

Anti Cancer Drugs

By - Dr. Shikha Sharma (NEETPG Squad, FitDocMed)

- **NEETPG**
- **INICET**
- **FMGE**

Join FitDocMed Courses at
www.fitdocmed.com

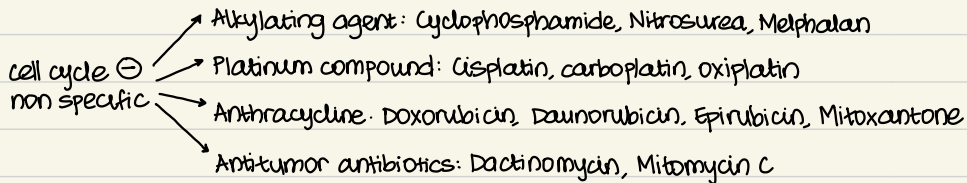
Cell cycle effects of anticancers

G₁ - Etoposide

S - Antimetabolites: Methotrexate, 6MP, 5FU, cladribine, capecitabine

G₂ - Topoisomerase $\ominus$: Irinotecan, Topotecan, Etoposide & Bleomycin.

M - Vinca alkaloids: Vincristine, vinblastine, vinorelbine. Taxanes: Paclitaxel, Docetaxel, Cabazitaxel. Eribulin, Estramustine, Ixabepilone.



Alkylating Agents

cell cycle non specific - Alkylate nucleophilic groups on DNA bases [N7 of guanine] $\rightarrow$ causing crosslinking + abnormal base pairing & DNA strand breakage.

MC ADRs - GI distress, bone marrow suppression, alopecia, 2^o leukemias & sterility.

Nitrogen Mustards Cyclophosphamide - Hepatic biotransformation. Degradation product acrolein $\rightarrow$ Hemorrhagic cystitis. $\downarrow$ by vigorous hydration & mesna. Also causes cardiac dysfunction, pulmonary toxicity & SIADH. DOC $\rightarrow$ Wegeners granulomatosis.

Ifosfamide - Acrolein & chloroacetaldehyde $\rightarrow$ Hemorrhagic cystitis $\uparrow$ & nephrotoxicity. $\uparrow$ R/O neurotoxicity also.

Mechlorethamine - Hodgkins disease. Powerful vesicant.

Melphalan - Multiple myeloma.

Nitrosureas carmustine, lomustine, semustine $\rightarrow$ lipid soluble cross BBB, thus used for brain tumors like gliomas $\oplus$ Delayed sustained neutropenia

Dacarbazine - 1^o action on RNA & protein synthesis.

Streptozocine - Destroys β cell of pancreas. Used for islet cell tumors. Minimum bone marrow toxicity.

Busulfan - Adrenal insufficiency, pulmonary fibrosis [sinusoidal obstruction syndrome], skin hyperpigmentation & hyperuricemia.

Procarbazine - Most leukemogenic, disulfiram like reaction $\bar{c}$ alcohol, hypnosis, dreams.

Chlorambucil - Sparing myelocytes, used for CLL.

Platinum compounds

Cisplatin, carboplatin, oxaplatin $\rightarrow$ use platinum to cross link DNA $\rightarrow$ dimers & breakage.

Nausea & vomiting maximum compared to all anticancer drugs

Nephrotoxicity, Ototoxicity & neurotoxicity. Maximum nephrotoxicity $\rightarrow$ cisplatin & maximum hematotoxicity / BM suppression $\rightarrow$ carboplatin.

Oxaliplatin effective against drugs resistant to cisplatin / carboplatin $\uparrow\uparrow$ Neurotoxicity

Chloride diuresis prior to cisplatin therapy $\rightarrow$ $\downarrow$ Renal toxicity, no effect on ototoxicity.

Slow IV infusion Inactivated by aluminium thus not used simultaneously.

Amifostine - $\downarrow$ cisplatin induced nephrotoxicity & xerostomia.

$\downarrow$ all serum ions $\rightarrow$ Hypermagnesemia, hypokalemia, hypocalcemia, hypophosphatemia

A/w development of AML $\bar{c}$ >4 yrs of treatment.

Anti metabolites

Sphase action $\rightarrow$ $\ominus$ dividing cells. Immunosuppressive properties also.

Folic acid analogues Methotrexate, pemetrexed, pralatrexate $\rightarrow$ $\ominus$ dihydrofolate reductase [DHFRase] & thymidylate synthase.

