Lecture 17 by Dr.Alaa Fadhil Alwan
Chemotherapeutic Agents

Antineoplastic drugs are classified according to their mode of action and the phase of the cell cycle in which the drug is active. This classification is not absolute; it is likely that more than one mechanism is involved. Multiple intracellular sites might be implicated and not confined to specific cycle events. However, it is always the rapidly dividing cells that are most sensitive to these drugs. Chemotherapeutic drugs that are most effective during a particular phase of the cycle are known as *cell cycle–specific drugs*.

CELL CYCLE–SPECIFIC AGENTS: ANTIMETABOLITES, VINCA ALKALOIDS, EPIPODOPHYLLOTOXINS, TAXANES

1. **Antimetabolites**

Antimetabolites are synthetically formulated to mimic the naturally produced Metabolites, purines, pyrimidines, or folates essential for the synthesis of nucleic acids and DNA. This results in cell death. They exert their effects during the S phase of the cell life cycle and are most effective against tumors that have a high growth fraction. Example of chemotherapy with major side effect

Cytosine arabinoside: Myelosuppression, neurotoxicity (at higher doses and in older patients' severe cerebellar syndrome, other neurologic disturbances
Deoxycoformycin: Myelosuppression, infection, nausea, hepatic and renal toxicity, rash
6-Mercaptopurine: Nausea, myelosuppression, liver toxicity (cholestasis), fever, skin rash
Methotrexate: Myelosuppression, severe mucositis (dose dependent), skin rash, acute encephalopathy, arachnoiditis with intrathecal administration
Fludarabine: Myelosuppression, neurotoxicity (encephalopathy at high doses), protracted immunosuppression, fatigue, and somnolence
Thioguanine: Myelosuppression, some nausea, diarrhea, cholestasis

2. Mitotic Inhibitors

Mitotic inhibitors interfere with the formation of the mitotic spindle, causing Metaphase arrest. They are primarily known as M-phase active. These drugs are the vinca alkaloids, and the epipodophyllotoxins.
asters.

3. VINCA ALKALOIDS

Vinblastine neurotoxicity
Vincristine
Vindesine
Vinorelbine

EPIPODOPHYLLOTOXINS

Etoposide Bone marrow depression
Teniposide

CELL CYCLE–NONSPECIFIC AGENTS: ALKYLATING AGENTS, NITROSOUREAS, ANTITUMOR ANTIBIOTICS, HORMONES, HORMONE ANTAGONISTS

Antineoplastic agents that are effective through all phases of the cell cycle and are not limited to a specific phase are called *cell cycle–nonspecific drugs*. These drugs directly affect the DNA molecule and display no specificity for cells that are dividing. They are considered more toxic than their cell cycle–

specific counterparts because their destructive action does not differentiate between normal and malignant cycling cells. Their toxicities are felt throughout the cell cycle. Non-specific agents are given in bolus doses because they cause death independently of the proliferative state of the cell. These agents also reduce the number of cells that make up a tumor, which is known as the *tumor burden*.

1. Alkylating Agents

Alkylating agents alter DNA structure through the poorly understood process of alkylation (H^+ ion alkyl substitution), which results in cross-linking and strand breaking of DNA and destruction of its template. Destruction of the DNA genetic template terminates replication of the information needed for cellular division and leads to cell lysis. The alkylating agents are described as *radiomimetic* because they mimic the actions of radiation therapy on the cells. The alkylating agents are as follows:

Busulfan: Severe pancytopenia, skin hyperpigmentation
Carboplatin: BM suppression
Melphalan: stem cell injury
Chlorambucil: Leukopenia
Cisplatin: Severe nausea/vomiting
Cyclophosphamide and Ifosfamide : hemorrhagic cystitis
Dacarbazine: Severe nausea/vomiting

2. Nitrosoureas

Nitrosoureas are alkylating agents that also destroy DNA so that synthesis can no longer occur, but they are unique in that they are lipid-soluble and cross the blood–brain barrier into the central nervous system. The nitrosoureas are:
Carmustine and Lomustine: Prolonged myelosuppression, cumulative lung toxicity

