Cancer Chemotherapy

Azadeh Mesripour (Pharm.D, Ph.D)
MUI.Pharm
2015
Theory of Chemotherapy

For the case of Chemotherapy bacteria, fungi, protozoa, helminths, viruses and cancer cell are considered parasites.

Find Qualitative (preferable) or Quantitative Biochemical difference between Host and Parasite which when exploited by a selective drug results in a cytotoxic effect to the parasite but not host.

Paul Ehrlich 1854-1915
Nobel Laureate 1908
1940’s – Successful use alkylating agent nitrogen mustard to treat human cancer.

1950-1960’s – major alkylating agents and anti-metabolites currently in use synthesized. Effective against wide range of cancer types, particularly rapidly growing leukemias and lymphomas.

Scientific principles of cancer chemotherapy developed.
Pathogenesis of cancer

Chemicals, viruses, irradiation, etc

Acquired Mutations

Protooncogenes $\rightarrow$ oncogenes (bcl2, ...)

$\downarrow$ expression of tumor suppressor genes (P53, ...)

Inherited Mutations

Promoters, co-carcinogen, hormones

Uncontrolled cell proliferation, dedifferentiation

$\downarrow$ apoptosis, alterations in telomerase

Development of primary tumor
Pathogenesis of cancer

Development of primary tumor

Production of metalloproteinases

Invasion of nearby tissue by tumor cells

Angiogenesis

Metastasis

Development of secondary tumors
Cancer

Definition:
Cancer* is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems, this process is called metastasis.

Categorized based on the functions/locations of the cells from which they originate:

1. **Carcinoma** - skin or in tissues that line or cover internal organs. E.g., Epithelial cells. 80-90% reported cancer cases are carcinomas.
2. **Sarcoma** - bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
3. **Leukemia** - White blood cells and their precursor cells such as the bone marrow cells, causes large numbers of abnormal blood cells to be produced and enter the blood.
4. **Lymphoma** - cells of the immune system that affects lymphatic system.
5. **Myeloma** – malignant tumor of bone marrow.
6. **CNS cancers** - cancers that begin in the tissues of the brain and spinal cord.

(*National Cancer Institute, NCI)
1. **Surgery**

   30% of patients without metastasis respond to surgery and radiation.

   If diagnosed at early stage, close to 50% cancer could be cured.

2. **Radiation**

3. **Chemotherapy**

   Patients will undergo chemotherapy to remove micrometastasis. However, chemotherapy is able to cure only about 10-15% of all cancer patients.
New types of cancer treatment

**Hormonal Treatments:** These drugs are designed to prevent cancer cell growth by preventing the cells from receiving signals necessary for their continued growth and division. E.g., Breast cancer – tamoxifen after surgery and radiation

**Specific Inhibitors:** Drugs targeting specific proteins and processes that are limited primarily to cancer cells or that are much more prevalent in cancer cells.

**Antibodies:** The antibodies used in the treatment of cancer have been manufactured for use as drugs. E.g., Herceptin, avastin

**Biological Response Modifiers:** The use of naturally occurring, normal proteins to stimulate the body's own defenses against cancer. E.g., Abciximab, rituximab

**Vaccines:** Stimulate the body's defenses against cancer. Vaccines usually contain proteins found on or produced by cancer cells. By administering these proteins, the treatment aims to increase the response of the body against the cancer cells.
Targeted therapy

- Ligand-targeted Therapy
- Therapeutic Antibodies ± Toxins
- Metalloproteinase Inhibitors
- Tumor Antigens
- Growth Factor Receptors
- Immunotherapy
- Cancer Cell
- Intracellular Signaling Molecules
- Apoptosis Agonists
- Antisense
- m-RNA
- Angiogenesis Inhibitors (Angiostatin, Endostatin, Avastin)
- Tyrosine Kinase Inhibitors (Glivec, Gefitinib)
Cancer Chemotherapy (Background)

A. Most of the recent progress using antineoplastic therapy is based on:

1. Development of *new combination therapy* of using existing drugs.
2. Better understanding of the mechanisms of antitumor activity.
3. Development of chemotherapeutic approaches to *destroying micrometastases*
4. Understanding the molecular mechanisms concerning the initiation of tumor growth and metastasis.
5. Recognition of the *heterogeneity* of tumors
B. Recently developed principles which have helped guide the treatment of neoplastic disease

1. A single clonogenic cell can produce enough progeny to kill the host.
2. The cytotoxic effects of anti-cancer drugs follow logcell-kill kinetics.
   ➢ A given agent would be predicted to kill a constant fraction of cells as opposed to a constant number.
3. The cardinal rule of chemotherapy— the inverse relation between cell number and curability—was established with this model
c. Malignancies which respond favorably to chemotherapy:

1. Acute leukemia,
2. Hodgkin's disease,
3. Testicular carcinoma,
4. Lymphoma
5. Rhabdomyosarcoma.

D. Antineoplastic drugs are most effective against rapidly dividing tumor cells.
The Main Goal of Antineoplastic Agents

Is to eliminate the cancer cells without affecting normal tissues (the concept of differential sensitivity). In reality, all cytotoxic drugs affect normal tissues as well as malignancies - aim for a favorable therapeutic index.

\[
\text{Therapeutic Index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}
\]

A therapeutic index is the lethal dose of a drug for 50% of the population (\(\text{LD}_{50}\)) divided by the minimum effective dose for 50% of the population (\(\text{ED}_{50}\)).
The effects of tumor burden, scheduling, dosing, and initiation/duration of treatment on patient survival.

