Cancer Chemotherapy-2
Drugs for Leukemias and Lymphomas

Dr. Alia Shatanawi

Chemotherapeutic Drugs: cell cycle dependence

Cell cycle specific:

Antimetabolites
- Methotrexate
- Fluorouracil
- Capecitabine
- Cytarabine
- Mercaptopurine

Antibiotic
- Bleomycin

Agents from plants
- Vincristine, Vinorelbine
- Vinblastine
- Paclitaxel, Docetaxel
- Etoposide

Cell cycle nonspecific:

Alkylating agents
- Mechlorethamine
- Cyclophosphamide
- Chlorambucil
- Ifosfamide
- Carmustine
- Lomustine
- Busulfan

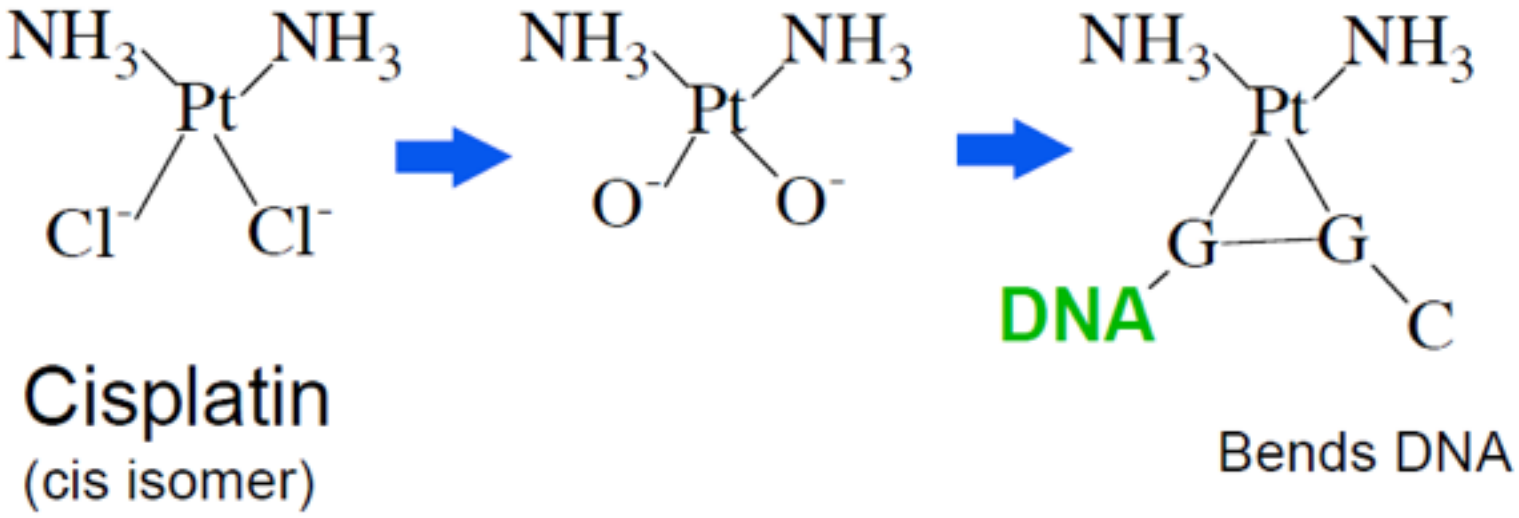
Platinum analogs
- Cisplatin, Carboplatin

Antibiotics
- Doxorubicin
- Epirubicin
- Dactinomycin

Platinum complexes: Cisplatin

- Mechanism:

Covalent crosslinks with GG base pairs (bends DNA)



Platinum complexes: Cisplatin

Pharmacology:

IV, not effective orally; most (90%) bound to plasma proteins; concentrates in liver, kidney, intestine and ovary; excreted in urine.

Toxicity:

N&V, diarrhea, hypersensitivity reactions (rashes), renal damage (reduced with hydration), ototoxicity with high frequency hearing loss and tinnitus, peripheral sensory neuropathy (paresthesia and loss of proprioception), bone marrow depression.

Carboplatin

Pharmacology:

half-life of 120 mins vs cisplatin's 25-50 mins; less chemically reactive (less bound to plasma proteins), less effective than cisplatin (i.e. less toxic);

IV administration; excreted in urine.

