

# Pharmacology – HLS

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# Drug Treatment of Hematopoietic Malignancy

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# Drugs used in Leukemias and Lymphomas

## Antitumor antibiotics:

- ▶ Bleomycin
- ▶ Doxorubicin, Daunorubicin

## Antimetabolites:

- ▶ Cladribine
- ▶ Cytarabine
- ▶ Methotrexate

## Alkylating agents:

- ▶ Busulfan
- ▶ Cyclophosphamide, ifosfamide
- ▶ Procarbazine

## Microtubule inhibitors:

- Vincristine
- Vinblastine

## Miscellaneous:

- Hydroxyurea
- Imatinib, dasatinib
- Rituximab

# Antitumor Antibiotics

## Bleomycin

- ▶ Induces free radical formation=> breaks in DNA strands.
- ▶ used in Testicular cancer, Hodgkin lymphoma
- ▶ causes **Pulmonary fibrosis** (not an easy side effect) ,**Flagellate erythema**, **Minimal myelosuppression**. (It avoids severe myelosuppression that many cancer treatments might cause )

## Doxorubicin, Daunorubicin

- Intercalates into DNA, preventing RNA synthesis.
- Useful in Solid tumors, leukemias, lymphomas.
- **Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia.**
- **Note:** Dexrazoxane (iron chelating agent) is used to prevent cardiotoxicity, but it decreases the effect

# Antimetabolites

## Cladribine:

- ▶ Purine analog => multiple mechanisms (e.g. inhibition of DNA polymerase, DNA strand breaks).
- ▶ useful in Hairy cell leukemia.
- ▶ **Myelosuppression, nephrotoxicity, and neurotoxicity.**

## Cytarabine:

- ▶ Pyrimidine analog => DNA chain termination.  
At higher concentrations, inhibits DNA Polymerase.
- ▶ useful in Leukemias (AML), lymphomas.
- ▶ **Myelosuppression with megaloblastic anemia.**
- ▶ **CYTarabine causes panCYTopenia.**

# Antimetabolites

## Methotrexate

- ▶ Folic acid analog that competitively inhibits dihydrofolate reductase => decreases dTMP =>decreases DNA synthesis.
- ▶ Useful inCancers: leukemias (ALL [acute lymphoblastic leukemia] ), lymphomas, choriocarcinoma (carcinoma of the placenta), sarcomas.
- ▶ also useful in Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.
- ▶ Side Effects:
  - ▶ Myelosuppression, which is reversible with folic acid = leucovorin “rescue.”
  - ▶ Hepatotoxicity. Mucositis (e.g. mouth ulcers).
  - ▶ Pulmonary fibrosis.
  - ▶ Folate deficiency, which may be teratogenic in pregnant women (neural tube defects) . (If a pregnant woman doesn't take folic acid supplements, the fetus might have some defects in the neural tube (CNS) )
  - ▶ Nephrotoxicity.

# Alkylating Agents

## Busulfan

- ▶ Cross-links DNA.
- ▶ Used to ablate patient's bone marrow before bone marrow transplantation. (BM transplantation has many applications in medicine as in the treatment of malignancies and hemoglobin synthesis abnormalities like in thalassemia)
- ▶ Severe myelosuppression , pulmonary fibrosis, hyperpigmentation.

## Procarbazine

- ▶ Cell cycle phase-nonspecific alkylating agent, mechanism not yet defined.
- ▶ useful in Hodgkin lymphoma, brain tumors.
- ▶ Side Effects:
  - ▶ Bone marrow suppression,
  - ▶ Pulmonary toxicity,
  - ▶ Leukemia,
  - ▶ Disulfiram-like reaction. ( a reaction in the body produces symptoms similar to those occurring when there's a consumption of alcohol after taking disulfiram (a drug for treatment of alcoholism))

# Alkylating Agents

## Cyclophosphamide

### Ifosfamide

- ▶ nitrogen mustards
- ▶ Cross-link DNA at guanine. Require bioactivation by liver..
- ▶ useful in Solid tumors, leukemia, lymphomas, rheumatic disease (e.g. SLE, granulomatosis with polyangiitis).
- ▶ Side Effects:
  - ▶ Myelosuppression
  - ▶ SIADH; (syndrome of inappropriate AD hormone)
  - ▶ Fanconi syndrome (ifosfamide);
  - ▶ Hemorrhagic cystitis and bladder cancer (very peculiar), prevented with adequate hydration and Mesna (sulfhydryl group of mesna binds toxic metabolites) .



# Microtubule inhibitors

## ▶ Vincristine

## ▶ Vinblastine

- ▶ Vinca alkaloids bind  $\beta$ -tubulin and inhibit its polymerization into microtubules => prevent mitotic spindle formation(M-phase arrest).  
(Cell cycle specific)
- ▶ useful in Solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas.
- ▶ Side Effects:
  - ▶ Vincristine: neurotoxicity (areflexia (diminishing of reflexes), peripheral neuritis), constipation (including paralytic ileus). Crisps the nerves.
  - ▶ Vinblastine: bone marrow suppression. Blasts the bone marrow.