- Infrequent scheduling of treatment courses.
  - Prolongs survival but does not cure.

  - Kill rate > growth rate.

- Early surgical removal of the primary tumor decreases the tumor burden. Chemotherapy will remove persistent secondary tumors.

Untreated patients
Chemotherapy

Cancer chemotherapy may be

• Primary
• Adjuvant
• Neoadjuvant
• Palliative
• **Primary chemotherapy** refers to chemotherapy administered as the primary treatment in patients who present with advanced cancer for which no alternative treatment exists.
General rules of chemotherapy

• **Adjuvant therapy**: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

• **Neoadjuvant therapy**: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy.
The Role of Drug Combinations

The use of combination chemotherapy is important for several reasons:

• First, it provides maximal cell kill within the range of toxicity tolerated by the host.

• Second, it provides a broader range of interaction between drugs and tumor cells.

• Finally, it may prevent or slow the subsequent development of cellular drug resistance.
The Role of Drug Combinations

Certain principles have guided the selection of drugs:

- Efficacy
- Toxicity
- Optimum scheduling
- Mechanism of interaction
- Avoidance of arbitrary dose changes
Dosage Factors

At present, there are 3 main approaches to dose-intense delivery of chemotherapy.

• **Dose escalation** whereby the doses of the anticancer agents are increased.

• Administer anticancer agents in a dose-intense manner by **reducing the interval** between treatment cycles,

• **Sequential scheduling** of either single agents or of combination regimens.
Drug Resistance

• Some tumor types, eg, malignant melanoma, renal cell cancer, and brain cancer, exhibit **primary resistance**.

✓ For example, mutations in the *p53* tumor suppressor gene occur in at least 50% of all human tumors.

• **Acquired resistance** develops in response to exposure to a given anticancer agent.

• A **multidrug-resistant** phenotype occurs, associated with increased expression of the *MDR1* gene, which encodes a cell surface transporter glycoprotein (**P-glycoprotein**)
• **Supportive therapy:**
  - Antiemetics (5-HT\textsubscript{3} -antagonists)
  - Antibiotic prophylaxis and therapy (febrile neutropenia)
  - Prophylaxis of urate nephropathy (allopurinol)
  - Enteral and parenteral nutrition
  - Pain – analgesic drugs
  - Psychological support
Chemotherapy: classification based on the mechanism of action

- **Topoisomerase Inh.**
  - DNA
- **Alkylation agents**
- **Purines and Pyrimidines**
- **Antimetabolites**
- **Asparaginase**
- **Protein tubulin**
- **Tubulin binders**
Classification of Antineoplastic agents

I. Cytotoxic drugs (directly act on cells)
   a) Alkylating agents
      i. Nitrogen mustards
      ii. Nitrosoureas
   b) Antimetabolites (act on metabolic pathway involved in DNA synthesis)
      i. Folate antagonist
      ii. Purine antagonist
      iii. Pyrimidine antagonist
   c) Plant derivatives
      i. Vinca alkaloids
      ii. Taxanes
      iii. Epipodophyllotoxin
   d) Antibiotics
II. Hormones (mainly steroids which suppress hormone secretion or antagonize hormone action)
   a) Glucocorticoids  
   b) Estrogen  
   c) Progestins  
   d) Antiandrogens

III. Miscellaneous (include Hydroxyurea, Cisplatin, Monoclonal antibodies and L.Asparaginase)
<table>
<thead>
<tr>
<th>Cell Cycle-Specific (CCS) Agents</th>
<th>Cell Cycle-Nonspecific (CCNS) Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimetabolites (S phase)</strong></td>
<td><strong>Alkylating agents</strong></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Altretamine</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Bendamustine</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Busulfan</td>
</tr>
<tr>
<td>Cytarabine (ara-C)</td>
<td>Carmustine</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>5-Fluorouracil (5-FU)</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>6-Mercaptopurine (6-MP)</td>
<td>Lomustine</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Mechlorethamine</td>
</tr>
<tr>
<td>Nelarabine</td>
<td>Melphalan</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>6-Thioguanine (6-TG)</td>
<td>Thiotepa</td>
</tr>
<tr>
<td><strong>Topoisomerase II inhibitor (G₁−S phase)</strong></td>
<td><strong>Antitumor antibiotics</strong></td>
</tr>
<tr>
<td>Etoposide</td>
<td>Dactinomycin</td>
</tr>
<tr>
<td></td>
<td>Mitomycin</td>
</tr>
<tr>
<td><strong>Topoisomerase I inhibitors</strong></td>
<td><strong>Platinum analogs</strong></td>
</tr>
<tr>
<td>(Camptothecins, G₂-M)</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Carbolplatin</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Cisplatin</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td><strong>Taxanes (M phase)</strong></td>
<td><strong>Anthracyclines</strong></td>
</tr>
<tr>
<td>Albumin-bound paclitaxel</td>
<td>Daunorubicin</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Idarubicin</td>
</tr>
<tr>
<td></td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td><strong>Vinca alkaloids (M phase)</strong></td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrotubule inhibitor (M phase)</strong></td>
<td></td>
</tr>
<tr>
<td>Ixabepilone</td>
<td></td>
</tr>
<tr>
<td>Eribulin</td>
<td></td>
</tr>
<tr>
<td><strong>Antitumor antibiotics (G₂−M phase)</strong></td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
</tr>
</tbody>
</table>
Cell cycle specificity of Anti-Neoplastic Agents

