ANTI-CANCER AGENTS

Prepared By

Doppalapudi Sandeep

M. Pharmacy,

Assistant Professor

Department of Physiology & Pharmacology

Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chandramoulipuram, Chowdavaram, Guntur, Andhra Pradesh, India – 522019

ANTI CANCER AGENTS

- Cancer – uncontrolled proliferation of cells.
- Anticancer drugs either kill cancer cells or modify their growth.
- Ability of cancer cells to distant sites in the body and to colonize in various organs is called as “Metastasis”.
- Current therapy mainly uses
  - Surgery
  - Irradiation
  - Chemotherapy

ANTI CANCER AGENTS

- Drugs acting on cells (Cytotoxic)
- 1. Alkylating agents

  - ❖ Nitrogen mustards – Mechlorethamine, Cyclophosphamide
  - ❖ Ethylenimine - Chlorambucil, Melphalan
  - ❖ Alkyl sulfonate - Busulfan
  - ❖ Nitrosoureas - Carmustine, Lomustine
  - ❖ Triazines - Dacarbazine

- 2. Antimetabolites

  - ❖ Folate antagonist – Methotrexate
  - ❖ Purine antagonist - 6-Mercaptopurine, Azathioprine
  - ❖ Pyrimidine antagonist - 5-fluorouracil, Cytarabine

ANTI CANCER AGENTS

- 3. Vinca alkaloids – Vincristine, Vinblastine
- 4. Taxanes – Paclitaxel, Docetaxel
- 5. Epipodophyllotoxin – Etoposide
- 6. Camptothecin analogues – Topotecan, Irinotecan
- 7. Antibiotics – Actinomycin-D, Doxorubicin, Mitomycin
- 8. Miscellaneous – Procarbazine, Cisplatin,

  L-asparginase (enzyme)
- 9. Radio-isotopes – I^{131}, P^{32}, Au^{198}

ANTI CANCER AGENTS

Drugs altering hormonal balance

- 1. Glucocorticoids – Prednisolone
- 2. Estrogens – Ethinylestradiol, Fosfestrol
- 3. Antiestrogen – Tamoxifen
- 4. Antiandrogen – Flutamide
- 5. 5-alpha reductase inhibitor – Finasteride
- 6. GnRH analogues - Goserelin

ANTI CANCER AGENTS

- **Cell cycle Non-Specific:** (Kills both resting and dividing cells)
- **Eg:** Nitrogen mustrads, Cyclophosphamide, Chlorambucil, Carmustine, Dacarbazine, 5-FU, L-Asparaginase, Cisplatin, Actinomycin-D.
- **Cell cycle specificty:** (Kills only dividing cells)

G1 PHASE	**Prednisolone, Asparaginase**
S PHASE	**Methotrexate, Cytarabine, 6-MP, Doxorubicin**
G2 PHASE	**Daunorubicin, Bleomycin, Etoposide, Topotecan**
M PHASE	**Vincristine, Vinblastine, Cisplatin**

ALKYLATING AGENTS

Produces highly reactive carbonium ion intermediates

transfers

alkyl groups to macromolecules

forms covalent bonds

Results in

Cross linking/ Abnormal base pairing/ Scission of DNA strand

- Have cytotoxic and radiomimetic actions.
- Acts on dividing as well as resting cells.
- Some have CNS stimulant and cholinergic properties.

- **Mechlorethamine (Mustine):**
- First nitrogen mustard. Highly reactive.
- Given only by I.V. route.
- Produces nausea, vomiting and haemodynamic changes.
- **DOSE:** 0.1 mg/Kg I.V daily for 4 days.
- **Cyclophosphamide:**
- Inactive as such. Wide range of action.
- Transformation to active metabolites (aldophosphamide, phosphoramide mustard) occurs in liver.
- Has immunosuppressant property.
- **ADR:** less damaging to platelets.
- Casues alopecia, cystitis.
- Chloramphenicol retards the metabolism.
- **DOSE:** 2-3 mg/Kg/day oral; 10-15 mg/Kg I.V every 7-10 days

