosphorous

6. Miscellaneous:

Eg.: Cisplatin, Hydroxyurea, Procarbazine, Interferon etc

CLASSIFICATION OF ANTICANCER DRUGS ACCORDING TO CELL CYCLE:

1. Cell cycle non Specific:

- Kills resting as well as dividing cells.

Eg.: Nitrogen Mustard, Cyclophosphamide, Chlorambucil, Carmustine, Dacarbazine, Actinomycin D

2. Cell Cycle Specific:

- Kill only actively dividing cells

G₁: Vinblastin

S: Mtx, Cytarabine, 6-TG, 6-MP, Hydroxyurea, Mitomycin C, Doxorubicin, Daunorubicin.

G₂: Daunorubicin, Bleomycin, Etoposide, Topotacan.

M: Vincristine, Vinblastin, paclitaxel.

ALKYLATING AGENTS:

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One of the frightening developments of World War I was the introduction of chemical warfare. These compounds were known as the nitrogen mustard gases. The nitrogen mustards were observed to inhibit cell growth, especially of bone marrow. Shortly after the war, these compounds were investigated and shown to inhibit the growth of cancer cells.

Mechanism of Action:

- These drugs work by alkylation with nucleophilic substitution. They alkylate a variety of cellular constituents, such as cell membranes, proteins, and most importantly **DNA**. More specifically, the nitrogenous bases of DNA are what get alkylated.
- The drugs start off as pro-drugs that become activated when a chlorine atom is extracted. A **carbonium ion** is thus formed. This “carbonium ion” is very electrophilic and will then attack any free pair of electrons (i.e. on the N7 of guanine). This electrophilic attack results in a bond being formed between the drug and the guanine of DNA. As a result of this “alkylation”, there are a few consequences:

1) **Miscoding (In transcription)**

2) **Cross linking** - This only occurs if the drug is bifunctional

- The net result is cancer cell undergo apoptosis.

1. Nitrogen Mustards:

- E.G.: Mechlorethamine, cyclophosphamid, melphalan & chlorambucil

A. Mechlorethamine

- First alkylating agent employed clinically
- Bifunctional, thus can crosslink DNA
- Extremely unstable and is inactivated within a few minutes following administration.
- Thus it is given IV.

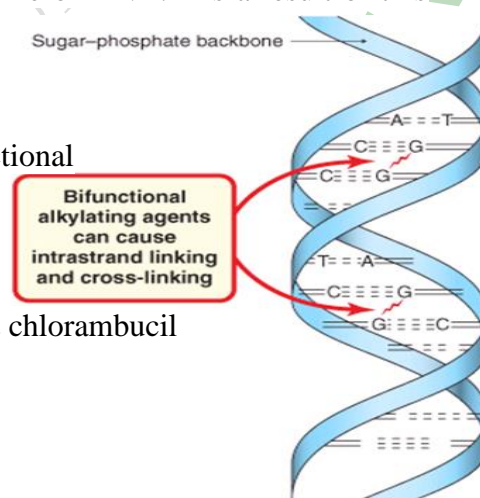
Clinical Uses

- Hodgkin’s Disease
- Non-Hodgkin’s Lymphoma

Toxicity/ Side Effects

- Dose limiting toxicity is bone marrow depression
- Nausea/ Vomiting
- Alopecia
- Diarrhea
- Sterility

B. Cyclophosphamid



3. ANTINEOPLASTIC – ANTICANCER DRUGS

- It acts as cytotoxic and immunosuppressor agent.
- Prodrug which must be activated by the cytochrome p450 system, which turns it into nitrogen mustard.
- Bifunctional agent
- Most widely used alkylating agent

Clinical Uses

- Hodgkin's Disease
- Non-Hodgkin's lymphoma
- Solid tumors of head, neck, ovaries, and breast
- Frequently used in combination with methotrexate (anti-metabolite) or doxorubicin (anti-tumor antibiotic), or fluorouracil as adjuvant therapy post breast cancer surgery
- Organ transplant recipients (due to immunosuppressive actions)

Toxicity/ Side Effects

- Bone marrow depression
- Severe nausea and vomiting
- Acute hemorrhagic cystitis and renal damage
- Sterility
- Hypersensitivity reactions

2. Nitrosoureas

E.G.: Carmustine, Lomustine

- Bifunctional molecules active against broad spectrum of neoplastic disease
- Inhibits synthesis of both DNA and RNA, as well as proteins
- These drugs are highly lipophilic, so they can easily cross blood-brain-barrier, and are great for CNS tumors.
- Big problem in this class is that they are highly mutagenic and highly carcinogenic.
- Major toxicity is delayed bone marrow depression & pulmonary fibrosis.