- **G₀** = resting phase
- **G₁** = pre-replicative phase
- **G₂** = post-replicative phase
- **S** = DNA synthesis
- **M** = mitosis or cell division

Drugs and Their Effects:

**G₀**:
- Hydrocortisone

**G₁**:
- Bleomycin
- Actinomycin D
- Purine antagonists (Methotrexate, 5-Fluorouracil, Cytosine arabinoside)

**G₂**:
- Actinomycin D
- Paclitaxel, Docetaxel

**M**:
- Vincristine, Vinblastine
- 5-Fluorouracil
- Cytosine arabinoside
- Methotrexate
- Mercaptopurine

- **G₀** = resting phase
- **G₁** = pre-replicative phase
- **G₂** = post-replicative phase
- **S** = DNA synthesis
- **M** = mitosis or cell division
PART II

4. Mechanisms of action
5. Side Effects
6. Drug Resistance
## Major Clinically Useful Alkylating Agents

<table>
<thead>
<tr>
<th>Bis(mechloroethyl)amines</th>
<th>Nitrosoureas</th>
<th>Aziridines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td></td>
<td><strong>Thiotepa</strong></td>
</tr>
<tr>
<td><strong>Mechlorethamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chlorambucil</strong></td>
<td></td>
<td><strong>Triethylmethemelamine</strong></td>
</tr>
<tr>
<td><strong>Melphalan</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BCNU** (carmustine)  
**CCNU** (lomustine)   
**Methyl-CCNU** (semustine)  

**FIGURE 54–3** Structures of major classes of alkylating agents.
Alkylation Agents (Covalent DNA binding drugs)

1. The first class of chemotherapy agents used.
2. They stop tumour growth by cross-linking guanine nucleobases in DNA double-helix strands - directly attacking DNA.
3. This makes the strands unable to uncoil and separate.
4. As this is necessary in DNA replication, the cells can no longer divide.
5. Cell-cycle nonspecific effect
6. Alkylation agents are also mutagenic and carcinogenic
E.g., Mechlorethamine (Nitrogen Mustards)

FIGURE 54–4 Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimionium ion that reacts with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.
• Alkylation of guanine can result in **miscoding through abnormal base pairing with thymine** or in **depurination** by excision of guanine residues.

• The latter effect leads to DNA strand breakage through scission of the sugar-phosphate backbone of DNA.

• Cross-linking of DNA appears to be of major importance to the cytotoxic action of alkylation agents,

• Replicating cells are most susceptible to these drugs. cells are most susceptible to them in late G1 and S phases of the cell cycle.
Cyclophosphamide

Cyclophosphamide one of the advantages of this compound is that it has high oral bioavailability. As a result, it can be administered via the oral and intravenous routes with equal clinical efficacy.

• It is inactive in parent form, and must be activated to cytotoxic form by liver CYT$p450$ liver microsomaal system to 4-Hydroxycyclophamide and Aldophosphamide.

• 4-Hydroxycyclophamide and Aldophosphamide are delivered to the dividing normal and tumor cells.

• Aldophosphamide is converted into acrolein and phosphoramidemustard.

• They crosslink DNAs resulting in inhibition of DNA synthesis
Cyclophosphamide Metabolism

Cyclophosphamide

Liver cytochrome P450 oxidase

4-Hydroxycyclophosphamide (active)

Carboxyphosphamidamide (inactive)

4-Ketocyclophosphamide (inactive)

Aldophosphamide (active)

Aldehyde oxidase

Nonenzymatic

Acrolein (cytotoxic)

Phosphoramidemustard (cytotoxic)
Mechanism of activation: Cyclophosphamide

Inactive Cyclophosphamide

Metabolised in the liver by P450 mixed function oxidases

Aldophosphamide is conveyed to other tissues

(Reversibly) forms aldophosphamide.

