Drugs for Leukemias and Lymphomas

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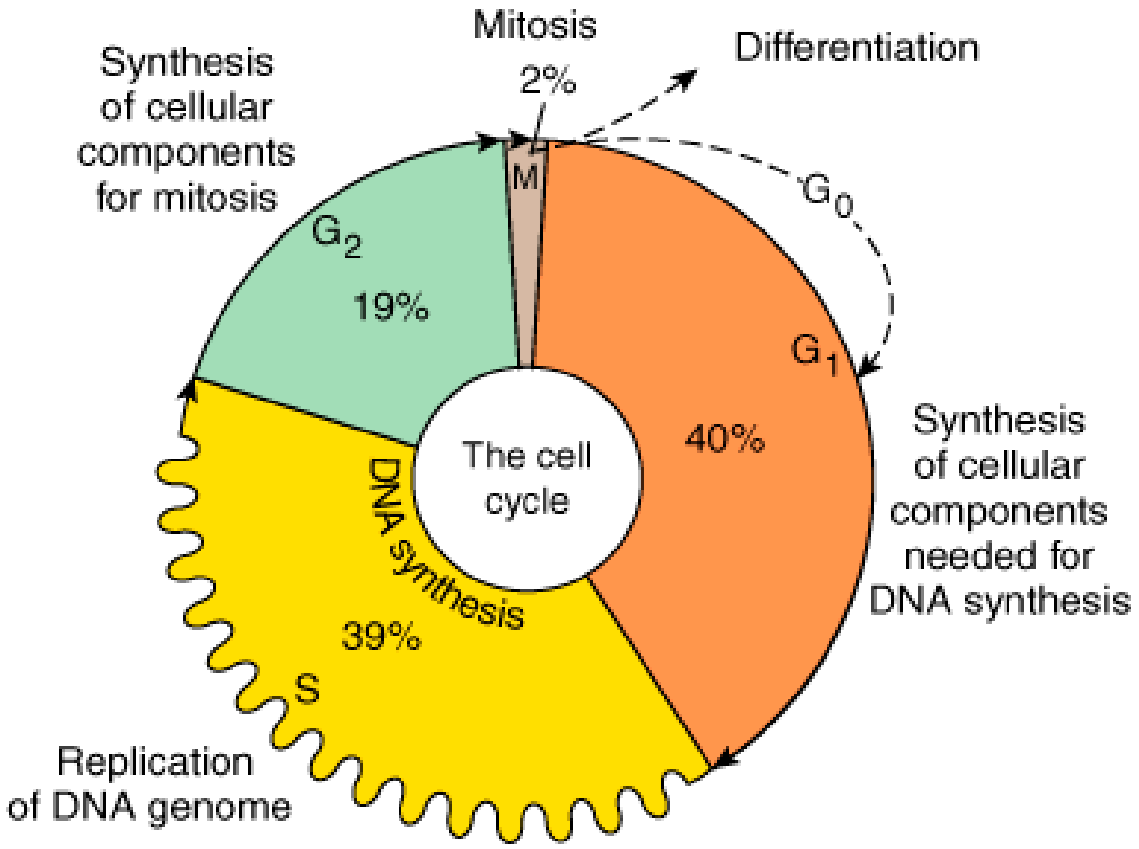

The cell cycle and cancer. A conceptual depiction of the cell cycle phases that all cells—normal and neoplastic—must traverse before and during cell division. The percentages given represent the approximate percentage of time spent in each phase by a typical malignant cell; the duration of G1, however, can vary markedly. Many of the effective anticancer drugs exert their action on cells traversing the cell cycle and are called cell cycle–specific (CCS) drugs. A second group of agents called cell cycle–nonspecific (CCNS) drugs can sterilize tumor cells whether they are cycling or resting in the G0 compartment. CCNS drugs can kill both G0 and cycling cells (although cycling cells are more sensitive).

Alkylating Agents

Examples: Cyclophosphamide and Chlorambucil.

