ANTINEOPLASTICS II

REFERENCES

Katzung Basic and Clinical Pharmacology (9th ed.)
   Chapter 55  Cancer Chemotherapy
   Chapter 56  Immunopharmacology

Lecture notes on antineoplastic drugs from the Histopathology course (as well as summary tables etc.) apply to this lecture as well, and are not duplicated here.
   i.e. YOU ARE STILL RESPONSIBLE FOR THE DRUGS TAUGHT IN HISTOPATH!

You should particularly review targets for drug development, general mechanisms of action, cell cycle specificity, mechanisms of resistance and principles of combination chemotherapy before this lecture.

CRITICAL FACTS

(if med school is a Minnesota forest with millions of trees, these are the red pines)

1. Antimetabolites are analogues of folic acid, pyrimidines or purines that interfere with key enzymes used during DNA synthesis. These agents are cell cycle specific (CCS), as their effects occur during S phase. A common mechanism for the development of resistance to these agents is modification of the target enzymes.

2. METHOTREXATE is a potent antineoplastic agent because it blocks both purine and thymidylate synthesis by inhibiting dihydrofolate reductase (DHFR). Administration of LEUCOVORIN (another folic acid analogue) can selectively reduce the METHOTREXATE toxicity in normal cells, as well as decrease the development of resistance.

3. 5-FLUOROURACIL inhibits the biosynthesis of pyrimidine nucleotides by inhibiting thymidylate synthase, the enzyme that catalyzes the rate limiting step in DNA synthesis. This results in the "thymineless death" of rapidly growing cells.

4. 6-MERCAPTOPURINE and 6-THIOGUANINE must be activated by HGPRT to T-IMP and 6-thioGMP. T-IMP and 6-thioGMP are poor substrates for guanylyl kinase, therefore T-IMP and 6-thioGMP accumulate, causing "pseudofeedback inhibition" of purine nucleoside phosphorylase and HGPRT.
5. **Tumor Lysis Syndrome** is caused by the sudden, rapid death of millions of cells, and results from the development of electrolyte and metabolic disturbances. **Allopurinol** (a xanthine oxidase inhibitor) is frequently used during chemotherapy of hematologic cancers to prevent hyperuricemia due to tumor cell lysis. Simultaneous administration of **allopurinol** and **6-mercaptopurine** results in excessive mercaptopurine toxicity (because **6-MP** is also metabolized by xanthine oxidase).

6. Signal transduction inhibitors have the potential to revolutionize cancer treatment. First generation tyrosine kinase inhibitors, such as **imatinib**, **erlotinib** and **gefitinib** bind to the ATP-binding site (not the substrate binding site) and prevent phosphate transfer from ATP to the substrate tyrosine. These agents generally have fewer side effects than conventional therapies because they are targeted toward the specific defect of a particular cancer: **imatinib** to **bcr-abl** in CML, and **erlotinib** and **gefitinib** to **EGFR** which is overexpressed in epithelial-derived cancers.

7. Bone marrow suppression is the dose-limiting complication of many antineoplastic drugs. Recombinant forms of several lineage-dependent colony stimulating factors have been developed. These factors activate specific progenitor cells, resulting in the production of: **erythropoietin** → red blood cells, **filgrastim** (G-CSF) → neutrophils, **sargramostim** (GM-CSF) → granulocytes, eosinophils, basophils and monocytes and **interleukin 11** and **thrombopoietin** → platelets.

8. Immunosuppressive agents (glucocorticoids, cyclosporine and tacrolimus) are used in the treatment of many types of cancers --- particularly those that express receptors for specific corticosteroids (e.g., prednisone-sensitive lymphomas). When used in cancer chemotherapy, these agents are given in higher doses, using a “pulse” regimen, compared to their use in immunosuppression (asthma, arthritis, lupus, etc.).

9. As molecular targets are identified that distinguish cancer cells from normal cells, monoclonal antibodies have been developed that can selectively recruit the immune system to destroy the cancer cells. Currently, antibodies have been designed that target CDs (CD20 in NHL, CD33 in AML, and CD52 in B-CLL), and cell surface proteins (HER2, 17-1A, VEGF, EGFR) that are overexpressed in specific cancers.
10. **THALIDOMIDE** is a developmental toxin whose only approved use is in the treatment of Hansen's disease, although it has significant off-label use in AIDS treatment and in multiple myeloma. **THALIDOMIDE** has significant teratogenic effects (especially **phocomelia**) in the children and grandchildren of women who take the drug while pregnant.

11. One hallmark of malignant transformation is differentiation block. Numerous chemicals --- including vitamin D and its analogues, retinoids (vitamin A derivatives such as **TREINOIN**), rexinoids (multifunctional nuclear retinoid X receptor ligands), benzamides and other inhibitors of histone deacetylase (HDAC) and inhibitors of DNA methylation --- can all induce tumour cell differentiation, ultimately leading to apoptosis.

