Drug Treatment of Hematopoietic Malignancy

Munir Gharaibeh, MD, PhD, MHPE

Department of Pharmacology

Faculty of Medicine

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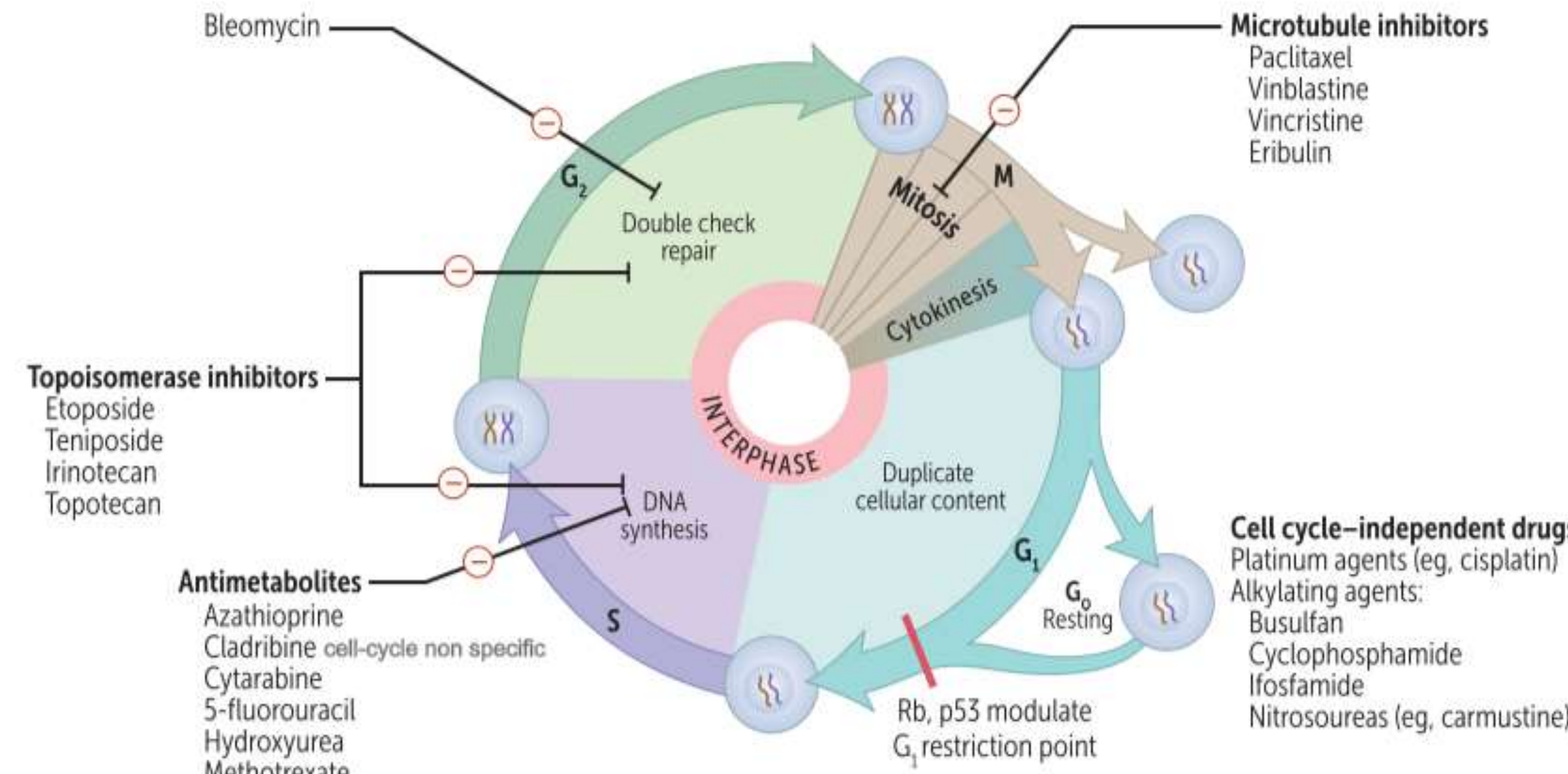
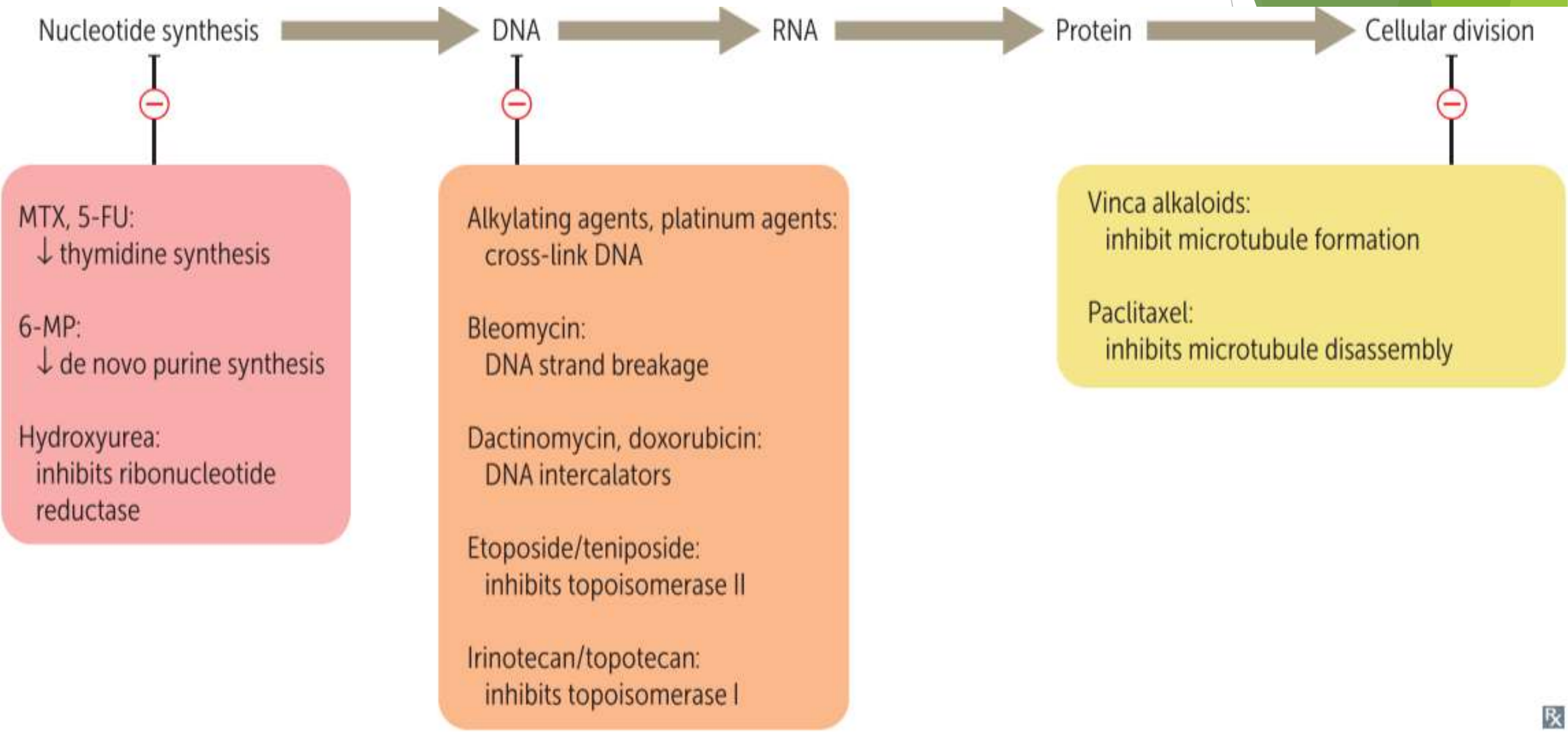
Cancer drugs—cell cycle