Converted to phosphoramidemustard, the actual cytotoxic molecule

4-hydroxycyclophosphamide
Clinical Applications:

1. Breast Cancer
2. Ovarian Cancer
3. Non-Hodgkin’s Lymphoma
4. Chronic Lymphocytic Leukemia (CLL)
5. Soft tissue sarcoma
6. Neuroblastoma
7. Wilms’ tumor
8. Rhabdomyosarcoma
Pharmacologic Effects

• The adverse effects are generally dose-related and occur primarily in rapidly growing tissues.
• N/V can be a serious issue with a number of these agents.
• They have direct vesicant effects and can damage tissues at the site of injection as well as produce systemic toxicity.
• Alkylating agents are carcinogenic in nature, and there is an increased risk of secondary malignancies.
Major Side effects

1. Nausea and vomiting
2. Decrease in PBL count
3. Depression of blood cell counts
4. Bleeding
5. Alopecia (hair loss)
6. Hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration
7. Skin pigmentation, pulmonary fibrosis (especially Busulfan)
Nitrosoureas
(Carmustine, Lomustine)

• These drugs appear to be non-cross-resistant with other alkylating agents;
• All require biotransformation, which occurs by nonenzymatic decomposition, to metabolites with alkylating activities.
• The nitrosoureas are highly lipid-soluble and are able to cross the BBB, making them effective in the treatment of brain tumors.
Nitrosoureas

• One naturally occurring sugar-containing nitrosourea, *streptozocin*, is interesting because it has minimal bone marrow toxicity. This agent has activity in the treatment of insulin-secreting islet cell carcinoma of the pancreas.
A. Alkylating agents

1. Interfere with cell division in all rapidly proliferating tissues

2. Most susceptible tissues are hematopoietic and GI epithelium

3. Mechanism of action: react with body fluid to form carbonium ions which bind guanine residue of DNA; such binding could result in:
   
a. Miscoding of DNA
   b. Imidazole ring cleavage
   c. Excision of guanine residue producing DNA chain scission
   d. Cross linkages between DNA strands; this effect thought to be primary mode of cytotoxic action

4. Development of resistance possibly due to
   
a. Decreased cellular permeability
   b. Production of substances which compete with DNA for alkylation
   c. Increased rate of DNA repair

5. Toxic side effects
   
a. Bone marrow depression
   b. Nausea and vomiting especially when given I.V.
   c. Can get additive effects when used with ionizing radiation and antimetabolites
Nonclassic Alkylating Agents

**Procarbazine**

- A variety of drug metabolites are formed that may be cytotoxic. One metabolite is a weak MAO inhibitor, and adverse events can occur when procarbazine is given with certain drugs.
- The carcinogenic potential of procarbazine is higher than that of most other alkylating agents.
- Dacarbazine is another synthetic compound.
Bendamustine

- It is a bifunctional alkylating agent consisting of a purine benzimidazole ring and a nitrogen mustard moiety.
- This molecule also induces mitotic catastrophe, which leads to cell death.
- Of note, no cross-resistance with other alkylating agents.
- Hypersensitivity infusion reactions, skin rash, and other skin reactions occur rarely.
Platinum Analogs

**Cisplatin, carboplatin, oxaliplatin**

- They exert their cytotoxic effects in the same manner as alkylating agents.
- As such, they kill tumor cells in all stages of the cell cycle and bind DNA through the formation of intrastrand and interstrand cross-links, thereby leading to inhibition of DNA synthesis and function.
- They bind to both cytoplasmic and nuclear proteins, which may also contribute to their cytotoxic and antitumor effects.
Platinum Analogs
Cisplatin, carboplatin, oxaliplatin

• The platinum complexes appear to synergize with certain other anticancer drugs, including alkylating agents, and taxanes.

• Platinum analogs are extensively cleared by the kidneys and excreted in the urine. As a result, dose modification is required in the setting of renal dysfunction.
CISPLATIN

Cisplatin has greater side effects than other platinum's:

• Nephrotoxicity
• Peripheral sensory neuropathy
• Ototoxicity
• Nerve dysfunction
Carboplatin

- As with cisplatin, carboplatin has broad-spectrum activity against a wide range of solid tumors.
- In contrast to cisplatin, it exhibits significantly less renal and GI toxicity. Its main dose-limiting toxicity is myelosuppression.
- It has therefore been widely used in refractory hematologic malignancies.
- It is viewed as an easier agent to administer to patients, since vigorous IV hydration is not required, it has widely replaced cisplatin in various combination chemotherapy regimens.
Oxaliplatin

- Tumors that are resistant to cisplatin or carboplatin are not cross-resistant to oxaliplatin,
- It is originally approved for use in combination with the (5-FU) and leucovorin, for metastatic colorectal cancer (the FOLFOX regimen).
- Activity has been observed in other GI cancers, such as pancreatic, gastroesophageal, and hepatocellular cancers.
Oxaliplatin

• Neurotoxicity is the main dose-limiting toxicity and is manifested by a peripheral sensory neuropathy.
• There are two forms of neurotoxicity, an acute form that is often triggered and worsened by exposure to cold, and a chronic form that is dose-dependent.
• Although this chronic form is cumulative, it tends to be reversible, in contrast to cisplatin-induced neurotoxicity.
ANTIMETABOLITES

**Folate Antagonist:** Methotrexate

- MTX is a folic acid analog that binds with high affinity to dihydrofolate reductase (DHFR), interfering with the synthesis of tetrahydrofolate (THF),
- Inhibition of these various metabolic processes thereby interferes with the formation of DNA, RNA, and key cellular proteins.
ANTIMETABOLITES

**Folate Antagonist**: Methotrexate

- Intracellular formation of *polyglutamate metabolites*, is critically important for the therapeutic action of MTX,
- MTX polyglutamates are selectively retained within cancer cells, and they display increased inhibitory effects on enzymes involved in de novo purine nucleotide and thymidylate biosynthesis, making them important determinants of MTX's cytotoxic action.
• MTX is administered by the **intravenous**, intrathecal, or oral route.