Methotrexate - sequestered in 3rd space $\rightarrow$ prolonged immunosuppression. Vigorously hydrate to $\ominus$ renal crystallisation

ADRs $\rightarrow$ Bone marrow suppression & mucositis. $\downarrow$ Toxicity to normal cells $\rightarrow$ coadminister leukovorin, folinic acid, citrovorum factor. [Leukovorin rescue]. Doesn't $\ominus$ neurotoxicity Alkalinisation of urine also $\downarrow$ toxicity.

Glucarpidase $\rightarrow$ MTX clearing enzyme. $\uparrow$ Toxicity $\bar{c}$ NSAIDs $\bar{c}$ $\downarrow$ renal excretion

Long term use $\rightarrow$ Hepatotoxicity, pulmonary infiltrates & fibrosis

Inhibit - Immunosuppressant

C - Crohn's disease

A - Abortions

N - Non Hodgkins lymphoma

C - choriocarcinoma [DOC]

E - Ectopic pregnancy

R - Rheumatoid arthritis & psoriasis

} Uses of methotrexate

Pemetrexed - Approved for mesothelioma treatment. Folic acid & vit. B12 ↓ toxicity w/o interfering w/ clinical actions

Pralatrexate - Peripheral T cell lymphoma.

Purine Analogs GMP & GTG → Activated by HGPRTase → ⊖ several enzymes in purine synthesis. Metabolised by xanthine oxidase → When given w/ allopurinol [xanthine oxidase ⊖] ↓ dose of GMP & azathioprine to 1/4th.

Treatment of acute & chronic leukemias.

Dose limiting bone marrow suppression & hepatotoxicity

Cladribine - Resistant to degradation by adenosine deaminase. DOC: Hairy cell leukemia

Fludarabine - DOC: CLL. Used along w/ pentostatin may cause severe pulmonary toxicity.

Immunosuppression on long term use → All patients are given cotrimoxazole prophylaxis for pneumocystis w/ purine analogs.

Pyrimidine Analogs Cytarabine - most effective for induction of remission in AML.

Activated by kinases → CTP arabinoside → ⊖ DNA polymerase

High dose → Neurotoxicity, cerebellar toxicity [ataxia, peripheral neuropathy]

5FU - converted to 5'dUMP → ⊖ TS. converted to CO₂ & eliminated via lungs. Oral prodrug →

capecitabine → Hyperbilirubinemia.

5FU/capecitabine → single strand breaks → ⊖ DNA & RNA

ADRS: Hand & foot syndrome [erythromelalgia $\bar{c}$ tingling, numbness, pain, erythema, swelling & $\uparrow$ pigmentation]. $\downarrow$ by uridine triacetate.

Gemcitabine - Potent radiosensitiser. DOC for pancreatic cancers.

5' Azacytidine - DNA hypomethylation. DOC myelodysplasia.

Mitotic spindle $\ominus$

Vinca Alkaloids vincristine, vinblastine & vinorelbine $\rightarrow \ominus$ polymerisation of microtubules thus $\ominus$ mitotic spindle formation. M phase specific.

Vinblastine - Metastatic testicular tumors. Bone marrow suppression & SIADH.

Vincristine - $\bar{c}$ glucocorticoids for remission of childhood leukemias [OC] Pediatric solid tumors [Wilms, neuroblastoma, rhabdomyosarcoma] & lymphomas. Marrow sparing but neurotoxic [peripheral neurotoxicity] & SIADH

Taxanes Paclitaxel, docetaxel $\rightarrow$ interfere $\bar{c}$ mitotic spindles $\rightarrow \ominus$ disassembly of the microtubules. Paclitaxel causes hypersensitivity reaction, $\downarrow$ by protein binding. Both cause bone marrow suppression & neurotoxicity.

Cabazitaxel $\rightarrow$ Microtubule $\ominus$ used $\bar{c}$ prednisone for hormone refractory metastatic prostate carcinoma.

Ixabepilone - Advanced breast cancer, given in combination $\bar{c}$ capecitabine. Binding to tubulin $\oplus$ microtubule stabilisation $\rightarrow$ arrest cell in G₂M.

Eribulin mesylate - Microtubule $\ominus$ for metastatic breast cancer & liposarcoma.

Estramustine - Estrogen + mechlorethamine used for prostatic cancer. Anti mitogenic drug by binding to tubulin. Estrogenic S/E $\rightarrow$ Gynecomastia & impotence.

Topoisomerase $\ominus$

Camptothecins - Irinotecan & topotecan $\rightarrow \ominus$ topoisomerase I [Nicks, introduces -ve supercoils & reseals DNA strand].