Anticancer Drugs Targets



Drugs used in Leukemias, Lymphomas

Antitumor antibiotics:

- Bleomycin
- Doxorubicin, Daunorubicin

Antimetabolites:

- Cladribine
- Cytarabine (arabinofuranosyl Cytidine)
- 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.
- Testicular cancer, Hodgkin lymphoma
- Pulmonary fibrosis, Flagellate erythema, Minimal myelosuppression.

Doxorubicin, Daunorubicin

- Intercalates into DNA, preventing RNA synthesis.
- 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 (eg, inhibition of DNA polymerase, DNA strand breaks).
- Hairy cell leukemia.
- Myelosuppression, nephrotoxicity, and neurotoxicity.

Cytrabine:

- Pyrimidine analog =>DNA chain termination.

  At higher concentrations, inhibits DNA Polymerase.
- 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.
- Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas.
- Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.
- Side Effects:
  - Myelosuppression, which is reversible with leucovorin “rescue.”
  - Hepatotoxicity. Mucositis (eg, mouth ulcers).
  - Pulmonary fibrosis.
  - Folate deficiency, which may be teratogenic (neural tube defects) without supplementation.
  - Nephrotoxicity.

Alkylating Agents

Busulfan

- Cross-links DNA.
- Used to ablate patient's bone marrow before bone marrow transplantation.
- Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.

Procarbazine

- Cell cycle phase–nonspecific alkylating agent, mechanism not yet defined.
- Hodgkin lymphoma, brain tumors.
- Side Effects:
  - Bone marrow suppression,
  - pulmonary toxicity,
  - leukemia,
  - disulfiram-like reaction.

Alkylating Agents

Cyclophosphamide
Ifosfamide

- Cross-link DNA at guanine. Require bioactivation by liver. A nitrogen mustard.
- Solid tumors, leukemia, lymphomas, rheumatic disease (eg, SLE, granulomatosis with polyangiitis).
- Side Effects:
  - Myelosuppression
  - SIADH;
  - Fanconi syndrome (ifosfamide);
  - hemorrhagic cystitis and bladder cancer, prevented with mesna (sulfhydryl group of mesna binds toxic metabolites) and adequate hydration.

Microtubule inhibitors

- **Vincristine**
- **Vinblastine**
- Vinca alkaloids bind ß-tubulin and inhibit its polymerization into microtubules => prevent mitotic spindle formation(M-phase arrest).
- 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).
- Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell (increases HbF).
- Side Effects: Severe myelosuppression.

Tyrosine Kinase Inhibitors

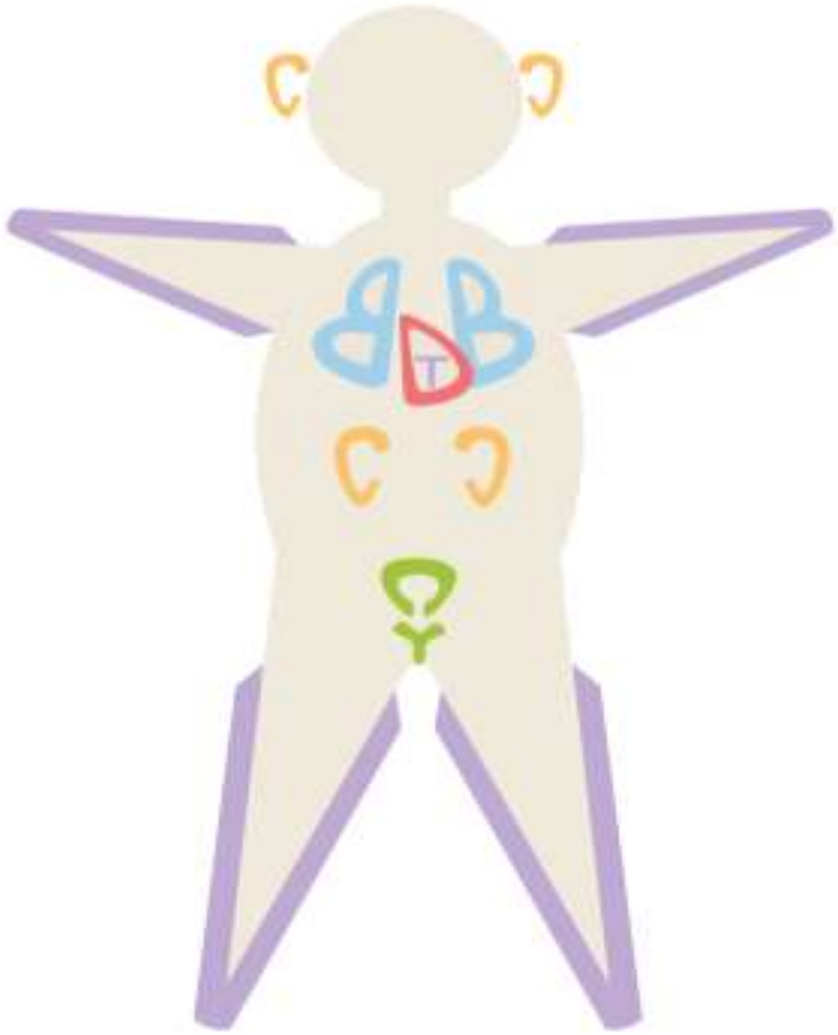
- **Imatinib**
- **Masitinib**
- Tyrosine kinase inhibitor of bcr-abl (encoded by Philadelphia chromosome fusion gene in CML) and c-kit (common in GI stromal tumors).
- CML, GI stromal tumors (GIST).
- Safe drugs, can cause fluid retention.

Monoclonal antibody

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 (reactivation of JC virus) and other Opportunistic infections, 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