- **Chlorambucil:**
- Very slow acting. Specially active on lymphoid tissue.
- Drug of choice for long term maintenance therapy for chronic lymphatic leukemia, Hodgkins disease and some solid tumors.
- Medium immunosuppressant property.
- **DOSE:** 4-10 mg daily for 3-6 weeks.Then 2mg daily (maintenance)
- **Melphalan:**
- Very effective in multiple myeloma.
- Used in advanced ovarian cancer.
- **ADR:** Causes Bone marrow depression
- Infections, diarrhoea and pancreatitis.
- **DOSE:** 10 mg daily for 7 days or 6 mg/day for 2-3 weeks. then 4 weeks gap. then 2-4 mg daily maintenance dose orally.

- **Thio-TEPA:**
- Ethylenimine derivative.
- Doesnt require any formation of active compound.
- Highly TOXIC. Rarely uesd.
- **DOSE:** 0.3-0.4mg/Kg I.V at 1-4 weeks intervals.
- **Busulphan:**
- Very effective in myeloma.
- Effective on granulocytes, followed by platelets and RBC.
- **ADR:** Hyperuricemia.
- Pulmonary necrosis, Sterility
- Drug of choice for Chronic myeloid leukaemia.
- **DOSE:** 2-6 mg/day orally.

- **Nitrosoureas:**
- Highly lipid soluble with wide range of anti-tumor action.
- Crosses BBB. Effective in meningeal leukaemias and brain tumor.
- **ADR:** Nausea, vomiting, bone marrow depression, renal damage.
- **DOSE: LOMUSTINE-** 100-130 mg/m^2 BSA single oral dose every 6 weeks.
- **Dacarbazine:**
- Different MOA.
- Primary inhibitory action on RNA and protein synthesis.
- Activated in liver. Used in malignant melanoma.
- **ADR:** Nausea, vomiting.
- **DOSE:** 3.25 mg/kg/day I.V for 10 days. repeat after 4 weeks.

- **ANTIMETABOLITES:**
- Analogues related to normal components of DNA or co-enzymes involved in nucleic acid synthesis.
- Competetively inhibits utilization of normal substrate or gets them incorporated, leading to formation of dysfunctional macromolecules.
- **Methotrexate: (FOLATE ANTAGONIST)**
- Oldest and highly efficacious.

- Dihydro folic acid **DHF REDUCTASE** Tetra hydro folic acid
- This leads to inhibition of denovo purine synthesis.
- Cell cycle specific - Kills cells in S phase.
- Also affects RNA and protein synthesis.

- **ADR:**
- Bone marrow depression.
- megaloblastic anemia, pancytopenia, desquamation, GI bleeding.
- **KINETICS:**
- absorbed orally. 50% plasma bound. little metabolized. excreted mostly in unchanged form in urine.
- Toxicity can be overcome by giving folic acid.
- **DOSE:** 15-30 mg/day for 5 days orally.
- **Purine antagonists:**
- Highly effective. Converted in body to respective mononucleotides.
- INHIBITS conversion of IMP to adenine and guanine. (denovo)
- **USES:** In childhood acute leukaemia, solid tumors.
- **Azathioprine:** Effect on T-lymphocytes. Suppresses cell mediated immunity. dose should be reduced if given with allopurinol.

- BM inhibition, revrsible jaundice, vomitings, hyperuricemia.
- **DOSES:**
- Azathioprine - 3-5 mg/kg/day. maintenance 1-2 mg/kg/day.
- 6-Mercaptopurine - 2.5 mg/kg/day. half dose maintenance.
- **PYRIMIDINE ANTAGONIST: 5-FU:**
- Converted to 5-fluoro deoxy uridine mono phosphate which inhibits thymidilate synthetase and blocks the conversion of deoxyuridilic acid to deoxythymidilic acid.
- Selective failure of DNA synthesis due to non-availability of thymidilate.
- 5-FU deposits itself in Nucleic acid.
- Resting cells are also effected.
- **DOSE:** 1g orally on alternative days.
- Used for breast, colon, urinary bladder, liver cancer.

