Wednesday October 6, 2021
08:00-10:00 am
Pharmacology Lecture - By Mr. Kasujja Henry, Medicare – "Department of Pharmacology".

Drugs: Anticancer Agents and COX2 Inhibitors

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Learning Objectives

1. To understand the role of chemotherapy in the treatment of cancer
2. To know the major classes of chemotherapeutic drugs and their mechanisms of action
3. To know the novel molecular targeting anticancer drugs in clinical uses
4. To understand the role of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) in chemoprevention of colon cancer
5. To know the common side effects and resistance mechanisms of chemotherapeutic drugs and NSAIDs

Background Reading

Goodman & Gilman's *Pharmacological Basis of Therapeutics*, 11th Edition: Chapter 51 and Chapter 26.

Lecture Outline

Role of chemotherapy in the treatment of cancer

- Used alone with curative intent (~5%): e.g. Testicular cancer
- Used as a component of multi-modality therapy with curative intent (~25%):
  Neoadjuvant chemotherapy is used before surgery, e.g. osteosarcoma. Adjuvant chemotherapy is used after surgery, e.g. colon cancer.
  Concurrent chemoradiotherapy is used concurrently with radiation, e.g. lung and head/neck cancers.
- Used to prolong life and/or to palliate symptoms (~70%): A majority of anticancer drugs are being used to prolong life and relieve symptoms of cancers which are not curable, such as solid tumors of the lung, prostate, breast and colon.

The treatment of most cancer patients requires a skillful interdigitation of multiple forms of treatment, including surgery, irradiation and

chemotherapy. Each of these forms of treatment carries its own risks and benefits.

Characteristics of chemotherapeutic drugs

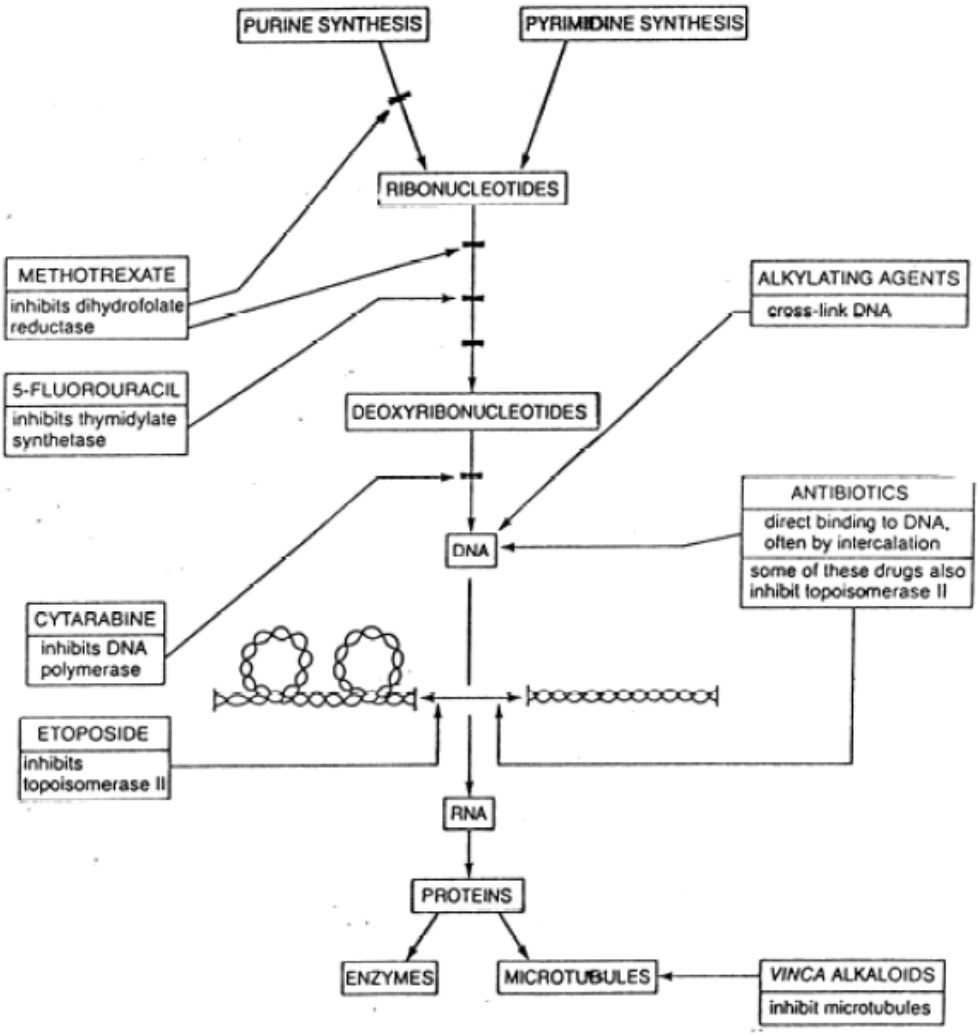
- Most anticancer drugs are cytotoxic agents that inhibit the synthesis of new genetic material or cause irreparable damage to DNA itself.
- Anticancer drugs often have a narrower therapeutic index and a greater potential for causing harmful side effects than other drugs.
- Anticancer Drugs are most effective when used in combination.
- Most of the side effects of anticancer drugs are manageable.