3. Antitumor Antibiotics

Most *antitumor antibiotics* are isolated from fermented broths of various *Streptomyces* bacteria. The focal point of their cytotoxicity is the DNA. These drugs interfere with DNA-directed RNA synthesis by intercalating between the base pairs of DNA and generating toxic oxygen-free radicals, causing single- or double-stranded DNA breaks. The antitumor antibiotics are as follows:

Dactinomycin
Mitomycin-C
Daunorubicin — all these cause cardiotoxicity
Mitoxantrone
Doxorubicin
Idarubicin

Hormones and Hormone Antagonists

Hormones and *hormone antagonists* (*antihormones*) are a diverse group of drugs that are beneficial in cancer therapy. Some hormones alter the cellular environment and affect the permeability of the cell membrane in ways that will affect cell growth. These drugs, which are hormonal or hormone-like agents,

inhibit tumor proliferation by blocking or antagonizing the naturally occurring substance that stimulates tumor growth.

Androgens: testosterone proprionate, methyltestosterone,
Antiandrogens: flutamide
Antiestrogens: tamoxifen
Aromatase inhibitors: aminoglutethimide
Estrogens: diethylstilbestrol, estradiol
Glucocorticoids: prednisone, hydrocortisone, dexamethasone
Gonadotropin inhibitors: leuprolide, goserelin
Progestins: megestrol acetate

MISCELLANEOUS AGENTS

Bleomycin: Pulmonary toxicity
Hydroxyurea: mild myelosuppression; some gastrointestinal toxicity; pigmentation
L-asparaginase: Hypersensitivity, fever, bronchospasm, hyperglycemia
Procarbazine: Myelosuppression

Imatinib (Gleevec)
ROUTE OF ADMINISTRATION: Oral
DRUG CLASS: Tyrosine kinase inhibitor
MECHANISM OF ACTION: Inhibition of BCR-ABL tyrosine kinase induces apoptosis
INDICATIONS: CML, gastrointestinal stromal tumors (GIST)
SIDE EFFECTS: Nausea/vomiting/diarrhea, fluid retention, muscle cramps, hemorrhage, musculoskeletal pain, skin rash, headache, fatigue.

Thalidomide (Thalomid)
ROUTE OF ADMINISTRATION: Oral
DRUG CLASS: Immunomodulatory agent
MECHANISM OF ACTION: Suppress excess tumor necrosis factor-〈 and vascular endothelial growth factor-inhibiting angiogenesis.
INDICATIONS: Multiple myeloma, myelodysplastic syndrome
SIDE EFFECTS: Somnolence, rash, headache, neutropenia
COMMENT: Because of teratogenic risk, patient must be registered in distribution monitoring program.

Rituximab (Rituxan)
ROUTE OF ADMINISTRATION: Intravenous injection
DRUG CLASS: Monoclonal antibody
MECHANISM OF ACTION: Antibody directed against CD20 antigen, which arrests Cell cycle initiation, compliment dependent cytotoxicity.
INDICATIONS: Refractory B-cell lymphoma, CD20-positive NHLs
SIDE EFFECTS: Headache, chills, rigors, nausea, hypotension, rash

Tretinoin (Vesanoid, all-trans retinoic acid, ATRA)
ROUTE OF ADMINISTRATION: Oral

DRUG CLASS: Vitamin A derivative
MECHANISM OF ACTION: Inhibits clonal proliferation and/or granulocyte differentiation
INDICATIONS: APL
SIDE EFFECTS: Arrhythmia, hypotension, peripheral edema, headache, fever, rash, Nausea/vomiting, abdominal pain, retinoic acid syndrome, myelosuppression, diaphoresis

Bortizomib (Velcade)
ROUTE OF ADMINISTRATION: Intravenous injection
DRUG CLASS: Proteasome inhibitor
MECHANISM OF ACTION: Reversibly inhibits chymotrypsin-like activity at the 26S proteasome leading to cell-cycle arrest and apoptosis.
INDICATIONS: Multiple myeloma patients who have received at least one prior therapy
SIDE EFFECTS: constipation, peripheral neuropathy