Clinical uses

- Primary and metastasis tumors of the brain
- Hodgkin's Disease and Non-Hodgkin's lymphoma
- Adenocarcinoma of stomach, colon, and rectal cancer
- Hepatocarcinoma

3. Alkyl Sulfonates

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Eg.: Busulfan

Clinical uses:

- Great effect on for Chronic granulocytic Leukemia

Toxicity/ Side Effects:

- Dose limiting toxicity is bone marrow depression.
- Pulmonary infiltrates and pulmonary fibrosis
- Tonic-clonic seizures in epileptics
- Nausea and vomiting
- Alopecia
- Sterility
- Skin hyper pigmentation
- Cataracts
- Hepatitis

ANTIMETABOLITES:

- An antimetabolite is a chemical with a similar structure to a metabolite required for normal biochemical reactions, yet different enough to interfere with the normal functions of cells, including cell division.
- All antimetabolites are used in cancer treatment, as they interfere with DNA production and therefore cell division and the growth of tumors (mainly in S-phase specific).

Mechanism of action:

- Purin and pyrimidine antagonists are phosphorelated inside the body into nucleotid form in order to be cytotoxic

1. Folic acid analogues:

Eg.: Methotrexate:

Mechanism of action:

- A folic acid analogue prevents the formation of tetrahydrofolate, essential for purine and pyrimidine synthesis, by inhibiting dihydrofolate reductase. This leads to inhibition of production of DNA, RNA and proteins (as tetrahydrofolate is also involved in the synthesis of amino acids as serine and methionine).
- It is actively taken up into the cells by the same transport system for folate.
- The most common toxicity is nephrotoxicity.

2. Purine analogues

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Eg.: 6-mercaptopurine or 6-MP

Mechanism of action:

- It is immunosuppressive cytotoxic substance. It is widely used in transplantations to control rejection reactions.
- It acts as a purine analogue and once enters the cell, it is converted to 6-MP-ribosephosphate and can be incorporated into RNA & DNA resulting in non functioning RNA & DNA & finally inducing cell cycle arrest and apoptosis.
- It also inhibits purring ring biosynthesis

Adverse reactions:

- Diarrhea, nausea, vomiting, loss of appetite,
- Allergic reaction include rash, itching, swelling, dizziness, trouble breathing.
- Mercaptopurine causes myelosuppression. Those taking mercaptopurine should get permission from a doctor in order to receive immunizations and vaccinations.

Azathioprine:

- It is one of the main immunosuppressive cytotoxic substance.
- It is widely used in transplantations to control rejection reactions.
- It is nonenzymatically cleaved to 6 - MP that acts as a purine analogue and inhibits DNA synthesis

3. Pyrimidine analogues:

Eg.: 5-fluorouracil (5-FU)

Mechanism of action:

- It act as a uracil analogue, it is transformed inside the cell into 5-FU deoxynucleotide which compete with deoxyuridine monophosphate (DUMP) for thymidylate synthase leading to inhibition of deoxythymidine monophosphate (DTMP) synthesis inhibition of DNA synthesis (Not RNA or protein)
- Also it is incorporated into DNA non functioning DNA.
- Finally inducing cell cycle arrest and apoptosis by inhibiting the cell's ability to synthesize DNA.
- It is an S-phase specific drug
- 5-FU may be used in combination with other chemotherapy agents to treat cancers of the breast, stomach, colon, rectum, and pancreas.

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Side effect:

- Most unwanted effect is GIT epithelial damage, diarrhea and mouth ulcers.
- The most dangerous side effect is bone marrow suppression

Cytarabine

- It is analogue to 2-deoxycytidine and in the body it is converted into cytosine triphosphate and inhibit DNA polymerase thus inhibiting DNA synthesis.