- **Cytarabine:** Inhibitor of DNA polymerase. Incorporation into DNA. Causes toxicity. Also interferes with DNA repair.
- Acts on S phase of cell cycle. Used mainly in leukaemia in children. Bonemarrow and GI toxicity.
- **VINCA ALKALOIDS:** Mitotic inhibitors.
- Binds to TUBULIN and prevents its polymerization and assembly of microtubules.
- Causes disruption of mitotic spindle. Chromosomes fail to move apart. Metaphase arrest occurs.
- Mainle affects mitosis.
- **Vincristine:** Rapidly acting. Used in chidren-leukamia. Lung cancer and other types of cancers.
- Peripheral neuropathy, alopecia. Low bone marrow depression.
- **DOSE:** 1.5-2 mg/m^2 BSA I.V. Weekly. **(ONCOVIN)**

- **Vinblastine:** Used with other drugs in testicular cancer.
- Low Peripheral neuropathy,alopecia.High bone marrow depression.
- **Dose:** 0.1-0.15 mg/kg I.V weekly for 3 weeks.
- **TAXANES: paclitaxel**
- Obtained from bark of western yew tree.
- Enhances TUBULIN polymerization and Stabilizes microtubules.
- Prevents depolymerization. Causes abnormal bundle formation.
- Used in breast and ovarian cancers. In head, neck, lung, oesophageal and prostate cancers.
- **DOSE:** 175 mg/m^2 BSA IV for 3 hours. repeated every 3 weeks.
- **EPIPODOPHYLLOTOXINS: ETOPOSIDE**
- Semisynthetic derivative of podophyllotoxin.
- Arrests cells in G2 phase and causes DNA breaks by affecting DNA topoisomerase-II function.

- Resealing of cleaved double strand DNA is prevented.
- Used in testicular and lung cancers.
- ADR: alopecia, leucopenia and GI disturbances.
- **DOSE: 50**-100 mg/m^2 BSA/ day I.V. or oral for 5 days.
- **CAMPTOTHECIN ANALOGUES:**
- Semisynthetic analogues of camptothecin. (Chinese tree)
- Similar action of etoposide, but acts on enzyme DNA topoisomease-I. Resealing of cleaved double strand DNA is prevented. Arrests cells in G2 phase.
- **Irinotecan:** Prodrug. inhibits AchE.
- Used in colorectal, lung, cervix and ovary cancers.
- **ADR:** Thrombocytopenia, haemorrhage, body pains.
- **DOSE:** 125 mg/m^2 BSA I.V. over 90 mins. then weekly for 4 weeks.

- **ANTIBIOTICS: ACTINOMYCIN-D:**
- Intercalates with DNA strands and interferes with its template function.
- Potent and highly efficacious in rhabdomyosarcoma.
- Vomiting, stomatitis, erythma, alopecia, BM depression.
- **Dose:** 15 µg/kg I.V daily for 5 days.
- **MISCELLANEOUS:**
- **Cisplatin:** Platinum complex which hydrolyzes intracellularly to produce highly reactive moiety which causes cross linking of DNA.
- Reacts with -SH groups in proteins. Has radiomimetic property.
- Bound to plasma proteins, enters tissues and slowly excreted unchanged in urine. very less entry into brain.
- Effective in testicular and ovarian cancers.
- **ADR:** Highly emetic. Renal impairment, tinnitus, deafness.
- **DOSE:** 50-100 mg/m^2 BSA I.V. every 3-4 weeks.

- **HORMONES:**
- They are not cytotoxic. But modifies the growth of hormone dependent tumors. All hormones are only palliative (gives Relief in serious cases).
- **Antiestrogen: TAMOXIFEN**
- Effective and 1st line drug in breast cancer. Response is better in old age women.
- **Glucocorticoids:** Lympholytic action. Treats childhood leukaemia. Controls complications like hyperuricemia, haemolysis, bleeding.
- **Antiandrogen: Flutamide**
- Treats prostate carcinoma. Increases androgenn levels.
- **5-α Reductase inhibitor: Finasteride**
- Inhibits conversion of testosterone to dihydrotestosterone in prostate.
- **Progestins:** Needs high dose.
- Temporary remission after surgery/radiotherapy and endometrial carcinoma. Used in breast cancer if tamoxifen not works.