Topotecan - Advanced ovarian cancer. Dose limiting reu-nepenic

Irinotecan - Prodrug, converted in liver to active metabolite & eliminated in bile. ↓ dose in hepatic failure. DOC for advanced colorectal cancer $\approx$ 5FU. Dose limiting diarrhoea
Myelosuppression & cholinergic syndrome

Epipodophyllotoxins Etoposide & teniposide $\rightarrow$ $\ominus$ topoisomerase II $\rightarrow$ DNA strand breaks.
Act at late S & early G₂ phase. GI distress & myelosuppression.

Etoposide - Testicular, prostate & oat cell carcinoma of lung. Results in ALL within 1-3y.
Absent myelodysplastic period preceding AML. High dose hepatotoxic.

Antitumor Antibiotics

Anthracycline antibiotics $\rightarrow$ CCNS except bleomycin [G₂] $\ominus$ Topoisomerase II.

Doxorubicin, daunorubicin - acute leukemias

Idarubicin, epirubicin - solid tumors [Breast carcinoma, Ewings & soft tissue sarcoma]

Generate semiquinone free radicals $\rightarrow$ cardiotoxicity [dilated cardiomyopathy & heart failure].
↓ $\bar{\alpha}$ -tocopherol & dexrazoxane [free radical scavenger]. Dose dependent effect maybe present after stopping drug. Earliest morphological feature = Swelling of ER fib myofibrillar dropout.

Red coloured urine & radiation recall reaction [Erythema & desquamation of skin at sites of previous radiation exposure]

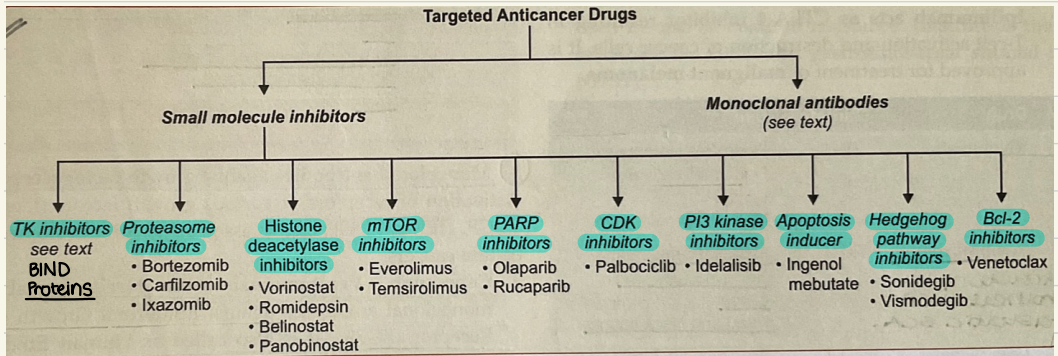
Mitoxantrone - ↓ cardiotoxic. AML, advanced hormone resistant prostate cancer & late stage, 2° progressive multiple sclerosis.

Valrubicin - Intravesicle therapy of BCG refractory urinary bladder carcinoma in situ.

Dactinomycin - $\ominus$ DNA dependent RNA synthesis. Used for solid tumors in children [Wilms tumor & rhabdomyosarcoma] & chorioc. Radiosensitizer.

Bleomycin - G₂ $\ominus$ DNA strand breaks & free radical formation. Cutaneous toxicity [ulcers, hyperpigmentation, hyperkeratosis, erythema]. Pulmonary fibrosis, hypersensitivity & mucocutaneous reaction. Earliest indicator of ADR $\rightarrow$ ↓ WBC. [Type 1 pneumocyte necrosis & type 2 pneumocyte hyperplasia].

Mitomycin - Alkylating agent. Intravesical therapy to treat superficial bladder cancers & anal carcinoma [w/ radiotherapy]. Can cause hemolytic uremic syndrome, delayed bronchospasm, tracheal / laryngeal stenosis.



Monoclonal Ab

Disinhibit T cell breaks - [Immune check point ⊖].

- Nivolumab - Hodgkins lymphoma, Non small cell lung CA, metastatic melanoma.
- PD1 ⊖ → Pembrolizumab - Metastatic melanoma, HNF cancers, urothelial cancers, colonic CA, Non small cell lung cancer
- Cemiplimab - SCC of skin.
- Avelumab - Merkel cell cancer
- PDL1 ⊖ → Durvalumab - urothelial cancers
- Atezolizumab - urothelial cancers, Non small cell lung cancer.
- CTLA4 ⊖ → Ipilimumab - Malignant melanoma.

