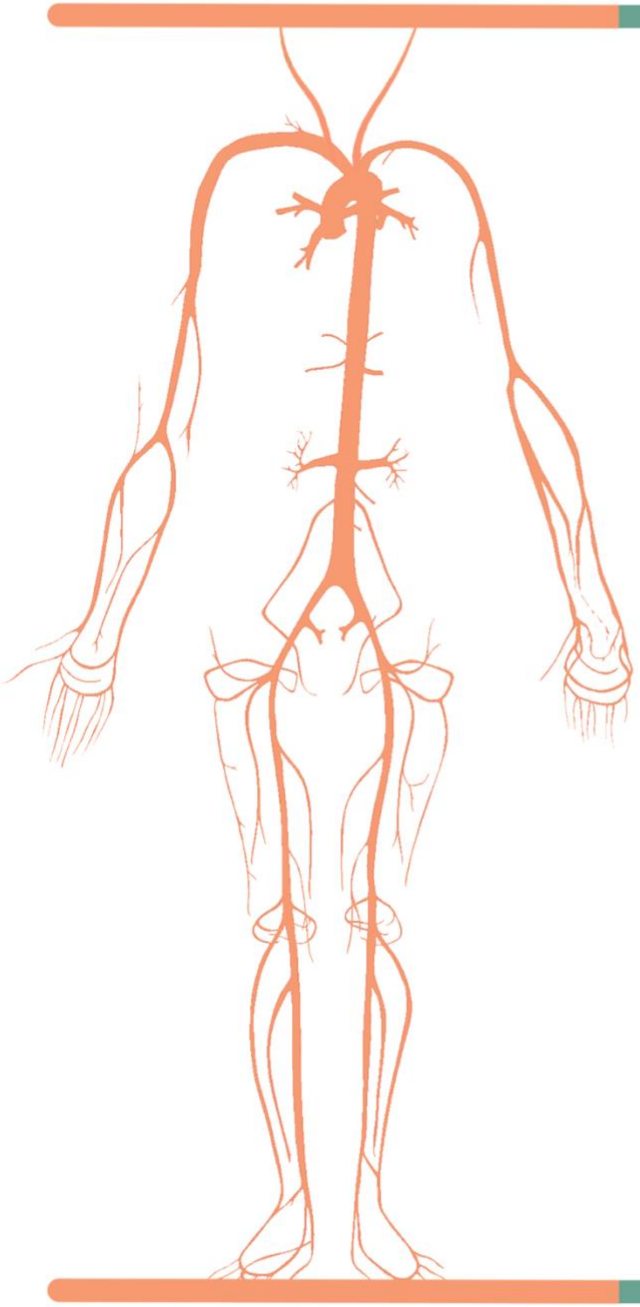
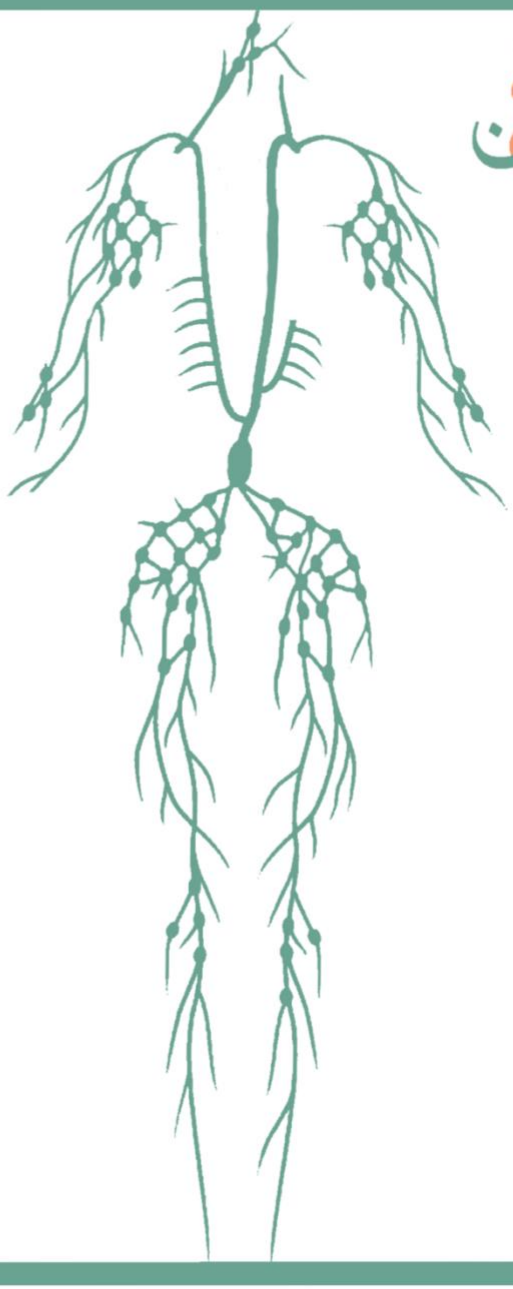
Pharmacology