Mechanism of Action:

- **Alkylation of DNA is the major interaction that leads to cell death.**
- **The major site of alkylation within DNA is the N^7 position of guanine.**
- **These interactions can occur on a single strand, or both strands of DNA through cross-linking.**

Alkylating Agents

Alkylation of guanine can result in:

1. Miscoding through abnormal base-pairing with thymine.

2. Depurination, by excision of guanine residues leading to DNA strand breakage.

3. Cross-linking is of major importance to the cytotoxic action, and replicating cells are most susceptible.

Alkylating Agents

Resistance to treatment occurs by:

1. **Increased capability to repair DNA lesions.**
2. **Decreased transport of drugs into the cell.**
3. **Increased production of glutathione.**
4. **Increased glutathione-S-transferase activity.**

Alkylating Agents

- **Cyclophosphamide is inactive and needs activation by microsomal enzymes to 4-hydroxycyclophosphamide and aldophosphamide.**

Alkylating Agents

Adverse Effects

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

1. **Nausea and vomiting can be serious.**
2. **Alopecia.**
3. **Carcinogenesis.**

Alkylating Agents

4. **Bone marrow depression: leukopenia and thrombocytopenia, and bleeding.**
5. **Direct vesicant effects and can damage tissues at site of injection.**

- **Hemorrhagic cystitis occurs with cyclophosphamide, and can be prevented by adequate hydration.**

Nonclassic Alkylating Agents

Procarbazine (PO) and Dacarbazine (Parenteral)

- **Inhibit DNA, RNA, and protein synthesis.**
- **Prolong interphase.**
- **Produce chromosome breaks, and DNA strand scission.**
- **Carcinogenic potential is higher than that of other alkylating agents.**

Nonclassic Alkylating Agents

Adverse effects:

- **Carcinogenesis– acute leukemia.**
- **Myelosuppression.**
- **Nausea and vomiting can be severe.**
- **Potent vesicants.**
- **CNS toxicity: neuropathy, ataxia, lethargy, and confusion.**

Antimetabolites

Methotrexate (MTX):

- **It is a folic acid analog that inhibits dihydrofolate reductase, interfering with the synthesis of tetrahydrofolate.**
- **THF serves as the key one-carbon carrier in the synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine.**
- **Thus, it interferes with the formation of DNA, RNA and key cellular proteins.**

Antimetabolites

- **Intracellular formation of polyglutamate metabolites, with the addition of up to 5-7 glutamate residues, is critically important for the therapeutic action of MTX.**
- **This process is catalyzed by folylpolyglutamate synthase.**
- **MTX polyglutamates are selectively retained within cancer cells.**

Antimetabolites

Resistance develops 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, dihydrofolate reductase, through gene amplification.**

Antimetabolites

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

Antimetabolites

- MTX is administered by oral, intravenous, and intrathecal routes.
- Oral bioavailability is saturable and erratic at doses greater than 26 mg/m^2.
- Mainly eliminated by the kidney through glomerular filtration and active tubular secretion, thus dose reduction is needed in renal dysfunction.
- Its renal excretion is inhibited by aspirin, other NSAIDs, penicillins, and cephalosporins.

Antimetabolites

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

Antimetabolites

Adverse effects:

- **Mucositis, diarrhea**
- **Myelosuppression (neutropenia and thrombocytopenia).**

Antimetabolites

Cytarabine (Ara-C):

- **It is an S phase specific antimetabolite that is converted by deoxycytidine kinase to the 5'-mononucleotide (ara-CMP).**
- **ara-CMP is further metabolized to the di- and tri-phosphate metabolites (ara-CTP).**
- **ara-CTP may be the main cytotoxic metabolite.**

Antimetabolites

- **It competitively inhibits DNA polymerase-α and DNA polymerase-β, thereby blocking DNA synthesis and DNA repair, respectively.**
- **It is also incorporated into DNA (and RNA) which interferes with chain elongation and defective ligation of fragments of newly synthesized DNA.**

Antimetabolites

- **Given by IV infusion over 5-7 days.**

Adverse effects:

- **Myelosuppression (neutopenia and thrombocytopenia)**
- **Mucositis, nausea and vomiting**
- **Neurotoxicity (cerebellar ataxia).**

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.**

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.**
- **The hydroxylated metabolites are active while the aglycone is not.**

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, or 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, conduction abnormalities, pericarditis and myocarditis.**

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.**

Platinum Analogs

Carboplatin:

- **It kills tumor cells in all stages of the cell cycle.**
- **It binds DNA through the formation of intrastrand and interstrand cross-links, thereby leading to inhibition of DNA synthesis and function.**
- **The primary binding site is the N7 position of guanine.**

Platinum Analogs

Adverse effects:

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

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.**