Anticancer drugs
Principles of cancer chemotherapy & antimetabolites-2

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ANTIBIOTICS AS ANTICANCERS

They are cell-cycle nonspecific.

Dactinomycin

Dactinomycin is used in combination with:

- **Surgery and vincristine for the treatment of some tumors**
- **MTX in the treatment of gestational choriocarcinoma.**

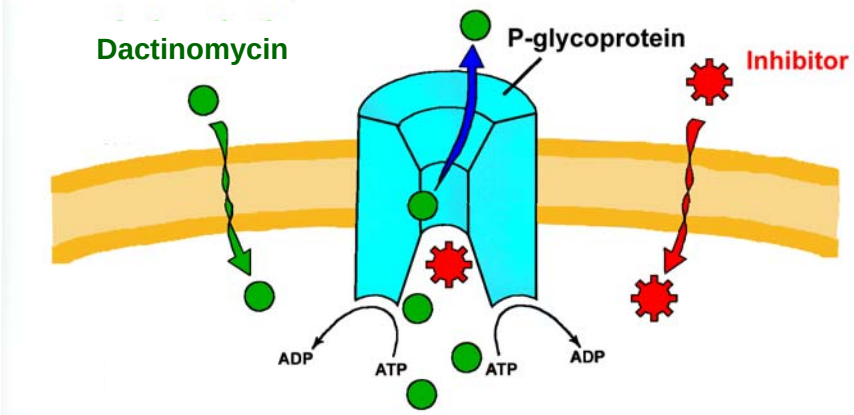
Dactinomycin

Mechanism of action:

Binding certain base pairs of DNA, forming a stable complex which interferes with DNA-dependent RNA synthesis

Resistance:

Due to an increased efflux of the antibiotic from the cell via P-glycoprotein.



Dactinomycin

Pharmacokinetics:

- Administered IV
- Distributes to many tissues but not CSF
- Minimally metabolized in the liver
- Most of the drug and its metabolites are excreted via bile

Adverse effects:

- Bone marrow depression
- Nausea, vomiting, and diarrhea
- Alopecia

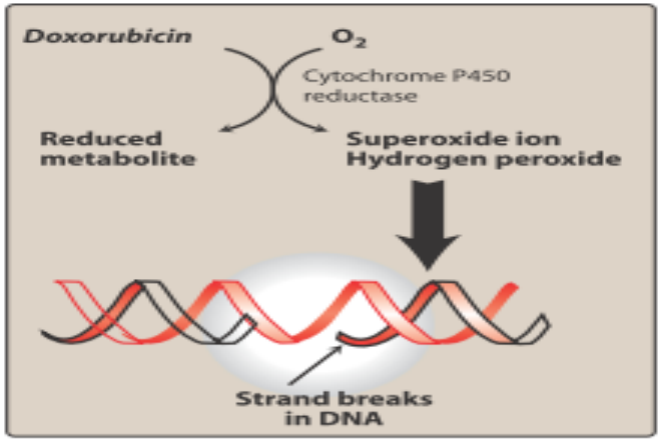
ANTHRACYCLINE ANTIBIOTICS

(*Doxorubicin - Epirubicin*)

Doxorubicin is used for treatment of breast and lung cancer, leukemia and lymphomas.

Mechanism of action:

Doxorubicin interacts with oxygen → superoxide ions & hydrogen peroxide → DNA strand scission



ANTHRACYCLINE ANTIBIOTICS

(*Doxorubicin - Epirubicin*)

Pharmacokinetics:

- administered IV
- bind to plasma proteins
- hepatic metabolism
- bile excretion

Because of the dark red color of anthracyclines, the veins become visible surrounding site of infusion, and a red color to the urine.

ANTHRACYCLINE ANTIBIOTICS

(*Doxorubicin - Epirubicin*)

Adverse effects:

- Irreversible, dose-dependent cardiotoxicity
- Transient bone marrow suppression
- GIT disturbances
- Increased skin pigmentation
- Alopecia

BLEOMYCIN

It is used in the treatment of testicular cancers in combination with other anticancers.

Mechanism of action:

It forms a complex with DNA →↑ superoxide or hydroxyl radicals → attack DNA → strand breakage

BLEOMYCIN

Resistance:

- **Increased efflux of the drug**
- **Increased levels of bleomycin hydrolase**

Pharmacokinetics:

- **Bleomycin-inactivating enzyme (hydrolase) is high in liver and spleen but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues).**
- **Most of the drug is excreted unchanged into the urine.**

BLEOMYCIN

Adverse effects:

- **Pulmonary toxicity (cough, fibrosis)**
- **Alopecia**
- **Hypertrophic skin changes**
- **Hyperpigmentation of the hands**
- **Fever and chills**
- **Bleomycin is unusual in that myelosuppression (bone marrow depression) is rare.**

ALKYLATING AGENTS

- Alkylating agents bind to various cell constituents.
- Used to treat lymphatic and solid cancers.
- They are mutagenic and carcinogenic.

A. Mechlorethamine

- It forms a reactive intermediate that alkylates one or both strands of DNA → DNA strand breakage.
- Alkylation can occur in both cycling and resting cells, proliferating cells are more sensitive to the drug.

A. Mechlorethamine

Resistance:

- Decreased permeability of the drug
- Increased DNA repair by the cell

Adverse effects:

- Severe nausea and vomiting
- Severe bone marrow depression

B. Cyclophosphamide

- Converted in the body to the active compounds: phosphoramide mustard and acrolein.
- Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

Resistance:

- Increased DNA repair
- Decreased drug permeability

B. Cyclophosphamide

Pharmacokinetics:

- **Oral route**
- **Excreted into the feces or urine**

Adverse effects:

- **Alopecia**
- **Nausea, vomiting, and diarrhea**
- **Bone marrow depression**
- **Bladder fibrosis (acrolein)**
- **Neurotoxicity**
- **Secondary malignancies.**