HematoLymphatic





Title: Sheet # – Main Topic

Writer: Name : Reham badaynеh

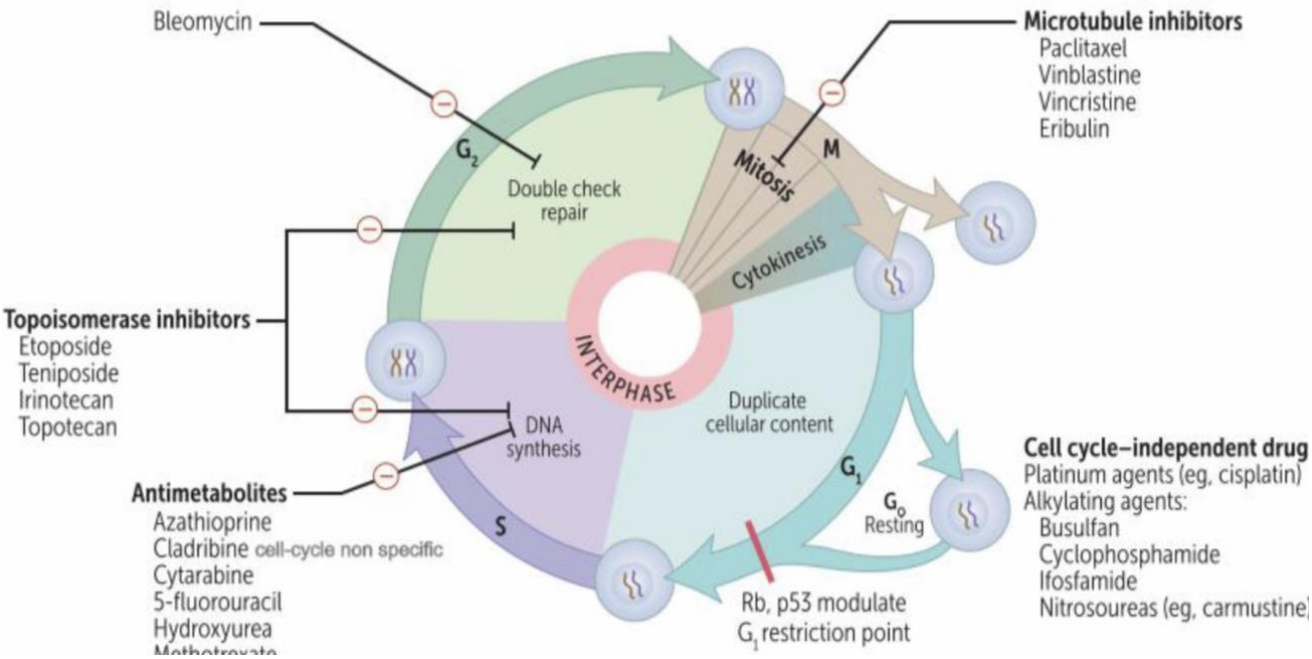
Scientific Correction: Razan Nassar

Final Correction: Laila nazzal

Doctor: Munir Gharaibeh

We are going to talk in this sheet about **drug treatment of Hematopoietic malignancy**

