Alkylating AgentsCell (cycle nonspecific)

• Mechlorethamine• Cyclophosphamide• Chlorambucil• Ifosfamide • Carmusti• Lomustine• Busulfan

-Alkylation of DNA is the major interaction that leads to cell death.

• Miscoding through abnormal base-pairing with thymine.

• Depurination, by excision of guanine residues leading to DNA strand breakage.

• Cross-linking is of major importance to the cytotoxic action, and replicating cells are most susceptible.

Nitrogen Mustards			
Cyclophosphamide	Prodrug: must be converted by liver cytochrome P450	N&V, cardiotoxicity, hemorrhagic cystitis (from acrolein), "bladder burn", or hematuria - blood in urine, bone marrow toxicity	oral o Further conversion of aldophosphamide can take place: -acrolein -phosphoramide mustard hemorrhagic cystitis or hematuria (prevented by concurrent MESNA), Chlorumbucil and cyclophosphamide are used for the treatment of chronic lymphocytic leukemia and non-Hodgkin's lymphoma.
Ifosfamide	Activity is similar but greater than cyclophosphamide	++++neurotoxicity, nephrotoxicity, cardiac toxicity, N,V , BM toxicity	Given IV hemorrhagic cystitis or hematuria (prevented by concurrent MESNA),
Nitrosoureas	inhibits DNA, RNA and protein synthesis • lipid soluble (cross blood-brain barrier)—> that's why they are mostly used in the treatment of brain cancer, and they have limited use in other types of cancer.	delayed and cumulative bone marrow depression N&V pulmonary fibrosis renal damage, reversible liver damage and leukemia.	• **Carmustine** (BCNU) : IV infusion ove 1-2hrs • **Lomustine** (CCNU) : taken orally
Alkyl sulfonates		N&V, bone marrow depression (stem cells), pulmonary infiltrates and fibrosis.	**Busulfan** well absorbed orally plasma half-life 2-3hrs treatment of chronic myelogenous leukemia.
Nonclassic Alkylating Agents			
Procarbazine (PO) orally active and **Dacarbazine** (Parenteral) parenteral compound,	Inhibit DNA, RNA, and protein synthesis. Prolong interphase. Produce chromosome breaks, and DNA strand scission. Carcinogenic potential is higher than that of other alkylating agents.	•Carcinogenesis– acute leukemia. •Myelosuppression. •Nausea and vomiting can be severe. •Potent vesicants. Meaning that they tend to cause blistering or extravasation.	procarbazine crosses the BBB.

			•CNS toxicity: neuropathy, ataxia, lethargy, and confusion.	
Platinum complexes:		• Cisplatin, Carboplatin	•Nausea and vomiting •Myelosuppression •Peripheral neuropathy •Renal toxicity •Hepatic dysfunction	
Cisplatin		Covalent crosslinks with GG base pairs (bends DNA) -most (90%) bound to plasma proteins; concentrates in liver, kidney, intestine and ovary; excreted in urine.	N&V, diarrhea, hypersensitivity reactions (rashes), renal damage (reduced with hydration), ototoxicity with high **frequency hearing loss** and tinnitus, peripheral sensory neuropathy (paresthesia and loss of proprioception), bone marrow depression.	IV
Carboplatin		half-life of 120 mins vs cisplatin's 25-50 mins; less chemically reactive (less bound to plasma proteins), **less effective** than cisplatin (i.e. less toxic); excreted in urine.	carboplatin is toxic but **less** than cisplatin to the nervous system (neurotoxicity & ototoxicity) and the kidneys (nephrotoxic)**myelosuppression is dose-limiting**	IV
Antitumor Antibiotics		• They bind to DNA through intercalation between specific bases, and block DNA and RNA synthesis, cause DNA strand scission, and interfere with cell replication. • Most are products of various strains of the soil microbe **Streptomyces**		
Doxorubicin, Daunorubicin:		•Their cytotoxic action is due to: 1.Inhibition of topoisomerase II. 2.Intercalation to DNA with high affinity. 3.Generation of semiquinone **free radicals**, and oxygen free radicals through iron-dependent, enzyme-mediated reductive process. 4. Binding to cellular membranes altering fluidity and ion transport. • Metabolized extensively in the **liver**, with reduction and hydrolysis. • ~ 50% of the dose is excreted in bile, and dose reduction is needed in hepatic dysfunction.	-**Myelosuppression** with leukopenia more than thrombocytopenia. -Mild N&S ,Mucositis ,Alopecia -Acute and chronic cardiac toxicity: arrhythmias, ECG changes, conduction abnormalities, pericarditis ,myocarditis. **-red urine (not hematuria)** -severe local tissue damage with extravasation, -anaphylactoid reactions	iv • Free radicals are the cause of cardiotoxicity • Can be used as once every weeks • low dose weekly or 3-4 day continuous IV infusion with comparable results. **-Dexrazoxane to protect from cardiotoxicity and trea extravasation from IV doxorubicin**
Antimetabolites Cell cycle specific agents.		Methotrexate, Fluorouracil ,Capecitabine Cytarabine ,Mercaptopurine		
Methotrexate (MTX)		folic acid analog that inhibits dihydrofolate reductase, interfering with the synthesis of tetrahydrofolate •THF serves as the key one-carbon carrier in the synthesis of thymidylate, purine	•Mucositis, diarrhea •Myelosuppression (neutropenia and thrombocytopenia).	oral, intravenous, and intrathecal routes. Oral bioavailability is saturable and erratic at doses greater than 26 mg/m2

