Cytotoxic Drugs

Classification	Subgroup	Drugs	Clinical use	Mechanism of action	Side effects	Special Note
DNA damaging	Alkylating agents	Cyclophosphamide	A prodrug. Hemato ca, solid organ. Wegener,ITP,GN,RA.	Interferes with DNA synthesis by cross-linking DNA strands causing strand breaks.	Myelosuppression Infertility Secondary malignancy (**AML)** Bladder toxicity with cyclo. Interstial pneumonitis and pulmonary fibrosis with long term busulfan.	Repeated dose of cyclophophamide results in induction of hepatic microsomal enzymes. Prevent cyclophosphamide induced bladder toxicity with hydration and MESNA **Acrolein** is a toxic metabolite responsible for bladder toxicity in cyclophosphamide.
		Chlorambucil	Hodgkin's lymphoma, CLL			
		Melphalan				
		Busulfan	CML			
		Dacarbazine	Malignant melanoma			
	Platinum compound	Cisplatin	Testicular cancer	Causes cross-links of DNA Intrastrand (70%) Interstrand (20%)	**Severe N+V with cisplatin.** Peripheral neuropathy with cumulative dose (**but not Carboplatin**) Nephrotoxicity (**but not carboplatin or oxaliplatin**) Myelosuppression main toxicity of carboplatin.	Cisplatin is 90% renally excreted Less nephro, neuro, emetogenic with carboplatin.
		Carboplatin Oxaliplatin	Lung, ovarian, head, neck Gastrointestinal ca			

					Peripheral neuropathy with oxaliplatin	
Anti-metabolite	Folic acid antagonist	Methotrexate Pemetrexed	Leukemia, breast, head, neck, lymphomas, bladder ca Mesothelioma Second therapy for advance NSCLS	Binds to Dihydrofolate reductase to prevent conversion of folic acid to folinic acid. Multi-targeted anti-folate.Inhibits DHFR and GARF.	Nephrotoxicity	Rescue therapy with folinic acid (Leucovorin) Vitamin B12 and folate supplement reduces toxicity
	Pyrimidine antagonist	5- Fluorouracil Capecitabine	Breast, CRC, UGI, head, neck,carcinoids.	Inhibits pyrimidine synthesis by blocking the enzyme thymidylate synthase	**Skin plantar–palmar dermatitis** 5-FU: Cardiac ischaemia secondary to coronary spasm. Acute neurological syndrome.	Biomodulation by Leucovorin. Radiation sensitiser
	Arabinoside	Cytosine Arabinoside Gemcitabine Fludarabine	AML Lung, breast, pancreas, bladder B-cell CLL	Inhibits DNA synthesis by inhibiting DNA polymerase.		
	Purine antagonist	6-mercaptopurine 6-thioguanine	Acute leukemia			
DNA Repair Inhibitors	Epipodophyllotoxins	Irinotecan Topotecan	Lung, colon, ovary, cervix Lung, colon, ovary, cervix	Inhibits Topoisomerase I Inhibits Topoisomerase I	**Diarrhea**-major dose limiting	Predominantly Hepatic metabolism.

		Etoposide		Inhibits Topoisomerase II	toxicity of irinotecan. Secondary malignancy (AML)	Gilbert syndrome increases risk of irinotecan toxicity.
	Cytotoxic antibiotics (Antracyclines)	Doxorubcin Epirubucin (less cardiotoxic) Bleomycin Mitoxantrone	Breast, bladder, lung, gynae, prostate, ovary, sarcomas, thyroid, lymphoma, leukemia.	Inhibit Topoisomerase II DNA repair Promote cleavage of DNA and RNA	**Cardiotoxicity- dose related.** Infertility Pulmonary toxicity Myelosuppression Extravasation	Overexpression of MDR 1gene encoding P-glycoprotein is responsible for chemo resistance Binding to heparin will reduce the half life of Doxorubicin. Radiosensitisation Use **Dexrazoxane** for anthracycline-induced extravasation
Anti-tubulin	Vinca Alkaloids	Vincristine Vinblastine Vinorelbine	Hematological ca Hematological ca Non-hematological ca	Inhibits microtubule formation by binding to tubulin	Neurotoxicity	Never give vincristine intrathecally as neurological damage is progressive and fatal.
	Taxanes	Paclitaxel Docetaxel	Ovarian, Breast, Lung.	Prevents microtubule formation by binding to tubulin dimers	Neurotoxicity Infertility Hypersensitivity reaction	Requires dose reduction in liver impairment.

Multidrug resistance:

- Most resistance occurs as a result of genetic mutation.
- Mediated by increased expression of **P-glycoprotein**, which mediates the **efflux of cytotoxic drugs** out of the cells.
- Other mechanism: upregulation of anti-apoptotic proteins Bcl-2 and Bax and DNA repair pathways.

What do they have in common?

Alopecia:

- 5- FU
- Anthracyline
- Irinotecan
- Paclitaxel-total alopecia

Vomiting:

- Cyclophosphamide
- Cisplatin-severe N+V
- Irinotecan

Myelosuppression:

- Anthracycline
- Cyclophosphamide
- Carboplatin
- Etoposide

Mucositis:

- 5-FU
- Anthracyline

Management of nausea and vomiting:

Step 1. Maxalon +Domperidone.
Step 2. Ondansetron + Dexamethasone.
Step 3. Aprepitant for prevention of acute and delayed N+V along with ondansetron and dex.

For persistent nausea:
cyclizine, haloperidol, levomepromazine, and BDZ