• Oral bioavailability is **saturable** and erratic at doses greater than 25 mg/m².

• Renal excretion is the main route of elimination and is mediated by glomerular filtration and tubular secretion.

• Drug interaction with:
  - aspirin, penicillin, cephalosporins, and nonsteroidal anti-inflammatory agents, as they inhibit the renal excretion of MTX.
• The biologic effects of MTX can be reversed by administration of the reduced folate leucovorin (5-formyltetrahydrofolate), which is the active enantiomer.
• **Leucovorin rescue** is used in conjunction with **high-dose MTX** therapy to rescue normal cells from toxicity, and it has also been used in cases of accidental drug overdose.
### Antimetabolites

<table>
<thead>
<tr>
<th></th>
<th>Clinical application</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Breast cancer, head and neck cancer, osteogenic sarcoma, primary central nervous system lymphoma, non-Hodgkin's lymphoma, bladder cancer, choriocarcinoma</td>
<td>Mucositis, diarrhea, myelosuppression with neutropenia and thrombocytopenia</td>
</tr>
</tbody>
</table>

Several resistance mechanisms to MTX have been identified, and they include:
(1) decreased drug transport via the reduced folate carrier or folate receptor protein,
(2) decreased formation of cytotoxic MTX polyglutamates,
(3) increased levels of the target enzyme DHFR through gene amplification and other genetic mechanisms, and
(4) Altered DHFR protein with reduced affinity for MTX
Antimetabolites (continued)

Fluoropyrimidines
5-Fluorouracil

• 5-FU is inactive in its parent form and requires activation via a complex series of enzymatic reactions to active metabolites.

• One of these metabolites, 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP),
This results in inhibition of DNA synthesis through "thymineless death."
5-FU cytotoxic mechanism

5-FU → FdUMP → TS → dNTP imbalances → DNA damage
5-FU → FUTP → Uridine → RNA damage

Increased TS expression → Increased dUTP → p53

Nature Reviews | Cancer
• 5-FU is administered IV.
• Not used orally. because up to 85% of an administered dose of 5-FU is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD).
• Of note, there is a pharmacogenetic syndrome that involves deficiency of the DPD enzyme, and in this setting, severe toxicity has been observed.
• The clinical activity of this drug is highly schedule-dependent and because of its extremely short half-life
5-FU

- 5-FU remains the most widely used agent in the treatment of colorectal cancer, both as adjuvant therapy and for advanced disease. It also has activity against a wide variety of solid tumors.

- **Major toxicities** include myelosuppression, gastrointestinal toxicity in the form of mucositis and diarrhea, skin toxicity manifested by the hand-foot syndrome, and neurotoxicity.
Capecitabine

- It is a fluoropyrimidine carbamate prodrug with 70–80% oral bioavailability.
- It undergoes extensive metabolism in the liver to become activated.
- Finally it is hydrolyzed by thymidine phosphorylase to 5-FU directly in the tumor.
- The expression of thymidine phosphorylase has been shown to be significantly higher in a broad range of solid tumors than in normal tissue, particularly in breast cancer and colorectal cancer.
Fluoropyrimidines
Capecitabine

• The main toxicities of capecitabine include diarrhea and the hand-foot syndrome.

• The incidence for myelosuppression, nausea and vomiting, and mucositis, is significantly less than that seen with intravenous 5-FU.
Cytosine arabinoside, Cytarabine, ara-C

The cellular retention of ara-CTP appears to correlate with its lethality to malignant cells. Ara-CTP competitively inhibits DNA polymerase. This metabolite is also incorporated into RNA and DNA.
• After IV, the drug is **cleared rapidly** by deamination to inactive forms.
• The clinical activity of this drug is highly **schedule-dependent**.
• It must be given by **continuous infusion** over a 5–7 day period.
• Its activity is limited exclusively to **hematologic malignancies**, including acute myelogenous leukemia and non-Hodgkin's lymphoma.
• The main adverse effects associated with cytarabine therapy include myelosuppression, mucositis, nausea and vomiting, and neurotoxicity when high-dose therapy is administered.
Antimetabolites (continued)

Purine Antagonists

• 6-Mercaptopurine (6-MP) This agent is used primarily in the treatment of childhood acute leukemia,
6-Thioguanine (6-TG)

- Interference with the formation of DNA and RNA; and incorporation of thiopurine nucleotides into both DNA and RNA.
- 6-TG has a synergistic action when used together with cytarabine in the treatment of adult acute leukemia.
• 6-MP is converted to an inactive metabolite by xanthine oxidase, whereas 6-TG undergoes deamination.

• **Allopurinol**, is frequently used as a supportive care measure in the treatment of acute leukemias to prevent the development of hyperuricemia that often occurs with tumor cell lysis.