Monoclonal Ab against CD Ag:

- | | |
|---|--|
| Blinatumomab - CD3/19. Philadelphia ⊖ ALL | Moxetumomab - CD22. Hairy cell leukemia |
| Ofatumomab - CD20. CLL | Brentuximab - CD30 HL, T cell lymphoma |
| Tositumomab - CD20. B cell lymphomas | Gemtuzumab - CD33. CD33 ⊕ AML |
| Ibritumomab - CD20. B cell lymphomas | Daratumumab - CD38. Multiple myeloma |
| Obintuzumab - CD20. B cell NHL, CLL | Alemtuzumab - CD22. CLL, hairy lymphoma |
| Inotuzumab - CD22. B cell ALL | Emapalumab - IFN-γ receptor 1. Lymphohistiocytosis |

Rituximab - CD20 monoclonal Ab

Re - Rheumatoid arthritis

L - lupus [systemic lupus erythematosus]

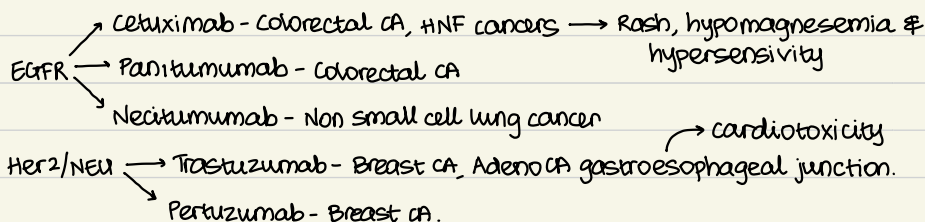
I - Immune thrombocytopenic purpura [ITP]

A - Autoimmune hemolytic anemia

N - Non Hodgkins lymphoma

Ce - CLL

Monoclonal Ab against growth factor receptors :



Ramucirumab - VEGFR2. Non small cell lung CA, gastroesophageal junction cancer.

Bevacizumab - VEGF. Colorectal CA, RCC, brain tumor, ovarian CA, non small cell lung CA

Olaratumab - PDGFR α . Soft tissue sarcoma. $\rightarrow$ HTN, thromboembolism, wound healing complication, GI perforation

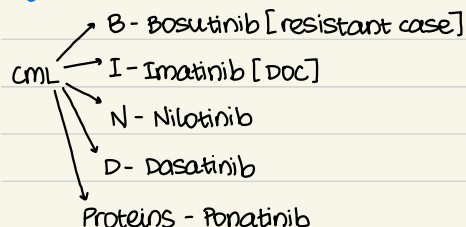
Denosumab - RANKL. Giant cell tumor of bone

Dinutuximab - Glycolipid GD2. Neuroblastoma.

Elotuzumab - SLAMF7. Multiple myeloma

Mogamulizumab - CCR4. Mycosis fungoides & Sezary syndrome.

Tyrosine kinase



RCC → P - Pazopanib
 → A - Axitinib
 → S - sorafenib
 → S - Sunitinib

malignant melanoma → C - Cotelmetinib
 → D - Dabrafenib
 → V - Vemurafenib
 → T - Trametinib

GIST → S - Sunitinib
 → I - Imatinib
 → R - Regorafenib

Proteasome ⊖

Bortezomib, carfilzomib, ixazomib → ⊖ proteasomes → Downregulate NFκB → ↓ cell survival. Used for resistant multiple myeloma.

Histone deacetylase ⊖

Vorinostat, Romidepsin → cutaneous T cell lymphoma

Panobinostat → Multiple myeloma

Belinostat → Relapsed / Refractory peripheral T cell lymphoma

mTOR ⊖

Everolimus, temsirolimus prodrugs → sirolimus → ⊖ mTOR.

Everolimus - breast, pancreatic, brain & renal cell carcinoma
 Temsirolimus - Advanced renal cell carcinoma

} Alw interstitial lung disease

PARP ⊖ Poly ADP ribose polymerase ⊖

Olaparib, rucaparib - Oral treatment of ovarian cancer

Niraparib - ovarian, fallopian tubes or 1° peritoneal cancers.

Talazoparib - Advanced breast cancers ± BRCA mutations

CDK ⊖ Palbociclib, abemaciclib, ribociclib → ⊖ CDK4/6. Post menopausal ER+, her2- breast cancer patients

PI3 kinase ⊖ Idelalisib - relapsing CLL, follicular B cell NHL & SLL.

Copanlisib - Follicular lymphoma → dual γ + δ ⊖

Duvelisib - CLL & follicular lymphoma

Hedgehog pathway ⊖ Sonidegib, vismodegib - Basal cell carcinoma.

Glasdegib - only hedgehog pathway ⊖ used for AML.

BCL2 ⊖ Venetoclax ⊖ BCL2 → ⊕ apoptosis. CLL.

IDH2 ⊖ Enasidenib, Ivosidenib → ⊖ Isocitrate dehydrogenase 2 → AML



FitDocMed

BY STUDENTS FOR STUDENTS

Join FitDocMed Courses at
www.fitdocmed.com