		nucleotides, and the amino acids serine and methionine.. •Thus, it interferes with the formation of DNA,RNA and key cellular proteins. • Intracellular formation of polyglutamate metabolites, with the addition of up to 5-7 glutamate residues, is critically important for the therapeutic action of MTX. • This process is catalyzed by folylpolyglutamate synthase. • MTX polyglutamates are selectively retained within cancer cells. This gives the specificity to cancer cells. • The biologic effects of MTX can be reversed by administration of the reduced folate leucovorin (5-formyltetrahydrofolate). • Leucovorin rescue is used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and in accidental overdose.		• Mainly eliminated by the kidney through glomerular filtration and activ tubular secretion, thus dose reduction is needed in renal dysfunction. • Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins. **Resistance develops due to:** **1. Decreased drug transport via the reduced folate carrier or folate receptor protein.** **2. Decreased formation of cytotoxic MTX polyglutamate.** **3. Increased levels of the target enzyme, dihydrofolate reductase, through gene amplification** **4. Altered DHFR protein with altered affinity for MTX.** **5. Activation of the multidrug resistance transporter P170 glycoprotein.**
Cytarabin (Ara-C):		• It competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby blocking DNA synthesis and DNA repair, respectively. • It is also incorporated into DNA (and RNA) which interferes with chain elongation and defective ligation of fragments of newly synthesized DNA.	• Myelosuppression (neutopenia and thrombocytopenia) • Mucositis, nausea and vomiting • Neurotoxicity (cerebellar ataxia).	•Given by IV infusion over 5-7 days. •It is an S phase specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP). •ara-CMP is further metabolized to the di- and tri-phosphate metabolites (ara-CTP). •ara-CTP may be the main cytotoxic metabolite.
Vinca alkaloids:				
Vincristine Vinblastine Vinorelbine		• binds to tubulin, inhibits tubulin polymerization into microtubules **(m phase)** which are a major component of the **mitotic spindle**		
(Vinblastine):		•It is an alkaloid derived from the periwinkle plant, Vinca rosea. •It inhibits tubulin polymerization, which disrupts assembly of **microtubules**, an **important part of the cytoskeleton and the mitotic spindle.** •This inhibition results in mitotic arrest in **metaphase**, resulting in cell death. • Dose reduction is needed in liver dysfunction.	• Nausea and vomiting, bone marrow suppression, mucositis, **Syndrome of inappropriate ADH secretion** (SIADH) and alopecia. • It is a **vesicant** (blusters) and care should be taken during administration. •⇑ uric acid	iv
(Vincristine):		•It is an alkaloid derived from the periwinkle plant, Vinca rosea. •Its mechanism of action, mechanism of resistance, and clinical pharmacology are	1.Peripheral sensoryneuropathy. 2.Autonomic dysfunction in the form of orthostatic hypotension, urinary retention,paralytic ileus,	

