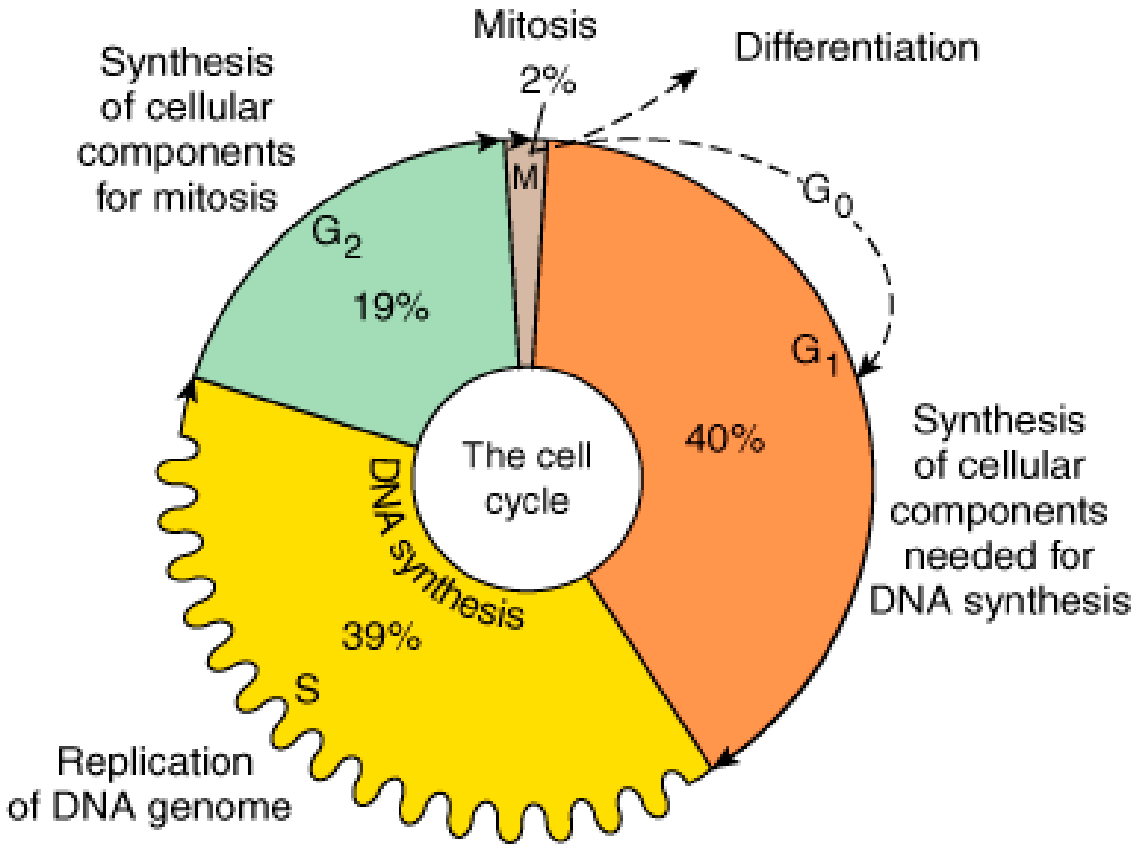
Drugs for Leukemias and Lymphomas

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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 G_1, 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 G_0**
- **compartment. CCNS drugs can kill both G_0 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

- **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 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:

1. **Carcinogenesis– acute leukemia.**
2. **Myelosuppression.**
3. **Nausea and vomiting can be severe.**
4. **Alopecia**
5. **Potent vesicants.**
6. **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

- **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:

1. **Mucositis, diarrhea**
2. **Myelosuppression (neutropenia anemia, and thrombocytopenia).**
3. **Infection**
4. **Alopecia**
5. **Nausea, vomiting, loss of appetite**
6. **Stomatitis**

Antimetabolites

7. Fatigue and headaches
8. Skin sensitivity to bright sunlight
9. Liver toxicity
10. Pulmonary toxicity
11. Edema of renal origin
12. Severe allergic reactions

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

Antimetabolites

Adverse effects:

1. **Myelosuppression (neutropenia, anemia and thrombocytopenia)**
2. **Mucositis, nausea and vomiting, diarrhea, abdominal pain, Loss of appetite**
3. **Hepatic dysfunction**
4. **Ocular toxicity**
5. **Pulmonary toxicity**

Antimetabolites

6. **Cardiomyopathy**
7. **Alopecia, dermatitis**
8. **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 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.**
- **Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA.**

Natural Products

- **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, mucositis, alopecia, myelosuppression, infection and bleeding.**

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.**

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

Adverse effects:

- Nausea and vomiting, abdominal pain
- Fluid retention with ankle or periorbital edema, diarrhea, and congestive heart failure
- Myalgias, joint pain
- Increased sensitivity to sunlight

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 therapy.**
- **It depletes leukemic and normal cells by direct antibody-dependent lysis.**

Adverse effects: 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.**