## Miscellaneous

### ▶ Hydroxyurea

- ▶ Inhibits ribonucleotide reductase => DNA Synthesis (S-phase specific).
- ▶ useful in Myeloproliferative disorders (e.g., CML (chronic myelogenous leukemia), polycythemia vera), sickle cell (increases HbF). (destroys RBCs carrying HbS and replaces them with RBCs carrying HbF)
- ▶ Side Effects: Severe myelosuppression.

# Tyrosine Kinase Inhibitors

## ▶ Imatinib

## ▶ Dasatinib

- ▶ Inhibitor of Tyrosine Kinase domains of Bcr-Abl oncoprotein(encoded by Philadelphia chromosome fusion gene in CML), PDGFR (Platelete derived growth factor receptor) , and c-kit (common in GI stromal tumors).(abnormal chromosome 21)
- ▶ CML, GI stromal tumors (GIST).
- ▶ Safe drugs but can cause fluid retention.(corrected by giving diuretics)

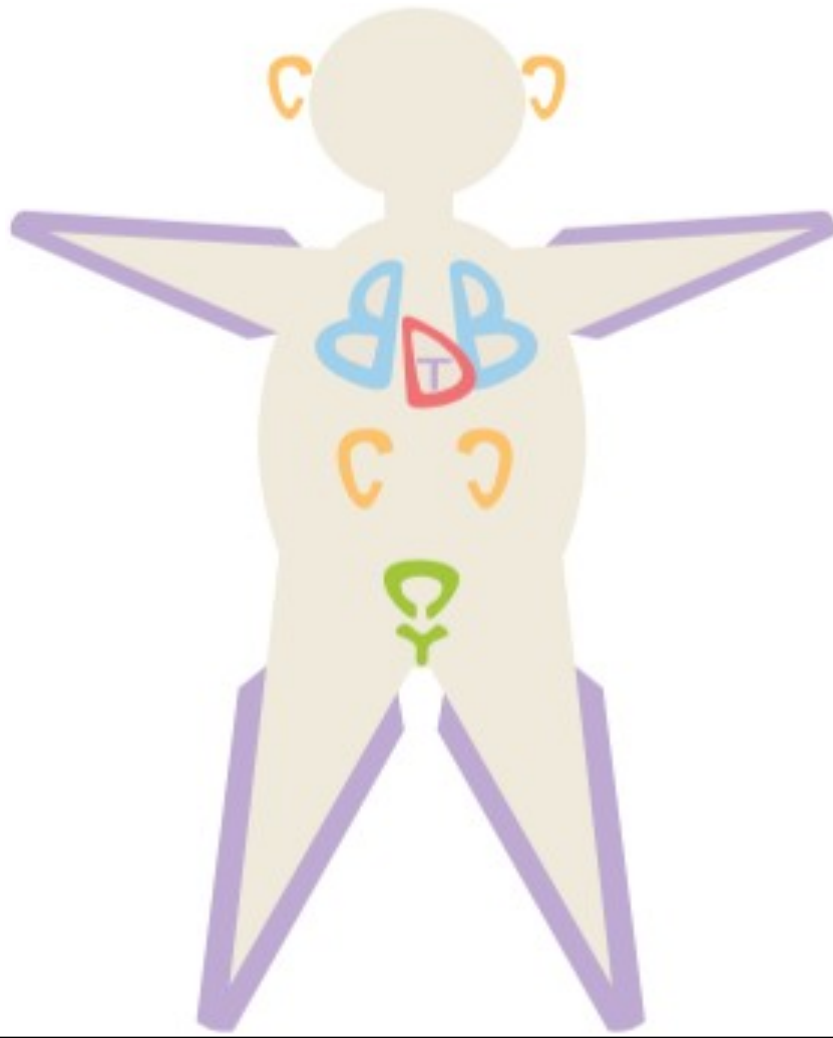
# Monoclonal Antibodies

## Rituximab

- ▶ Monoclonal antibody against CD20, which is found on most B-cell neoplasms.
- ▶ Non-Hodgkin lymphoma, CLL (chronic lymphocytic leukemia), ITP (idiopathic thrombocytopenic purpura), rheumatoid arthritis.
- ▶ **Carry the risk** of progressive multifocal leukoencephalopathy (by reactivation of JC virus (dormant virus in the brain)) and other Opportunistic infections, also Hepatitis B reactivation

Hepatitis B reactivation could be more serious than the cancer itself

# Key chemotoxicities



Cisplatin/Carboplatin → ototoxicity

Refers to the ear

Vincristine → peripheral neuropathy

Bleomycin, Busulfan → pulmonary fibrosis

Doxorubicin → cardiotoxicity

Trastuzumab → cardiotoxicity

Cisplatin/Carboplatin → nephrotoxicity

CYclophosphamide → hemorrhagic cystitis