• Simultaneous therapy with allopurinol and 6-MP would result in increased levels of 6-MP, thereby leading to excessive toxicity. In this setting, the dose of mercaptopurine must be reduced by 50–75%.

• In contrast, such an interaction does not occur with 6-TG, which can be used in full doses with allopurinol
<table>
<thead>
<tr>
<th>Clinical application</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purine analogs:</strong> 6-Mercaptopurine (6-MP) and Thioguanine (6-TG)**</td>
<td>ALL, AML</td>
</tr>
<tr>
<td></td>
<td>Myelosuppression, immunosuppression, and hepatotoxicity,</td>
</tr>
</tbody>
</table>
GENERAL MECHANISM OF ACTION OF ANTIMITABOLITE

Purine & Pyrimidine synthesis

METHOTREXATE
inhibition of dihydrofolate reductase leads to an inhibition of purine ring & dTMP biosynthesis

6-Mercaptopurine, Thio guanine
Inhibit de novo purine synthesis

Ribonucleotides

5-Fluorouracil
Inhibit dTMP synthesis

Deoxyribonucleotides

DNA

RNA

PROTEINS
dTMP = DEOXYTHYMIDINE MONOPHOSPHATE
Natural Product Cancer Chemotherapy Drugs

Vinca Alkaloids

• Discovered in 1953 by Robert L. Noble, and cleared by the FDA in 1963 as Oncovin, marketed by Eli Lilly.

Catharanthus roseus
How vinca works

- Stops division of cells
- Inhibition of tubulin polymerization, which disrupts assembly of microtubules.
- Enters cell during mitosis and blocks formation of microtubules of the mitotic spindle during metaphase
B. Natural Products

1. Antimitotic Drugs

<table>
<thead>
<tr>
<th>Clinical application</th>
<th>Route</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Vincristine</strong></td>
<td>I.V.</td>
<td><em>Neurotoxicity</em> with peripheral neuropathy, paralytic ileus, myelosuppression, alopecia, SIADH</td>
</tr>
<tr>
<td>ALL, Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma, Wilms' tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B. Vinblastine</strong></td>
<td>I.V.</td>
<td>Acute: Nausea and vomiting, chronic: Myelosuppression, mucositis, alopecia, SIADH, vascular events.</td>
</tr>
<tr>
<td>Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, breast cancer, Kaposi's sarcoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Vincristine has a strikingly different spectrum of clinical activity and safety profile compared to vinblastine
  - Vincristine has been effectively combined with prednisone for remission induction in acute lymphoblastic leukemia in children
Vinorelbine

• It is a **semisynthetic derivative** of vinblastine.

• This agent has activity in **non-small cell lung cancer, breast cancer, and ovarian cancer**.

• Myelosuppression with neutropenia is the dose-limiting toxicity, nausea and vomiting, transient elevations in liver function tests, neurotoxicity, and SIADH
Taxanes & Related Drugs

• **Paclitaxel** is an alkaloid ester derived from the *Taxus brevifolia* and the *Taxus baccata*.

• Paclitaxel (*taxol*) was discovered beginning in 1962 as a result of a U.S. National Cancer Institute-funded screening program.
Tubulin Binding Agents

*Vincristine,* *Vinblastine,* *Vindesine* and *Vinorelbine:* Inhibition of mitotic spindle formation by binding to tubulin. M-phase of the cell cycle.

*Paclitexal:* Binds to tubulin, promotes microtubule formation and retards disassembly; results in mitotic arrest.
## B. Natural Products

### 2. Antimitotic Drugs

<table>
<thead>
<tr>
<th>Paclitaxel (Taxol)</th>
<th>Clinical application</th>
<th>Route</th>
<th>Side effects</th>
</tr>
</thead>
</table>
|                   | Breast cancer, non-small cell and small cell lung cancer, ovarian cancer, gastroesophageal cancer, prostate cancer, bladder cancer, head and neck cancer | I.V.  | Acute: Nausea, vomiting, hypotension, arrhythmias, hypersensitivity  
|                   |                                                                                      |       | Chronic: Myelodepression and neuropathy                        |

**Hypersensitivity reactions** may be observed in up to 5% of patients, but the incidence is significantly reduced by premedication with dexamethasone, diphenhydramine, and an H₂ blocker.
• A novel albumin-bound paclitaxel formulation.
• It is approved for use in metastatic breast cancer.
• In contrast to paclitaxel, it is not associated with hypersensitivity reactions.
• Moreover, this agent has significantly reduced myelosuppressive effects compared with paclitaxel, and the neurotoxicity is more readily reversible than is typically observed with paclitaxel.
Epipodophyllotoxins

• **Etoposide** is a semisynthetic derivative of podophyllotoxin, which is extracted from the root of *Podophyllum peltatum*.

• The primary mode of action involves inhibition of topoisomerase II, which results in DNA damage through strand breakage induced by the formation of a ternary complex of drug, DNA, and enzyme.
### 3. Epipodophyllotoxins (These are CCS)  
Act on Topoisomerase II

<table>
<thead>
<tr>
<th></th>
<th>Clinical application</th>
<th>Route</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. Teniposide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The oral bioavailability is about 50%.
Irinotecan

• Natural products.
• It inhibit the activity of topoisomerase I.
• Irinotecan is a prodrug that is converted mainly in the liver.
• Mainly eliminated in bile and feces.
Irinotecan

• It is used in patients with metastatic colorectal cancer.