Development of anticancer drugs

- Traditionally, cancer drugs were discovered through large-scale testing of synthetic chemicals and natural products against animal tumor systems.
- In recent years, a number of new drugs have been discovered that inhibit novel molecular targets that play an important role in tumor development.

Definitions of Phase I, Phase II and Phase III clinical trials:
Phase I: To define the maximal tolerated dose and pharmacokinetics of a new anticancer drug.
Phase II: To test the efficacy and side effects of a new anticancer drug or a new combined anticancer regimen in patients with a specific tumor type.
Phase III: To compare a new drug or regimen with a standard therapy in patients with a specific tumor type.

Mechanisms of action of anticancer drugs: An overview


PURINE SYNTHESIS
PYRIMIDINE SYNTHESIS
RIBONUCLEOTIDES
METHOTREXATE
inhibits dihydrofolate reductase
ALKYLATING AGENTS
cross-link DNA
5-FLUOROURACIL
inhibits thymidylate synthetase
DEOXYRIBONUCLEOTIDES
ANTIBIOTICS
direct binding to DNA, often by intercalation
some of these drugs also inhibit topoisomerase II
DNA
CYTARABINE
inhibits DNA polymerase
ETOPOSIDE
inhibits topoisomerase II
RNA
PROTEINS
ENZYMES
MICROTUBULES
VINCA ALKALOIDS
inhibit microtubules

Major classes of chemotherapeutic drugs

a. Alkylating agents:
Mechanism of action: cross-link 2 strands of DNA leading to impairment of DNA replication and RNA transcription.

Examples:
cyclophosphamide: creates guanine adducts that block cell proliferation.
cisplatin and its analogues: form DNA adducts and creates inter or intrastrand crosslinks that disrupt DNA synthesis.

b. Anti-metabolites: analogues of normal metabolites
Mechanism of action: incorporated into DNA or RNA, resulting in abnormal nucleic acids and inhibition of enzymes involved in nucleotide biosynthesis.

Examples:
Methotrexate: a folate analog inhibits dihydrofolate reductase (DHFR), the enzyme essential for nucleic acid synthesis.
5-fluorouracil (5-FU): a pyrimidine analog that inhibits thymidylate synthase and also interferes with RNA synthesis and function.

c. Antibiotics: Bacterial or fungal derivatives
Mechanism of action: interfere with cellular processes such as DNA or protein synthesis.

Examples:
Doxorubicin: Fungal anthracycline that intercalates within the DNA, causes single and double strand breaks, and inhibits topoisomerase II.
Mitomycin C: binds to DNA and form cross-links and DNA adducts.

d. Antimitotics:
Mechanism of action: interfere with microtubule synthesis and degradation, leading to inhibition of cell division.