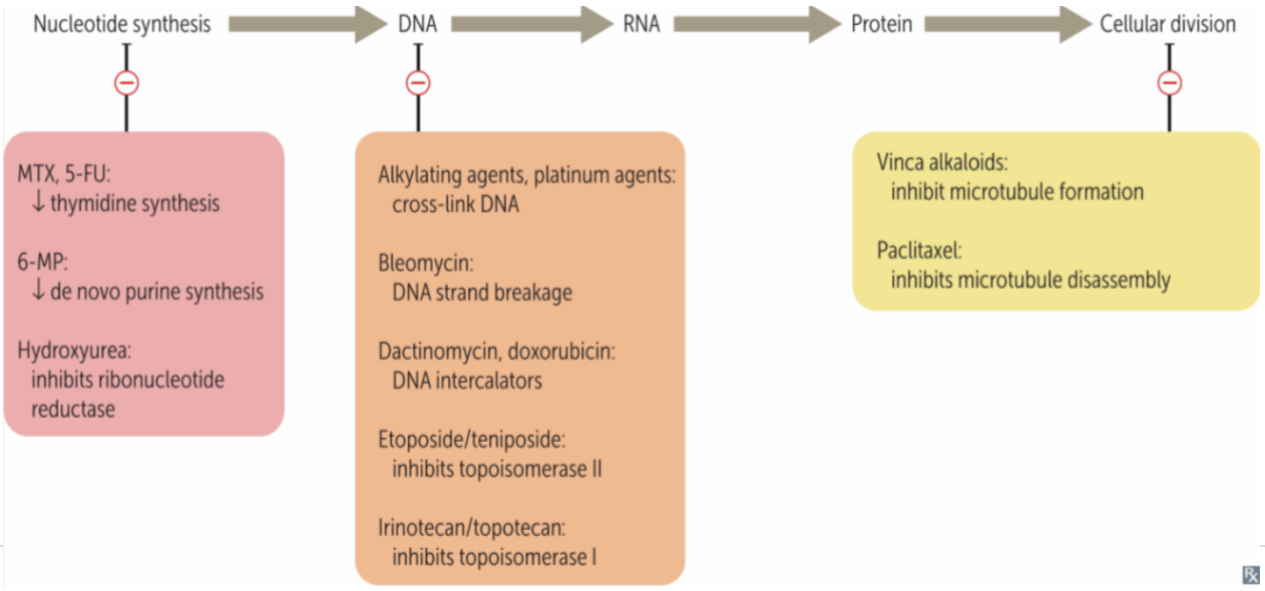
In the last lecture we have talked about cell cycle and the drugs that work on each stage of the cell cycle .



Also, the figure below is related to the last lecture and it is talking about Anticancer drugs targets, which are :-

1-Nucleotide synthesis / 2- DNA synthesis / 3- RNA synthesis / 4- Protein synthesis

5- Cellular division process



Drugs used in leukemias and Lymphomas :- (DON'T MEMORIZE KNOW RETURN BACK TO THEM)

Antitumor antibiotics:

1-Bleomycin / 2-Doxorubicin, Daunorubicin

Antimetabolites:

1- Cladribine / 2-Cytarabine / 3- Methotrexate

Alkylating agents:

1-Busulfan / 2-Cyclophosphamide, ifosfamide / 3-Procarbazine

Microtubule inhibitors:

1-Vincristine / 2- Vinblastine

Miscellaneous:

1-Hydroxyurea / 2- Imatinib, dasatinib / 3-Rituximab

A- Antitumor Antibiotics:

These antibiotics originally have anticancerous effect; they might have effect on hematopoietic as well as non-hematopoietic malignancies and other cancerous conditions

Drug name	Bleomycin	Doxorubicin, Daunorubicin
Mechanism of action	**Induces free radical formation which causes breaks in DNA strands.**	**Intercalates into DNA, preventing RNA synthesis.**
Hematopoietic malignancies and other conditions affected by this Drug	**1-Testicular cancer 2-Hodgkin lymphoma**	**1-Solid tumors 2-leukemias 3-lymphomas.**
Adverse effects	**1-Pulmonary fibrosis (VIP)**	**Cardiotoxicity (dilated**

	2-Flagellate erythema 3-Minimal myelosuppression (and this is good because it avoids severe myelosuppression since many anticancer drugs cause severe myelosuppression)	cardiomyopathy), myelosuppression, alopecia (many anticancer drugs causes alopecia , but it is reversible and not serious as cardiotoxicity and myelosuppression)
Note		Note:- Dexrazoxane (iron chelating agent) is used to prevent cardiotoxicity, but it decreases the effect.