		identical to vinblastine.	constipation, and cranial nerve palsies. 3.Ataxia, seizures and coma. 4.Mild myelosuppression. 5. SIADH.	
Etoposide		• Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA • This complex induces breaks in double stranded DNA and **prevents repair by topoisomerase II binding**. • Accumulated breaks in DNA prevent entry into the **mitotic phase** of cell division, and lead to cell death • 30-50% of the drug is excreted in urine, and dose reduction is needed in **renal** dysfunction.	• Nausea, vomiting, hypotension, alopecia and myelosuppression	•It is a semisynthetic derivative of podophyllotoxin, which is extracted from Mayapple root. •Oral bioavailability is ~ 50%, requiring an oral dose double that of IV dose.
Bleomycin		• It is a cell-cycle specific drug that causes accumulation of cells in the **G2 phase** of the cell cycle. • Eliminated mainly by the kidney, and dose reduction is needed in renal dysfunction. • **free radical**	•Pulmonary toxicity: pneumonitis, cough, dyspnea, dry inspiratory crackles, and chest infiltrates.	**Antitumor Antibiotics BUT ITS CCS** • Can be given subcutaneously, IM or IV.

Tyrosine Kinase Inhibitors

Imatinib	•It is an inhibitor of the tyrosine kinase domain of an oncoprotein and prevents phosphorylation of the kinase substrate by ATP. •It is indicated for the treatment of **chronic myelogenous leukaemia**, a pluripotent hematopoietic stem cell disorder characterized by the **t(9:22) Philadelphia chromosome** translocation.	• Fluid retention with ankle or periorbital edema, diarrhea, and congestive heart failure. • Myalgias.	orally.
Asparaginase	• It is L-asparagine amidohydrolase. • It hydrolyzes circulating L-asparagine to aspartic acid and ammonia → depletion of L-asparagine → effective inhibition in protein synthesis. • acute lymphocytic leukaemia cells lack, whereas normal cells have asparagine synthetase.	•Hypersensitivity reactions – fever, chills, nausea and vomiting, skin rash and urticaria, bronchospasm, respiratory failure and hypotension. •Increased risk of clotting and bleeding. •Pancreatitis (in some patients), renal toxicity, hepatic toxicity. •Neurologic toxicity.(lethargy, confusion, hallucinations, coma in sever cases)	

Bortezomib	•It is a dipeptide boronic acid analogue •It is a highly selective, reversible inhibitor of **the 26S proteasome**, and inhibits many proteins that cancer cells need to survive and multiply. •Used in combination with other drugs for **multiple myeloma**.	1. Complete AV-block 2. Disseminated and fulminant plasmacytomas 3. Others (30% of patients): Fatigue, peripheral neuropathy 4. Nausea and vomiting, diarrhea, poor appetite, constipation 5. Low platelet count, fever, anemia.	
Alemtuzumab	• It is a humanized IgG1 with a kappa chain that binds to **CD52** found **in normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and a small population of granulocytes**. • Indicated for treatment of **B-cell chronic lymphocytic leukaemia in patients treated with alkylating agents and failed** fludarabine therapy. • It depletes leukemic and normal cells by direct antibody-dependent lysis.	lymphopenia, neutropenia, anemia, thrombocytopenia, opportunistic infections.	**Monoclonal Antibodies**
Rituximab	•It is a chimeric murine-human monoclonal IgG1 antibody (human Fc). •It binds CD20 molecules on **normal and malignant B lymphocytes.** •Used for relapsed or refractory **low-grade or follicular B-cell non-Hodgkin's lymphoma** • The mechanism of action includes complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis in malignant lymphoma cells.	•**Melena , hematuria** •**Swelling of the face**, arms, hands, lower legs, or feet. •Back pain, burning or stinging of the skin. •Chest tightness. •Dyspnea.	**Monoclonal Antibodies**