Examples:
Paclitaxel (Taxol): stabilizes microtubules, inhibit the cell cycle during mitosis.

e. Hormones and antagonists

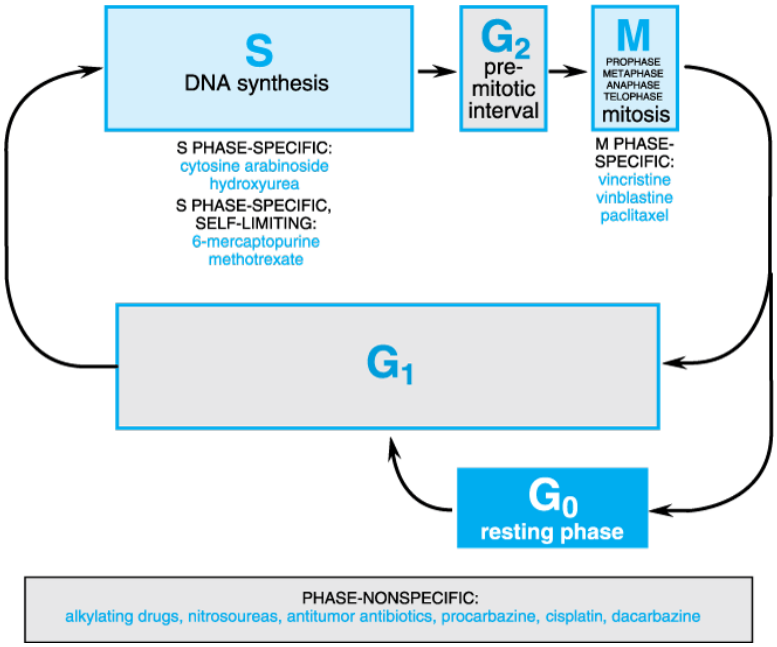
Mechanism of action: inhibits synthesis or effects of the steroid hormones that are necessary for growth of certain tumors, such as breast tumors.

Examples:
Tamoxifen: binds to estrogen receptors (ER) as an antagonist of estrogen.

Cell cycle and action of chemotherapeutic drugs

Many chemotherapeutic drugs inhibit progression of cell cycle. An understanding of cell cycle kinetics is essential for the proper use of anticancer drugs. The cell division cycle is the fundamental mechanism to maintain tissue homeostasis. The cell cycle can be divided into 4 phases (1) G1: a phase that precedes DNA synthesis; (2) S: a DNA synthesis phase; (3) G2: an interval following the termination of DNA synthesis; and (4) M: the mitotic phase in which the cell, containing a double complement of DNA, divides into two daughter G1 cells. Each of these daughter cells may immediately re-enter the cell cycle or pass into a nonproliferative stage, referred to as G_0.

Chemotherapeutic drugs can be divided into three classes based on their relationship with cell cycle: 1. Cell cycle active, phase specific; 2. Cell cycle active, phase non-specific; 3. Non-cell cycle active: e.g. hormones.



Cellular response to DNA damage

Many chemotherapeutic drugs directly or indirectly cause DNA damage, which can be repaired by DNA repair machinery, or triggers cellular response to DNA damage. DNA damage is initially sensed by ATM and

other kinases, which stabilize the p53 tumor suppressor. p53 in turn activates inhibitors of cell cycle progression, such as p21, leading to cell cycle arrest at G1 or G2 phases. p53 can also activate Bcl-2 family proteins to cause programmed cell death, or apoptosis, in cancer cells.

Molecular targeted therapy: Anticancer therapy beyond cytotoxic drugs

Therapy that targets aberrant molecules or pathways which are critical for tumor growth

Examples:
Imatinib mesylate (Gleevec): inhibits the Bcr-Abl tyrosine kinase that is activated in chronic myelogenous leukemia (CML); used for treatment of CML.
Gefitinib (Iressa) and *Erlotinib* (Tarceva): inhibit the intracellular tyrosine kinase domain of EGFR; used for treatment of non-small cell lung cancer refractory to standard chemotherapy.
Bevacizumab (Avastin): An antibody that inhibits new blood vessel formation in tumor cells (angiogenesis); used for the treatment of colon cancer.

Common toxicities of chemotherapeutic drugs

Organs with active cell division are typically affected by most anticancer drugs, for examples, bone marrow, mucosa of GI tract and hair follicles.

- Bone marrow: most anticancer drugs
- Gastrointestinal: e.g. cisplatin and 5-FU
- Alopecia: e.g. paclitaxel
- Renal: e.g. cisplatin.
- Pulmonary: e.g. bleomycin
- Peripheral neuropathy: e.g. cisplatin, paclitaxel
- Long-term complications: cardiomyopathy, leukemia and infertility

Principles for choice of anticancer drugs

- Histology and stage of cancer: Histologic diagnosis is mandatory, and staging is essential for therapeutic choice and prognosis.
- Patient status: Patients should have acceptable performance status and organ functions.

