

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.
- ▶ Useful in Testicular cancer, Hodgkin lymphoma
- ▶ Pulmonary fibrosis, Flagellate erythema, Minimal myelosuppression.

Doxorubicin, Daunorubicin

- Intercalates(يقحم) 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 in leukemias (ALL), lymphomas, choriocarcinoma, sarcomas.
- ▶ Also useful in non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.
- ▶ Side Effects:
 - ▶ Myelosuppression, which is reversible with folinic acid = leucovorin “rescue.”
 - ▶ Hepatotoxicity. Mucositis (e.g. mouth ulcers).
 - ▶ Pulmonary fibrosis.
 - ▶ Folate deficiency may cause teratogenic effects in pregnant women (neural tube defects).
 - ▶ Nephrotoxicity.

Alkylating Agents

Busulfan

- ▶ Cross-links DNA.
- ▶ Used to ablate patient's bone marrow before bone marrow transplantation.
- ▶ Severe myelosuppression, pulmonary fibrosis, hyperpigmentation.

Procarbazine

- ▶ Cell cycle phase-nonspecific alkylating agent, mechanism not yet defined.
- ▶ Useful in Hodgkin lymphoma and brain tumors.
- ▶ Side Effects:
 - ▶ Bone marrow suppression,
 - ▶ Pulmonary toxicity,
 - ▶ Leukemia,
 - ▶ Disulfiram-like reaction.

Alkylating Agents

Cyclophosphamide Ifosfamide

- ▶ Nitrogen mustards
- ▶ Cross-link DNA at guanine. Require bioactivation by liver.
- ▶ Useful in solid tumors, leukemia, lymphomas, rheumatic diseases(e.g., SLE, granulomatosis with polyangiitis).
- ▶ Side Effects:
 - ▶ Myelosuppression
 - ▶ SIADH
 - ▶ Fanconi syndrome (ifosfamide);
 - ▶ Hemorrhagic cystitis and bladder cancer, prevented with adequate hydration and **Mesna** (sulfhydryl group of mesna binds toxic metabolites).

Microtubule inhibitors

▶ Vincristine

▶ Vinblastine

- ▶ Vinca alkaloids bind β -tubulin and inhibit its polymerization into microtubules => prevent mitotic spindle formation(M-phase arrest).
- ▶ Useful in solid tumors, leukemias, Hodgkin and non-Hodgkin lymphomas.
- ▶ Side Effects:
 - ▶ Vincristine: neurotoxicity (areflexia, 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).
- ▶ Used in myeloproliferative disorders (e.g., CML, polycythemia vera), sickle cell (increases HbF).
- ▶ Side Effects: Severe myelosuppression.

Tyrosine Kinase Inhibitors

▶ Imatinib

▶ Dasatinib

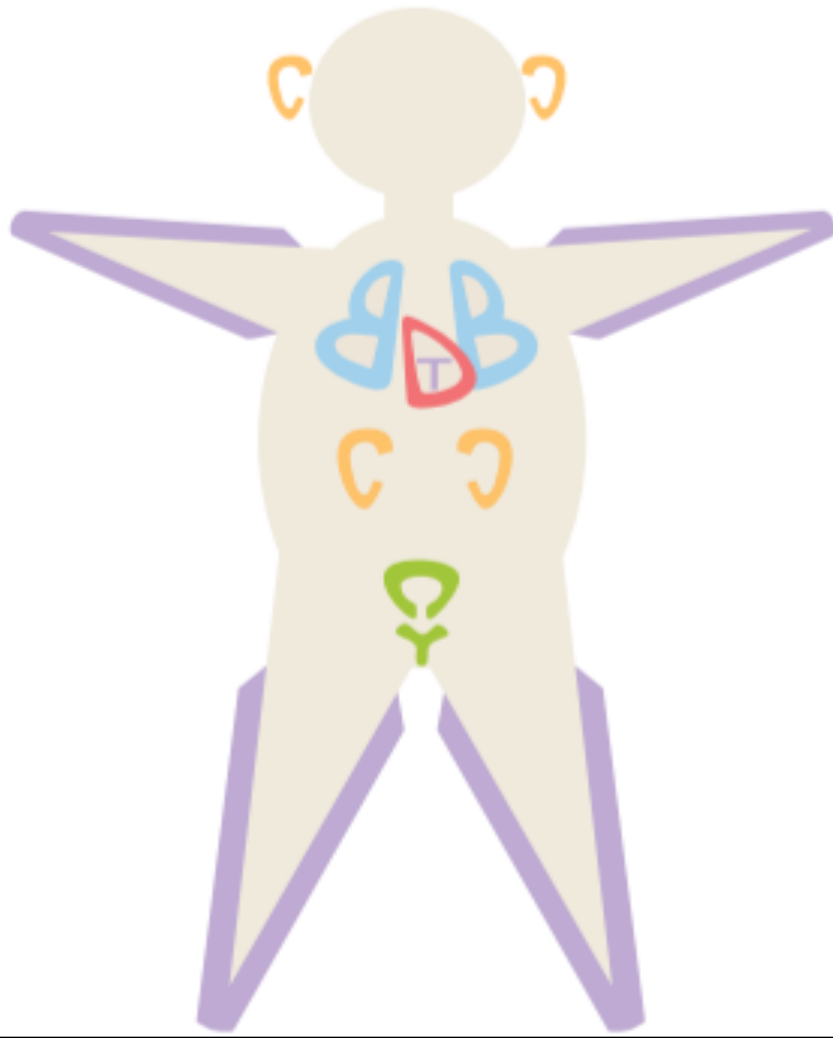
- ▶ Inhibitors of Tyrosine Kinase domains of Bcr-Abl oncoprotein(encoded by Philadelphia chromosome fusion gene in CML), PDGFR, and c-kit (common in GI stromal tumors).
- ▶ CML, GI stromal tumors (GIST).
- ▶ Safe drugs but can cause fluid retention.

Monoclonal Antibodies

Rituximab

- ▶ Monoclonal antibody against CD20, which is found on most B-cell neoplasms.
- ▶ Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis.
- ▶ **Carry the risk** of progressive multifocal leukoencephalopathy (by reactivation of JC virus) and other Opportunistic infections, also Hepatitis B reactivation
- ▶ Must screen for Hepatitis B and C before giving Rituximab

Key chemotoxicities



Cisplatin/Carboplatin → ototoxicity

Vincristine → peripheral neuropathy

Bleomycin, Busulfan → pulmonary fibrosis

Doxorubicin → cardiotoxicity

Trastuzumab → cardiotoxicity

Cisplatin/Carboplatin → nephrotoxicity

Cyclophosphamide → hemorrhagic cystitis