Drugs Used in Neoplasms of the Urogenital System

Yacoub Irshaid MD, PhD, ABCP
Department of Pharmacology

Drugs for Breast Cancer

Cyclophosphamide

- **An alkylating agent.**
- **It is inactive and needs activation by microsomal enzymes to 4-hydroxycyclophosphamide and aldophosphamide.**
- **These active metabolites are delivered to both tumor and normal cells, where aldophosphamide is cleaved nonenzymatically to the cytotoxic forms phosphoramide mustard and acrolein.**

Cyclophosphamide

Therapeutic uses:

- **Breast cancer**
- **Ovarian cancer**
- **Wilm's tumor**
- **Others**

Cyclophosphamide

Adverse effects:

- **Are dose-related, and occur primarily in rapidly growing tissues such as bone marrow, GIT, and reproductive system.**

1. **Nausea and vomiting.**
2. **Direct vesicant effects and can damage tissues at site of injection.**
3. **Hemorrhagic cystitis which can be prevented by adequate hydration.**

Cyclophosphamide

4. **Carcinogenic, with increased risk of secondary malignancies, especially acute myelogenous leukemia.**
5. **Bone marrow depression may be associated with leukopenia and thrombocytopenia, and bleeding.**
6. **Alopecia**

Methotrexate (MTX)

- **It is a folic acid analog that inhibit dihydrofolate reductase and prevent the formation of tetrahydrofolate (THF).**
- **THF serves as the key one-carbon carrier in the synthesis of thymidylate, purine nucleotides, and the amine acids serine and methionine.**

Methotrexate

- **Thus, it interferes with the formation of DNA and RNA and key cellular proteins.**
- **Intracellular formation of polyglutamate metabolites by folylpolyglutamate synthase, with the addition of up to 5-7 glutamate residues, is needed for the therapeutic action of MTX.**
- **MTX polyglutamates are selectively retained within cancer cells.**

Methotrexate

Development of resistance is due to:

1. **Decreased drug transport via the reduced folate carrier or folate receptor protein.**
2. **Decreased formation of cytotoxic MTX polyglutamate.**
3. **Increased levels of the target enzyme, DHFR, through gene amplification.**

Methotrexate

4. **Altered DHFR protein with altered affinity for MTX.**
5. **Activation of the multidrug resistance transporter P170-glycoprotein.**

Methotrexate

- **It is administered by oral, intravenous and intrathecal routes.**
- **Mainly eliminated by the kidney through active transport, and dose reduction is needed in renal dysfunction.**
- **Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins.**

Methotrexate

- **The effects of MTX can be reversed by administration of leucovorin (5-formyltetrahydrofolate).**
- **Leucovorin rescue can be used in conjunction with high-dose MTX therapy to rescue normal cells from undue toxicity, and in accidental overdose.**

Methotrexate

Therapeutic uses:

- **Breast cancer**
- **Bladder cancer**
- **Choriocarcinoma.**
- **Others.**

Methotrexate

Toxicity:

1. **Mucositis (GIT), diarrhea**
2. **Hepatotoxicity**
3. **Myelosuppression with neutropenia and thrombocytopenia**
4. **Neurological & cognitive impairment**
5. **Immunoallergic pneumonia leading to pulmonary fibrosis**
6. **Chemical pneumonitis**
7. **Renal dysfunction**

Doxorubicin

- **Belongs to anthracyclines, the most widely used cytotoxic anticancer antibiotic drugs.**

Mechanism of action:

1. **Inhibition of topoisomerase II.**
2. **Intercalation to DNA.**
3. **Generation of semiquinone free radicals and oxygen free radicals (iron-dependent, enzyme-mediated reductive process), which cause cardiotoxicity.**

Anthracyclines

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

- **They are administered IV.**
- **Metabolized extensively in the liver.**
- **~ 50% of the dose is excreted in bile, and dose reduction is needed in hepatic dysfunction.**

Anthracyclines

Therapeutic uses:

1. **Breast cancer**
2. **Endometrial cancer**
3. **Cancer of ovary**
4. **Cancer of testis**
5. **Bladder cancer**
6. **Others.**

Paclitaxel

- **Belongs to taxanes.**
- **It is an alkaloid derived fro the Pacific and European *yew* (صنوبريات).**
- **It functions as mitotic spindle poison which results in inhibition of mitosis and cell division.**
- **Metabolized by CYPs, and 80% of the drug is excreted in feces.**
- **Dose reduction is required in hepatic dysfunction.**

Paclitaxel

Therapeutic uses:

1. **Ovarian cancer**
2. **Advanced breast cancer**
3. **Prostate cancer**
4. **Bladder cancer**
5. **Others**

Paclitaxel

Adverse reactions:

- **The primary dose-limiting toxicities are nausea, vomiting, hypotension, arrhythmias, myelosuppression, peripheral sensory neuropathy.**
- **Hypersensitivity (5%), requires premedication with dexamethasone, diphenhydramine (H_1-blocker) and an H_2-blocker.**

Paclitaxel

- **An albumin-bound formulation used for breast cancer does not require premedication, with milder myelosuppression and reversible neurotoxicity.**

Ixabepilone

- **It is not a taxane, but it is a microtubule inhibitor.**
- **Used for metastatic breast cancer.**
- **Main adverse effects are hypersensitivity reactions, myelosuppression, neurotoxicity, with peripheral sensory neuropathy.**