• Myelosuppression and diarrhea are the two most common adverse events
Anticancer antibiotics

Anthracyclines antibiotics, are among the most widely used cytotoxic anticancer drugs doxorubicin and daunorubicin

- Cell cycle non specific drugs
- Derived from streptomyces species
Anthracyclines antibiotics

- They exert their cytotoxic action through four major mechanisms:
  1. Inhibition of topoisomerase II;
  2. High-affinity binding to DNA, with consequent blockade of the synthesis of DNA and RNA, and DNA strand scission;
  3. Generation of free radicals and oxygen free and
  4. Binding to cellular membranes to alter fluidity and ion transport
The main dose-limiting toxicity of all anthracyclines is myelosuppression, with neutropenia more commonly observed than thrombocytopenia.

<table>
<thead>
<tr>
<th>2. Clinical application</th>
<th>3. Route</th>
<th>4. Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. Dactinomycin</strong> <em>(ACTINOMYCIN D)</em></td>
<td>Rhabdomyosarcoma and Wilm's tumor in children; choriocarcinoma (used with methotrexate)</td>
<td>I.V.</td>
</tr>
<tr>
<td><strong>b. Daunorubicin</strong> <em>(CERUBIDIN)</em></td>
<td>ALL, AML</td>
<td>I.V.</td>
</tr>
<tr>
<td><strong>Doxorubicin</strong> <em>(ADRIAMYCIN)</em></td>
<td>Breast cancer, Hodgkin's and non-Hodgkin's lymphoma, soft tissue sarcoma, ovarian cancer, non-small cell and small cell lung cancer, thyroid cancer, Wilms' tumor, neuroblastoma</td>
<td>I.V.</td>
</tr>
</tbody>
</table>

Inhibit DNA and RNA syntheses
Anthracyclines antibiotics (continued)

- **Dactinomycin** is mainly used to treat pediatric tumors such as **Wilms' tumor**, but it has activity also against germ cell tumors and. Dactinomycin can also induce a "**radiation recall reaction**."
• Doxorubicin is one of the most important anticancer drugs.

• It is generally used in combination with other anticancer agents (eg, cyclophosphamide, cisplatin, and fluorouracil), and responses and remission duration tend to be improved with combination regimens as opposed to single-agent therapy.

• Daunorubicin has a far narrower spectrum of activity than doxorubicin.
Anthracyclines antibiotics (continued)

- **Idarubicin** is a semisynthetic glycoside analog of daunorubicin.

- When combined with cytarabine, idarubicin appears to be more active than daunorubicin in producing complete remissions and in improving survival in patients with AML.

- **Epirubicin** is a doxorubicin analog

- It was initially approved for use as a adjuvant therapy of early-stage, node-positive breast cancer but is now also used for the treatment of metastatic breast cancer.
2 type of cardiotoxicity are observed.

- **Acute** form occurs within the first 2–3 days as arrhythmias or conduction abnormalities, other ECG changes, pericarditis, and myocarditis.
- The **chronic** form results in a dose-dependent, cardiomyopathy associated with heart failure.
- It appears to result from increased production of **free radicals within the myocardium**.
- This effect is rarely seen at total doxorubicin dosages **below 500 mg/m2**.
• Use of lower weekly doses or continuous infusions of doxorubicin appear to reduce the incidence of cardiac toxicity.

• Treatment with the iron-chelating agent dexrazoxane (ICRF-187) is currently approved to prevent or reduce anthracycline-induced cardiotoxicity.

• All anthracyclines can produce "radiation recall reaction," with erythema and desquamation of the skin observed at sites of prior radiation therapy.
Mitomycin

• Derived from Streptomyces caespitosus.
• It is thought to be a CCNS alkylating agent,
• **Hypoxic tumor stem cells** are more sensitive to the cytotoxic actions of mitomycin than normal cells and oxygenated tumor cells
• It is the best available drug for **use in combination with radiation** therapy to attack hypoxic tumor cells.
Antibiotics (CCS)

<table>
<thead>
<tr>
<th></th>
<th>2. Clinical application</th>
<th>3. Route</th>
<th>4. Side effects</th>
</tr>
</thead>
</table>
Chronic: Skin toxicity, pulmonary fibrosis, mucositis, alopecia |

Bleomycin is a small peptide that contains a DNA-binding region and an iron-binding domain. It acts by binding to DNA, which results in single-strand and double-strand breaks following free radical formation, and inhibition of DNA biosynthesis.
• **Pulmonary toxicity** is dose-limiting for bleomycin and usually presents as: pneumonitis with cough, dyspnea, and infiltrates on chest x-ray.