Toxicity:

carboplatin is toxic but less than cisplatin to the nervous system (neurotoxicity & ototoxicity) and the kidneys (nephrotoxic); myelosuppression is dose-limiting

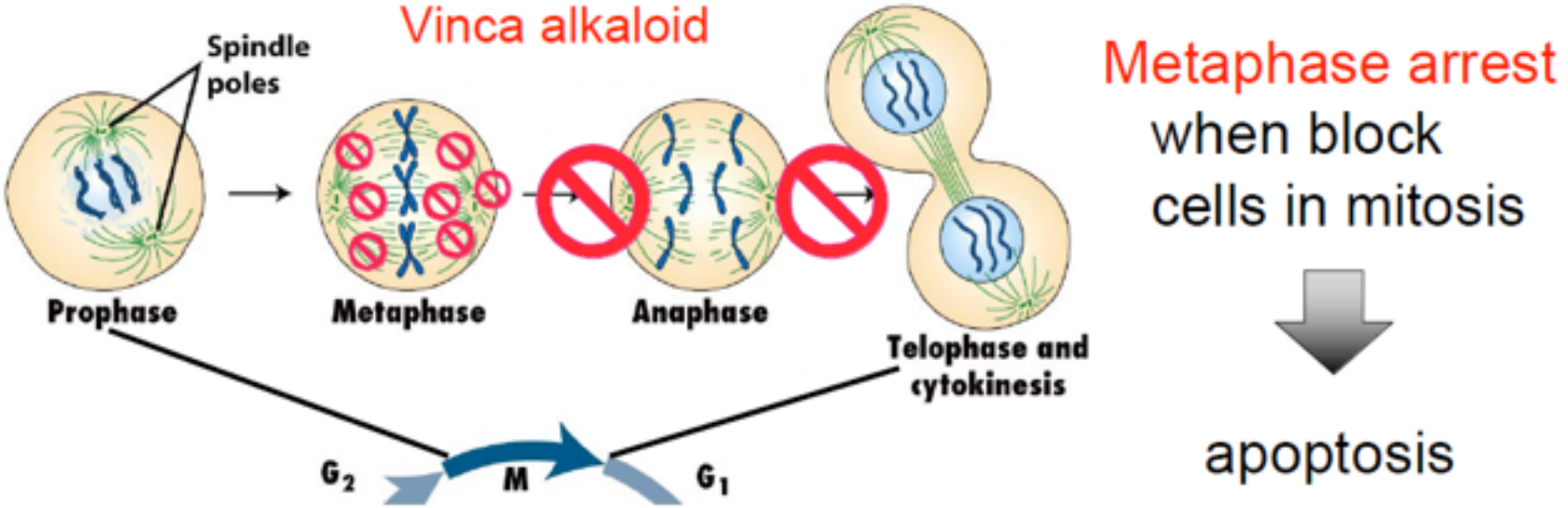
Platinum Analogs

Adverse effects:

- Nausea and vomiting
- Myelosuppression
- Peripheral neuropathy
- Renal toxicity
- Hepatic dysfunction

Vinca alkaloids: (Vincristine, Vinblastine, Vinorelbine)

- Mechanism:
- binds to tubulin, inhibits tubulin polymerization into microtubules which are a major component of the mitotic spindle



Natural Products

Vinca Alkaloids (Vinblastine):

- It is an alkaloid derived from the periwinkle plant, *Vinca rosea*.
- It inhibits tubulin polymerization, which disrupts assembly of microtubules, an important part of the cytoskeleton and the mitotic spindle.
- This inhibition results in mitotic arrest in metaphase, resulting in cell death.