NATURAL PRODUCTS:

A. Plant Products:

I. Vinca Alkaloids: Vincristine, Vinblastine, Vindesine, Navelbine.

Mechanism of action

- Act on M – Phase.
- Tubulin is a structural protein which polymerises to form microtubules.
- The cell cytoskeleton and mitotic spindle, amongst other things, are made of microtubules.
- Vincristine binds to tubulin inhibiting polymerization of microtubule structures.
- Disruption of the microtubules arrests mitosis in metaphase.
- The vinca alkaloids therefore affect all rapidly dividing cell types including cancer cells, but also intestinal epithelium and bone marrow.

Side effects:

- The main side-effects of vincristine are peripheral neuropathy.
- Accidental injection of vinca alkaloids into the spinal canal (intrathecal administration) is highly dangerous, with a mortality rate approaching 100%.
- Vinblastin is less neurotoxic.

Uses

- Non Hodgkin's & Hodgkin's disease, malignant lymphomas and leukemia.

II. Taxanes: Paclitaxel, Docetaxel

- It is used for treatment of lung, ovarian and breast cancer.

Mechanism of action

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- Paclitaxel hyper-stabilizes microtubule structure (freezes them). Paclitaxel binds to the β subunit of tubulin, the resulting microtubule/paclitaxel complex does not have the ability to disassemble. This adversely affects cell function because the shortening and lengthening of microtubules is necessary for their function.
- Further research has indicated that paclitaxel induces programmed cell death (apoptosis) in cancer cells by binding to an apoptosis stopping protein called Bcl-2 (B-cell leukemia 2) and thus arresting its function.

Side effects

- Bone marrow suppression and neurotoxicity

III. Epipodophyllotoxins: Etoposide

- Chemically it is derived from podophyllotoxin, a toxin found in the mandrake root.

Mechanism of action:

- An inhibitor of the enzyme topoisomerase II. It causes breaks in the DNA inside the cancer cells and prevents them from further dividing and multiplying. Then the cells die.

Side effect:

- Vomiting & alopecia
- Bone marrow suppression

Uses:

- It has been useful for treatment of testicular cancer and small cell lung cancer.

B. Microorganism Products

I. Antibiotics:

a. Dactinomycin

- It is isolated from soil bacteria of the genus *Streptomyces*.
- It was the first antibiotic shown to have anti-cancer activity and used in treatment of a variety of cancers.
- It inhibits transcription by binding to DNA at the transcription initiation complex and preventing elongation by RNA polymerase.
- As it can bind DNA duplexes, it can also interfere with DNA replication

b. Adriamycin

Mechanism of action

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- Doxorubicin is anthracyclin antibiotic interferes with the cells' production of DNA and RNA by inserting itself between adjacent base pair causing local uncoiling thus blocking DNA and RNA synthesis.
- Also its antitumor effect is related to its inhibition of topoisomerase II enzyme (responsipole for DNA repair).
- CYT P450 catalyzes the conversion of Dox. into semiquinone free radicals which produce superoxide ion & H₂O₂ that mediate single strand scission in DNA

Uses

- Multiple cancers including breast, bone, ovarian & leukemia.
- Acute lymphocytic leukemia (ALL).
- Non-Hodgkin's lymphoma

Side effects

- A major problem with the use of doxorubicin is that it causes irreversible heart problems specially heart failure.
- Hypersensitivity, myelosuppression
- Nausea, vomiting & diarrhea
- Urine and tears may take on a red color.

c. Mitomycin-C

- Mitomycin-C is an antitumor antibiotic. Mechanistically however, it belongs to DNA alkylating agents.
- Upon bioactivation inside the cell, it preferentially alkylates O₆ of guanine base in DNA leading to cross linking of DNA.
- It also degrades DNA through formation of free radicals.

Side effects

- Mitomycin-C may cause bone marrow suppression.
- Lung fibrosis may occur. If these lung problems do occur, corticosteroids may provide effective therapy. Stopping mitomycin-C therapy may also be recommended.

d. Bleomycin

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- It is cytotoxic in any phase of the cycle even on G₀ phase
- Bleomycin degrades performed DNA causing chain fragmentation and release of free bases through the formation of free radicals (superoxide and hydroxyl radicals).