The incidence of this adverse event is increased in patients older than **70 years** of age and with cumulative doses >>400 units.
Miscellaneous agents
Asparaginase (L-asparagine amidohydrolase)

• It is an enzyme that is isolated from various bacteria for clinical use.
• It is used to treat childhood acute lymphocytic leukemia.
• It hydrolyzes circulating L-asparaginase to aspartic acid and ammonia.
## Enzymes: L-asparaginase

<table>
<thead>
<tr>
<th>L-asparaginase</th>
<th>2. Clinical application</th>
<th>3. Route</th>
<th>4. Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL, Induction of remission in acute lymphoblastic leukemia when combined with vincristine, prednisone, and anthracyclines</td>
<td>I.V. or I.M.</td>
<td>Poor appetite, Stomach cramping, Mouth sores, Pancreatitis. Less common: blood clotting problems</td>
</tr>
</tbody>
</table>

The main side effect Acute: **hypersensitivity reaction** manifested by fever, chills, nausea and vomiting, skin rash, and urticaria. Severe cases can present with **bronchospasm**, respiratory failure, and hypotension.

Neurologic toxicity with lethargy, confusion, hallucinations, and coma.
Miscellaneous agents

Imatinib

• It is indicated for the treatment of CML.
• Imatinib is administered orally and is well absorbed.
• Imatinib is effective also for treatment of gastrointestinal stromal tumors.
• It is an inhibitor of the tyrosine kinase domain of the Bcr-Abl oncoprotein and prevents the phosphorylation of the kinase substrate by ATP.
Miscellaneous

Sex hormones & adrenocortical

• Since sex hormones are actively involved in the stimulation and control of proliferation and function of certain tissues, including the mammary and prostate glands, cancers arising from these tissues may be inhibited or stimulated by appropriate changes in hormonal balance.

• Cancer of the breast and cancer of the prostate can be effectively treated with sex hormone therapy or ablation of appropriate endocrine organs.
Bevacizumab (Avastin)

- It is an angiogenesis inhibitor, a drug that slows the growth of new blood vessels.
- It is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A).
- For combination use with standard chemo for metastatic colon cancer.
- Certain lung cancers, renal cancers, ovarian cancers, and glioblastoma multiforme of the brain.
General rules of chemotherapy

- **Aggressive high-dose chemotherapy**
  - **Dose** - limiting its toxicity towards normal cells
  - **Cyclic regimens** - repeated administrations
  - **Supportive therapy** - to reduce toxicity
    - **Hematotoxicity** – bone marrow transplantation, hematopoietic growth factors
    - **Specific antagonists**: antifolate (methotrexate) – folate (leucovorin)
    - **Dexrazoxane**: chelates iron, reduced anthracycline cardiotoxicity
    - **Amifostine**: reduces hematotoxicity, ototoxicity and neurotoxicity of alkylating agents
Summary

1. The main goal of anti-neoplastic drug is to eliminate the cancer cells without affecting normal tissues.

2. Log-Kill Hypothesis states that a given therapy kills a percentage of cells, rather then a constant number, therefore, it follows first order kinetics. **Aim for a favorable therapeutic index.**

3. Early diagnosis is the key.

4. Combination therapy and adjuvant chemotherapy are effective for small tumor burden.

5. Two major classes of antineoplastic agents are:
   a. **Cell Cycle Specific**
   b. **Cell Cycle Non-Specific**

5. Because chemotherapeutic agents target not only tumor cells, but also affect normal dividing cells including bone marrow, hematopoietic, and GI epithelium. **Know what the side effects are.**

6. Drug resistance is often associated with loss of p53 function, DNA mismatch repair system, and increased MDR1 gene expression.
DRUG RESISTANCE

CELLULAR MECHANISMS

Drug target alterations:
- Upregulation of enzyme target e.g. TS, DHFR
- Enhanced drug metabolism e.g. cytidine deaminase

Multidrug resistance:
- Drug efflux via P-glycoprotein transporters
- Drug conjugation by glutathione

Enhanced survival:
- Suppression of apoptosis (e.g. Bcl-2, p53, PI3-kinase signaling)
- Enhanced DNA repair systems

NON-CELLULAR MECHANISMS

Pharmacological sanctuaries:
- Blood-brain barrier
- Poor penetration of drugs into solid tumours

Altered in vivo growth kinetics:
- Non-cycling cells in hypoxic regions distant from blood vessels
- Tumour repopulation between treatments
## Important drug combinations

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>CANCER</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP</td>
<td>Hodgkins</td>
<td>Mechlorethamine, oncovin, prednisolone, procarbazine</td>
</tr>
<tr>
<td>ABVD</td>
<td>Hodgkins</td>
<td>Doxorubicin, bleomycin, vinblastine, dacarbazine</td>
</tr>
<tr>
<td>CMF</td>
<td>Breast</td>
<td>Cyclophosphamide, methotrexate, 5-FU</td>
</tr>
<tr>
<td>CAF</td>
<td>Breast</td>
<td>Cyclophosphamide, doxorubicin, 5FU</td>
</tr>
<tr>
<td>ALL</td>
<td></td>
<td>Vincristine, prednisolone, asparagine, daunorubicin</td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td>Cytarabine, methotrexate</td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td>Hydroxyurea, interferon</td>
</tr>
<tr>
<td>Wilms</td>
<td></td>
<td>Actinomycin, vincristine, doxorubicin</td>
</tr>
</tbody>
</table>