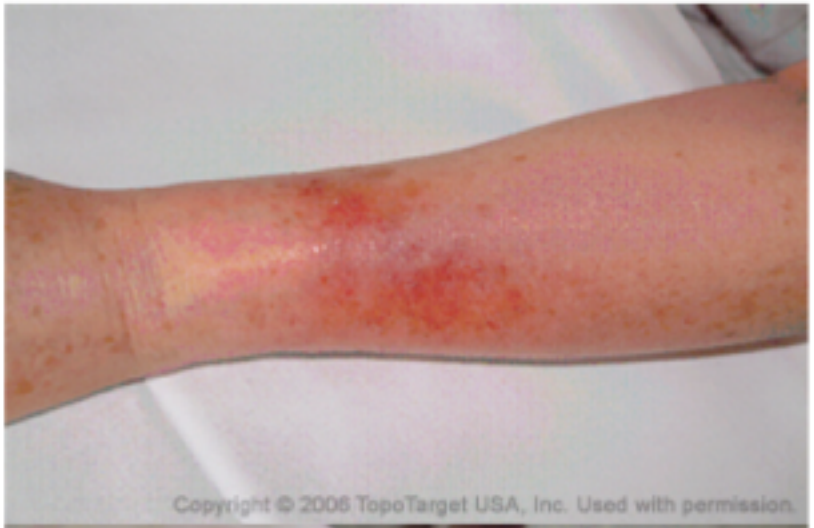
Natural Products

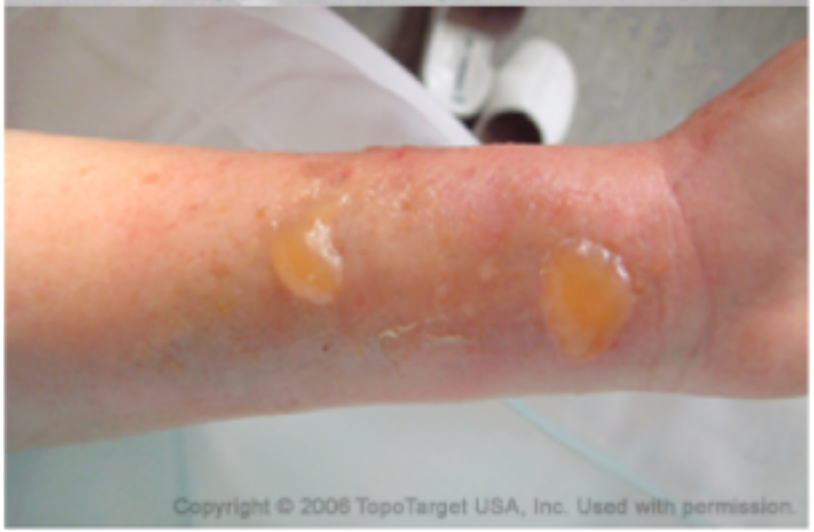
- Dose reduction is needed in liver dysfunction.

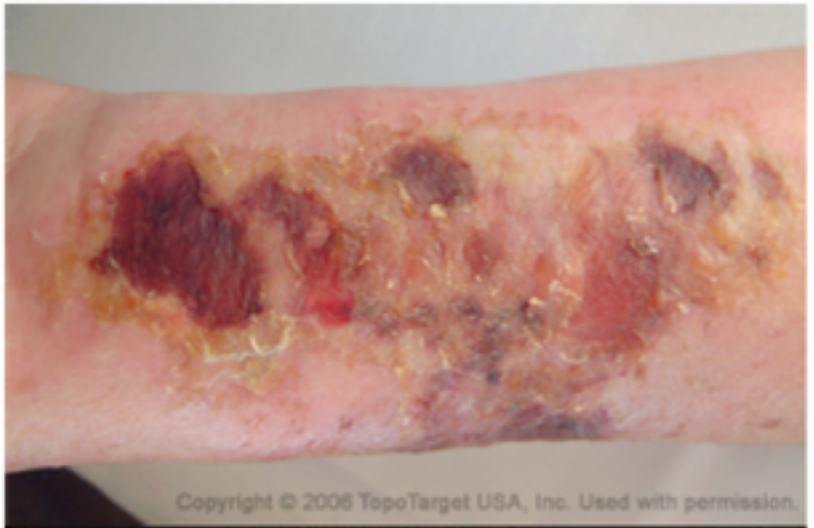
Adverse effects:

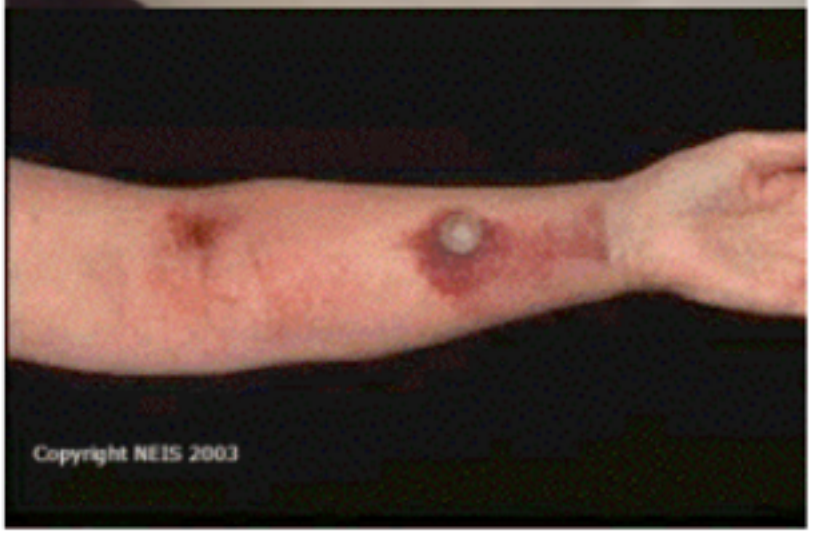
- Nausea and vomiting, bone marrow suppression, mucositis, Syndrome of inappropriate ADH secretion (SIADH) and alopecia.
- It is a vesicant and care should be taken during administration.

Extravasation from IV chemotherapy









Natural Products

Vinca Alkaloids (Vincristine):

- It is an alkaloid derived from the periwinkle plant, *Vinca rosea*.
- Its mechanism of action, mechanism of resistance, and clinical pharmacology are identical to vinblastine.

Natural Products

Adverse reactions:

1. Peripheral sensory neuropathy.
2. Autonomic dysfunction in the form of orthostatic hypotension, urinary retention, paralytic ileus, constipation, and cranial nerve palsies.
3. Ataxia, seizures and coma.
4. Mild myelosuppression.
5. SIADH.

Natural Products

Epipodophyllotoxins (Etoposide).

- It is a semisynthetic derivative of podophyllotoxin, which is extracted from Mayapple root.
- Oral bioavailability is ~ 50%, requiring an oral dose double that of IV dose.

Natural Products

- Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA.
- This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding.
- Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, and lead to cell death.

Natural Products

- 30-50% of the drug is excreted in urine, and dose reduction is needed in renal dysfunction.

Adverse effects:

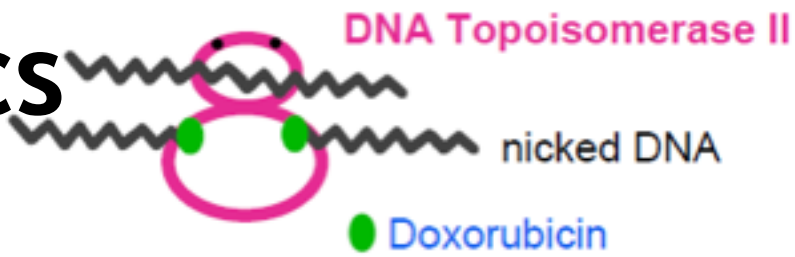
- Nausea, vomiting, hypotension, alopecia and myelosuppression.

Antitumor Antibiotics

- They bind to DNA through intercalation between specific bases, and block DNA and RNA synthesis, cause DNA strand scission, and interfere with cell replication.
- Most are products of various strains of the soil microbe *Streptomyces*.

Examples: Doxorubicin, Daunorubicin, Bleomycin.

Antitumor Antibiotics



Doxorubicin, Daunorubicin:

- Are among the most widely used cytotoxic anticancer drugs.
- Their cytotoxic action is due to:

1. Inhibition of topoisomerase II.
2. Intercalation to DNA with high affinity.
3. Generation of semiquinone free radicals, and oxygen free radicals through iron-dependent, enzyme-mediated reductive process.

Antitumor Antibiotics

4. **Binding to cellular membranes altering fluidity and ion transport.**

- **Free radicals are the cause of cardiotoxicity of these agents.**
- **They are administered IV.**
- **Metabolized extensively in the liver, with reduction and hydrolysis.**

Antitumor Antibiotics

- ~ 50% of the dose is excreted in bile, and dose reduction is needed in hepatic dysfunction.
- Can be used as once every 3 weeks
- low dose weekly, or 3-4 days continuous IV infusion, with comparable results.