Uses

- Bleomycin is used in the treatment of a number of different cancers, including cancer of the head and neck, skin, esophagus, lung, testis, and genitourinary tract.
- In addition, it is used in the treatment of Hodgkin's disease and non-Hodgkin's lymphomas.

Side effects

- Pulmonary fibrosis
- Raynaud's phenomenon (which affects the fingers and toes, may involve pain, pale color, and abnormal sensation as burning)
- In addition, headache, and nausea and vomiting may occur.

e. Procarbazine

- Procarbazine is an anticancer agent inhibits DNA and RNA synthesis in cells
- Interfering with mitosis.

Uses

- Procarbazine is used in the treatment of various cancers, although the best established usage is with Hodgkin's disease.
- Other cancers in which procarbazine is sometimes used include lymphomas, brain tumors, skin cancer, lung cancer, and multiple myeloma.

Side effects

- It decreases the white blood cells and the platelet cells.
- The most severe side effect is nausea and vomiting.
- There may be neurological side effects such as confusion, sleepiness, depression, nightmares, agitation, and nervousness.

II. Enzymes: L-Asparaginase, Crisantapase

- It is a preparation of asparaginase which kills cancer cells by breaking down certain protein (L-asparagine) that is necessary for survival and growth of certain tumors incapable of forming such protein e.g. Acute Lymphoblastic Leukemia (ALL).

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- Fortunately, normal cells are not dependent on L-asparagine for survival.
- Asparaginase is mainly given in combination with vincristine and steroids (either prednisone or dexamethasone).

HORMONES:

1. Corticosteroids:

- Corticosteroids have broad use in cancer treatment. Some are used to treat adult leukemias, adult lymphomas, and acute childhood leukemia.

Immunosuppressive mechanism:

- Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines interleukin and TNF- γ , the most important of which is the IL-2. The inhibition of cytokine production reduces the T cell proliferation.
- Glucocorticoids also suppress the expansion and antibody synthesis.

Side effects

- Hyperglycemia due to increased gluconeogenesis, insulin resistance caution in those with diabetes mellitus
- Reduced bone density (osteoporosis, higher fracture risk, slower fracture repair)
- Weight gain due to increased visceral and truncal fat deposition (central obesity) and appetite stimulation
- Adrenal insufficiency (if used for long time and stopped suddenly without a taper)
- Muscle breakdown (proteolysis), weakness; reduced muscle mass and repair
- Growth failure, pubertal delay
- Increased urea formation; negative nitrogen balance

The most common corticosteroids used in cancer treatment are:

- Dexamethasone (Decadron)
- Hydrocortisone
- Methylprednisolone (Medrol)

2. Estrogens & Progestons:

- Mainly used in androgen dependent prostatic tumors

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3. Gonadotropin–releasing hormone analogues

Eg. Goserelin Acetate:

- Goserelin acetate is a synthetic hormone that acts similarly to the naturally occurring gonadotropin – releasing hormone (GnRH).
- In men, this results in decreased blood levels of the male hormone testosterone. In women, it decreases blood levels of the female hormone estrogen.

Use:

- It is used for treatment of breast and prostatic cancer

Side effects

- Sweating, hot flashes, impotence (erectile dysfunction), sterility & gyncomestia.
- Depression or other mood changes
- Other common side effects in women include: light, irregular, vaginal bleeding & no menstrual period

4. Hormone antagonists:

Eg. Tamoxifen

- Tamoxifen selectively inhibits the effects of estrogen on breast tissue, while selectively mimicking the effects of estrogen on bone (by increasing bone mineral density) and uterine tissues. These qualities make tamoxifen an excellent therapeutic agent against breast cancer. It is known to compete with estrogen by binding to estrogen receptors on the membrane of target cells, thus limiting the effects of estrogen on breast tissue.
- Tamoxifen may also has other anti–tumor activities: affecting oncogene expression & promotion of apoptosis (cancer cell death)

Adverse Effects

- CNS: Depression, light headedness, dizziness, headache, decreased visual acuity &retinopathy
- GI: Nausea, vomiting
- Hematological: Hypercalcemia
- GU: Vaginal bleeding, vaginal discharge & menstrual irregularities
- Dermatologic: Hot flashes, skin rash