- Combined chemotherapy is the choice: Preferably each drug is active against the cancer; each drug has a different mechanism of action, a different mechanism of resistance, and non-overlapping toxicities.

Resistance to chemotherapeutic drugs

Tumor host resistance

Changes in the tumor
- Location of tumor cells
- Effect of tumor size
- Growth Characteristics

Changes in the Host
- Altered absorption, distribution or excretion of a drug so that less reaches the tumor
- Increased synthesis of enzymes from non-malignant cells which inactivate the drug
- Increased sensitivity of normal tissues to the effect of a drug

Cellular resistance

- Natural Drug Resistance – lack of sensitivity of a tumor cell to drugs prior to therapy
- Acquired Drug Resistance – genotypic and phenotypic changes during therapy that render a tumor cell insensitive to the lethal effects of a drug

Mechanisms of acquired drug resistance
- Defects in drug transporting and drug metabolizing enzymes
- Increased drug inactivation and amplification of drug targeting enzymes
- Multidrug or pleotropic resistance: Tumor cells exposed to a single drug develop cross-resistance to other drugs. Mechanisms include overexpression of P-glycoprotein, the protein product of MDR1 gene and defective apoptosis regulation.

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs represent a large class of chemically heterogeneous, antiinflammatory, analgesic, and antipyretic drugs. NSAIDs inhibit cyclooxygenese (COX) enzymes, which catalyze synthesis of prostaglandins (PGs) from arachadonic acid (AA). There are two types of COX enzymes:

- COX-1: constitutively expressed, involved in GI protection and platelet aggregation.

- COX-2: inducible and involved in inflammation.

Traditional NSAIDS, such as sulindac, indomethacin and aspirin, are nonselective COX inhibitors that inhibit both COX-1 and COX-2. COX-2 selective inhibitors, such as celecoxib (Celebrex) and rofecoxib (Viaax), can selectively inhibit COX-2.

NSAIDs can be classified on the basis of their chemical structure:

- Salicylates (Aspirin)
- Acetic Acid Derivatives (Sulindac)
- Propionic Acid Derivatives (ibuprofen)
- Fenamates (meclofenamate)
- Enolic acids (piroxicam)

NSAIDs in chemoprevention of colon cancer

Chemoprevention refers to the use of pharmacologic or natural agents to inhibit or even reverse of the process of cancer development. An ideal chemopreventive agent should intervene early in the process of cancer development before premalignant cells become malignant.

NSAIDs as chemopreventive agents:

- Epidemiological studies suggested that frequent use of aspirin is associated with as much as a 50% decrease in the risk of colon cancer.
- NSAIDs have been used in patients with familial adenomatous polyposis (FAP). In clinical trials, NSAIDs reduce the size and number of colon ploops in FAP patients (Sulindac, Aspirin, Celebrex).
- In animal studies, NSAIDs also reduce the size and number of ploops in *APC*$^{+/min}$ mice, which is an animal model of FAP (Sulindac, Aspirin, Indomethacin, Celebrex).

Mechanisms of NSAID-mediated chemoprevention

- Inhibition of COX-2
  COX-2 is often overexpressed in tumors. COX-2 expression leads to activation of antiapoptotic proteins.
- Induction of apoptosis
  Apoptosis is a major mechanism regulating turnover of intestinal epithelial cells from which colon tumors are derived. NSAIDs have been found to induce apoptosis in adenomas from FAP patients. The resistance to NSAIDs such as sulindac can be caused by defects in apoptosis regulation.

Toxicities of NSAIDs

- Gastrointestinal
  Traditional NSAIDs cause GI bleeding. The inhibition of COX-2 mediates, in large part, the antipyretic, analgesic, and antiinflammatory actions of NSAIDs, while the simultaneous inhibition of COX-1 largely accounts for unwanted adverse effects in the gastrointestinal tract.
- Cardiovascular
  It has been found that long-term use of selective COX-2 inhibitors, such as Viaax and Celebrex, causes increase in cardiovascular risk.
- Other toxicities: Hepatic, hematologic, CNS and renal