Antitumor Antibiotics

Adverse reaction:

- **Myelosuppression with leukopenia more than thrombocytopenia.**
- **Mild nausea and vomiting**
- **Mucositis**
- **Alopecia**
- **Acute and chronic cardiac toxicity: arrhythmias, ECG changes, conduction abnormalities, pericarditis and myocarditis.**
- **red urine (not hematuria)**
- **severe local tissue damage with extravasation,**
- **anaphylactoid reactions**
- **Dexrazoxane to protect from cardiotoxicity and treat extravasation from IV doxorubicin**

Antitumor Antibiotics

Bleomycin:

- It is a small peptide that contains a DNA-binding region, and an iron binding domain at opposite ends of the molecule.
- It acts by binding to DNA, which results in single-strand and double-strand breaks following free radical formation, and inhibition of DNA synthesis.

Antitumor Antibiotics

- It is a cell-cycle specific drug that causes accumulation of cells in the G_2 phase of the cell cycle.
- Can be given subcutaneously, IM or IV.
- Eliminated mainly by the kidney, and dose reduction is needed in renal dysfunction.

Antitumor Antibiotics

Adverse effects:

- **Pulmonary toxicity: pneumonitis, cough, dyspnea, dry inspiratory crackles, and chest infiltrates.**
- **Other toxicities: allergic reactions, fever, hypotension, skin toxicity, alopecia, and mucositis.**

Tyrosine Kinase Inhibitors

Imatinib:

- **It is an inhibitor of the tyrosine kinase domain of an oncoprotein and prevents phosphorylation of the kinase substrate by ATP.**
- **It is indicated for the treatment of chronic myelogenous leukemia, a pluripotent hematopoietic stem cell disorder characterized by the t(9:22) Philadelphia chromosome translocation.**

Tyrosine Kinase Inhibitors

- Imatinib is well absorbed orally.

Adverse effects:

- Nausea and vomiting,
- Fluid retention with ankle or periorbital edema, diarrhea, and congestive heart failure.
- Myalgias.

Asparaginase

- It is L-asparagine amidohydrolase.
- It hydrolyzes circulating L-asparagine to aspartic acid and ammonia → depletion of L-asparagine → effective inhibition in protein synthesis.
- ALL cells lack, wheras normal cells have asparagine synthetase.

Asparaginase

Adverse effects:

- **Hypersensitivity reactions – fever, chills, nausea and vomiting, skin rash and urticaria, bronchospasm, respiratory failure and hypotension.**
- **Increased risk of clotting and bleeding.**
- **Pancreatitis, renal toxicity, hepatic toxicity.**
- **Neurologic toxicity.**

Proteasome Inhibitors

Bortezomib:

- It is a dipeptide boronic acid analogue
- It is a highly selective, reversible inhibitor of the 26S proteasome, and inhibits many proteins that cancer cells need to survive and multiply.
- Used in combination with other drugs for multiple myeloma.

Proteasome Inhibitors

Adverse Effects:

1. Complete AV-block
2. Disseminated and fulminant plasmacytomas
3. Others (30% of patients): Fatigue, peripheral neuropathy
4. Nausea and vomiting, diarrhea, poor appetite, constipation.
5. Low platelet count, fever, anemia.

Monoclonal Antibodies

Alemtuzumab:

- It is a humanized IgG_1 with a kappa chain that binds to CD52 found in normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and a small population of granulocytes.

Monoclonal Antibodies

- Indicated for treatment of B-cell chronic lymphocytic leukemia in patients treated with alkylating agents and failed fludarabine therapy.
- It depletes leukemic and normal cells by direct antibody-dependent lysis.
- Causes lymphopenia, neutropenia, anemia, thrombocytopenia, opportunistic infections.

Monoclonal Antibodies

Rituximab:

- It is a chimeric murine-human monoclonal IgG_1 antibody (human Fc).
- It binds CD20 molecules on normal and malignant B lymphocytes.
- Used for relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma.

Monoclonal Antibodies

- **The mechanism of action includes complement-mediated lysis, antibody-dependent cellular cytotoxicity, and induction of apoptosis in malignant lymphoma cells.**

Monoclonal Antibodies

Adverse Reactions:

- Melena, hematuria
- Swelling of the face, arms, hands, lower legs, or feet.
- Back pain, burning or stinging of the skin.
- Chest tightness.
- Dyspnea.

- "Melena: Black tarry stool associated with upper GI bleeding."