B- Antimetabolites

Drug name	Cladribine	Cytrabine	Methotrexate
Mechanism of action	Purine analog —> multiple mechanisms (e.g. inhibition of DNA polymerase, DNA strand breaks).	Pyrimidine analog ->DNA chain termination. -At higher concentrations, inhibits DNA Polymerase.	Folic acid analog that competitively inhibits dihydrofolate reductase => decreases dTMP => decreases DNA synthesis.
Hematopoietic malignancies and other conditions affected by this drug	Hairy cell leukemia.	1-Leukemias (AML: Acute myeloid leukemia) 2-lymphomas.	1-Cancers:- A-leukemias (ALL: Acute lymphocytic leukemia) B-lymphomas C-choriocarcinoma (malignant tumor of the placenta)

			D-sarcoma 2- Other medical applications:- A-ectopic pregnancy B-medical abortion (with misoprostol) C-rheumatoid arthritis D-psoriasis E-IBD (Inflammatory Bowel Disease) F- vasculitis.
Adverse effects	1- Myelosuppression 2- Nephrotoxicity 3- Neurotoxicity.	1- Myelosuppression with megaloblastic anemia. Remember :- CYTarabine causes panCYTopenia.	1-Myelosuppression, which is reversible with leucovorin "rescue." 2-Hepatotoxicity. 3-Mucositis (e.g. mouth ulcers). 4-Pulmonary fibrosis. 5-Folate deficiency, which may be teratogenic (neural tube defects) without supplementation. 6-Nephrotoxicity.

C-Alkylating agents

Drug name	Busulfan	Procarbazine	Cyclophosphamide Ifosfamide
Mechanism of action	Cross-links DNA.	Cell cycle phase–nonspecific alkylating agent, mechanism not yet defined.	Cross-link DNA at guanine. * Require bioactivation by liver.

Hematopoietic malignancies and other conditions affected by this drug	**Used to ablate patient's bone marrow before bone marrow transplantation. Bone Marrow transplant is used in numerous applications (in cancers, Bone marrow defects, problems in hemoglobin synthesis as in thalassemia …etc) so before we transplant the new bone marrow in the patient we should ablate his own bone marrow totally!! And this is done using this agent.**	**1-Hodgkin lymphoma** **2- brain tumors.**	**1-Solid tumors** **2-leukemia** **3-lymphomas** **4-rheumatic disease (e.g. SLE -Systemic Lupus Erythematous -, granulomatosis with polyangiitis).**
Adverse effects	**1-Severe myelosuppression (in almost all cases)** **2-pulmonary fibrosis** **3-hyperpigmentation**	**1-Bone marrow suppression** **2- Pulmonary toxicity,** **3-Leukemia,** **4-Disulfiram-like reaction (this reaction is used in treating alcoholism; alcoholic patients are given a drug called Disulfiram**	**1-Myelosuppression** **2- SIADH (Syndrome of inappropriate antidiuretic hormone secretion)** **3-Fanconi syndrome (ifosfamide)** **4-Hemorrhagic cystitis and bladder cancer (VIP) , prevented with Mesna (sulfhydryl group of Mesna**

		and then when they accidentally or intentionally ingest alcohol, a reaction (called Disulfiram reaction) takes place producing bad effects, thus the patient won't like alcohol due to the effect of this reaction) .	binds toxic metabolites) and adequate hydration
Notes			*A nitrogen mustard

D-Microtubule inhibitors

Drug name	Vincristine / Vinblastine -plant products-
Mechanism of action	Vinca alkaloids bind β-tubulin and inhibit its polymerization into microtubules => prevent mitotic spindle formation (M-phase arrest).
Hematopoeitic malignancies and other conditions affected by this drug	1-Solid tumors 2-leukemias 3-Hodgkin lymphomas 4- non-Hodgkin lymphomas
Adverse effects	Vincristine: neurotoxicity (areflexia (diminished reflexes) , peripheral neuritis), constipation (including paralytic ileus). It Crisps the nerves. Vinblastine: bone marrow suppression. It Blasts the bone marrow.

E-Miscellaneous

Drug name	Hydroxyurea
Mechanism of action	Inhibits ribonucleotide reductase => DNA Synthesis (S-phase specific).
Hematopoietic malignancies and other conditions affected by this drug	1-Myeloproliferative disorders (e.g., CML, polycythemia vera) 2-sickle cell (increases HbF).
Adverse effects	Severe myelosuppression.