Bevacizumab

- **The growth of both primary and metastatic tumors requires an intact vasculature.**
- **The vascular endothelial growth factor (VEGF) signaling pathway is an attractive target for chemotherapy.**
- **Bevacizumab is a recombinant humanized monoclonal antibody that targets all forms of VEGFs particularly VEGF-A.**

Bevacizumab

- **This antibody binds to and prevents VEGF-A from interacting with its receptor.**

Toxicity:

- **Hypertension**
- **Arterial thromboembolism (TIA, stroke, angina, & MI)**
- **Wound healing impairment**
- **GI perforations and proteinuria**

Trastuzumab

- **Is a recombinant, humanized monoclonal antibody that binds to human epidermal growth factor receptor (HER-2/neu), preventing the natural ligand from binding to the receptor, and it down regulates the receptor.**
- **Cause cardiotoxicity manifested as a reduced left ventricular ejection fraction**
- **It may be used in metastatic breast cancer in patients whose tumors overexpress HER-2/neu.**

Drugs for Prostate Cancer

Drugs for Prostate Cancer

- **The treatment of choice is elimination of testosterone production, either by surgical castration or hormonal therapy.**
- **Discussed before.**

Mitoxantrone

- **It is an anthracycline antibiotic.**
- **Act by intercalation with the DNA molecule, which in turn causes single- and double-stranded disruptions and suppresses DNA repair via inhibition of topoisomerase II.**
- **Used for advanced, hormone-refractory prostate cancer.**

Mitoxantrone

Toxicity:

1. **Myelosuppression, leukopenia, is the dose-limiting toxic effect.**
2. **Thrombocytopenia**
3. **Nausea and vomiting**
4. **Alopecia**
5. **Mucositis**
6. **A blue discoloration of fingernails, sclera, and urine is observed 1-2 days after drug administration.**

Drugs for Ovarian Cancer

Drugs for Ovarian Cancer

- Cisplatin, Carboplatin
- Cyclophosphamide
- Paclitaxel
- Topotecan
- Doxorubicin
- Altretamine

Platinum Analogs

Cisplatin, Carboplatin.

- **They exert their cytotoxic effects like the alkylating agents.**
- **They kill tumor cells in all stages of the cell cycle.**
- **Bind to DNA and form intra- and inter-strand cross-links, leading to inhibition of DNA synthesis and function.**

Cisplatin

Therapeutic uses:

1. **Breast cancer**
2. **Testicularcancer**
3. **Ovarian cancer**
4. **Bladder cancer**
5. **Others**

- **It is eliminated by the kidney and dose reduction is needed in renal dysfunction.**

Cisplatin

Toxicity:

1. **Nausea and vomiting**
2. **Nephrotoxicity**
3. **Peripheral sensory neuropathy**
4. **Ototoxicity**

- **Carboplatin is less toxic to the kidney, but its main dose-limiting toxicity is myelosuppression.**

Camptothecins

- They are natural products derived from a tree grown in China.
- They inhibit the activity of topoisomerase I, the key enzyme responsible for cutting and re-ligating single DNA strands.
- This results in DNA damage and cell death.

Topotecan

- **It is used for advanced ovarian cancer as second-line therapy following platinum-based chemotherapy.**
- **The dose should be adjusted in renal function.**
- **The main toxicities are nausea, vomiting and myelosuppression.**

Altretamine

- **It is an alkylating agent that forms DNA cross-links, resulting in inhibition of DNA synthesis and function.**

Toxicity:

- **Nausea and vomiting**
- **Myelosuppression**
- **Peripheral neuropathy**
- **Flu-like syndrome.**

Drugs for Testicular Cancer

Drugs for Testicular Cancer

- **Cisplatin**
- **Etoposide**
- **Bleomycin**
- **Ifosfamide (similar to cyclophosphamide).**

Etoposide

- **It is a semisynthetic derivative of podophyllotoxin, which is extracted from mayapple root.**
- **IV, and oral formulations are available.**
- **Dose reduction is needed in renal dysfunction.**
- **Teniposide is a related drug.**

Etoposide

- **They inhibit topoisomerase II, resulting in DNA damage through strand breakage induced by formation of a ternary complex of drug, DNA, and enzyme.**

Toxicity:

1. **Nausea, and vomiting,**
2. **Hypotension**
3. **Myelosuppression**
4. **Alopecia.**

Bleomycin

- **Anticancer antibiotic**
- **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.**

Bleomycin

- **It is a cell-cycle specific drug that arrest cells in the G_2 phase of the cell cycle.**
- **It is used also in squamous cell cancer of the cervix and vulva.**
- **Dose reduction is needed in renal dysfunction.**

Bleomycin

- **Dose-limiting toxicity is pulmonary in the form of pneumonitis, cough, dyspnea, dry inspiratory crackles, and chest infiltrates.**
- **This is more in patients:**

a) **older than 70 years of age**
b) **who receive a cumulative dose greater than 400 units**
c) **with underlying pulmonary disease**
d) **with prior chest radiation.**

Bleomycin

Other toxicities:

1. **Allergic reactions**
2. **Fever**
3. **Hypotension**
4. **Dermatotoxicity,**
5. **Alopecia,**
6. **Mucositis.**