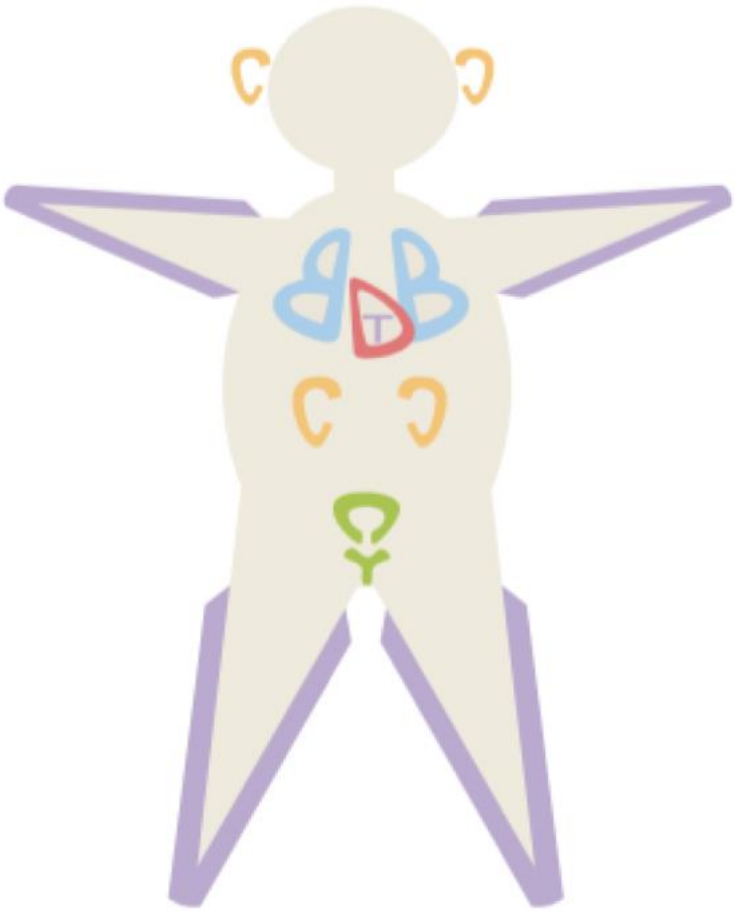
F- Tyrosine kinase inhibitors

Drug name	Imatinib / Dasatinib
Mechanism of action	Inhibitor of Tyrosine Kinase domains of :- 1)Bcr-Abl oncoprotein (encoded by Philadelphia chromosome fusion gene in CML) 2)PDGFR (platelet-derived growth factor receptor) 3) and c-kit (common in GI stromal tumors).
Hematopoietic malignancies and other conditions affected by this drug	1-CML (Chronic Myelogenous Leukemia) 2-GI stromal tumors (GIST)
Adverse effects	Safe drugs but can cause fluid retention (giving diuretics).

F- Monoclonal antibodies

Drug name	Rituximab
Mechanism of action	**Monoclonal antibody against CD20, which is found on most of B-cell neoplasms.**
Hematopoietic malignancies and other conditions affected by this drug	**1-Non-Hodgkin lymphoma** **2-CLL (chronic Lymphocytic leukemia).** **3-ITP (immune Thrombocytopenic purpura).** **4-rheumatoid arthritis.**
Adverse effects	**Carry the risk of progressive multifocal leukoencephalopathy (by reactivation of JC virus ; JC virus remains dormant in the central nervous system and becomes activated after giving this drug) and other Opportunistic infections, also Hepatitis B reactivation (hepatitis B reactivation is very serious and it could be more dangerous than the tumor itself)** *** Must screen for Hepatitis B and C before giving Rituximab**

To remember the adverse effects of the drugs the figure below simplifies these effects:-



Cisplatin/Carboplatin → ototoxicity

Vincristine → peripheral neuropathy
Bleomycin, Busulfan → pulmonary fibrosis
Doxorubicin → cardiotoxicity
Trastuzumab → cardiotoxicity
Cisplatin/Carboplatin → nephrotoxicity

CYclophosphamide → hemorrhagic cystitis