12. Antineoplastic agents are almost always given in combination. Correct selection of drugs in a regimen can result in decreased development of resistance, synergistic effects and decreased toxic effects. Other common chemotherapeutic strategies include pulse and rescue therapy, recruitment and synchrony.

**CRITICAL MATERIAL FROM OTHER LECTURES**

<table>
<thead>
<tr>
<th>Applied Anatomy</th>
<th>HHD</th>
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<tbody>
<tr>
<td>Congenital Malformations, Dr. Forbes</td>
<td>Folate/tetrahydrofolate biochemistry and pharmacology, Drs. Prohaska and Trachte</td>
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<tr>
<td><strong>Principles</strong></td>
<td></td>
</tr>
<tr>
<td>Synthesis of amino acids nucleotides and DNA, Drs. Huntley and Perkins <strong>esp. pyrimidine and purine biosynthesis and degradation</strong>, and asparagine synthesis</td>
<td>Signal transduction esp. tyrosine kinases, Dr. Clarke (also Dr. Drewes in Principles)</td>
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<tr>
<td>Chromosome translocations, Dr. Perkins</td>
<td>CML module, Drs. Perkins, Krafts and Fitzakerley (after this lecture)</td>
</tr>
<tr>
<td>Protein degradation, esp. role of ubiquitin</td>
<td>Immunosuppressive drugs, Dr. Regal, esp. glucocorticoids</td>
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<tr>
<td>Retinoic acid, Dr. Holy (also Dr. Prohaska in HHD)</td>
<td>Lymphokines, Dr. Clarke</td>
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<tr>
<td></td>
<td>Antibodies as drugs, Dr. Fitzakerley</td>
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<tr>
<td></td>
<td>Hematopoiesis, esp. colony stimulating factors</td>
</tr>
</tbody>
</table>

**PRIMARY LEARNING OBJECTIVES**

1. Chart the specific enzymes and pathways that are blocked by antimetabolite cancer drugs.

2. List the mechanisms that make cancer cells more susceptible than normal cells to the actions of methotrexate, and understand the principles underlying the rescue of normal cells by leucovorin.
3. Compare and contrast the mechanisms underlying the development of resistance to methorexate, 5-fluorouracil, 6-mercaptopurine and 6-thioguanine.

4. Identify the unique pharmacokinetic properties of methotrexate, 5-fluorouracil and 6-mercaptopurine.

5. Identify the common and unique side effects of methotrexate, 5-fluorouracil and 6-mercaptopurine.

6. What is tumour lysis syndrome? How can its effects be minimized? Explain the concerns related to co-administration of ALLOPURINOL and 6-MP.

7. Describe the mechanism of action of the currently approved signal transduction inhibitors, and explain the success of imatinib vs. gefitinib. Contrast conventional therapy for the treatment of CML with the use of STIs with respect to cure rates, remission and side effects.

8. Understand the mechanism of action of L-asparagine. Why is the sequence of administration of this agent important when it is used in combination chemotherapy?

9. Distinguish among hematopoietic agents with respect to progenitors affected and the mature cells produced.

10. Why are immunosuppressive drugs effective in the treatment of hematologic cancers? Describe differences in the use of these agents for cancer chemotherapy vs. immunosuppression.

11. Identify the lymphokines that have been approved for use in cancer treatment. What aspects of their pharmacokinetics and toxicities are common among this class of drugs, and which of these drugs have unique side effects?

12. Be able to match the monoclonal antibodies used in cancer treatment to their targets and to their unique, serious side effects.

13. What is the tremendous potential associated with the use of angiogenesis inhibitors? What are the mechanisms of action and side effects attributed to bevacizumab and thalidomide?

14. What are the advantages of combination chemotherapy? List the strategies that should be used to design combination therapies, and apply these concepts to the components in commonly used combination therapies for the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, testicular carcinoma and breast cancer.

15. Define the terms pulse therapy, recruitment, synchrony, and rescue therapy as they apply to the use of chemotherapeutic drugs. Be able to give examples of each.
**DRUGS YOU NEED TO KNOW**
*(TODAY’s in BOLD throughout the handout; prototype agents are underlined here)*

### ALKYLATING AGENTS
*(blue cards)*
- BUSULFAN
- CARMUSTINE (BCNU)
- CYCLOPHOSPHAMIDE
- DACARBAZINE
- LOMUSTINE (CCNU)
- MECHLORETHAMINE
- MELPHALAN
- THIOTEPA

### NATURAL PRODUCTS
*(green cards)*
- BLEOMYCIN
- DACTINOMYCIN
- DAUNORUBICIN
- DOXORUBICIN
- ETOPOSIDE (VP-16)
- IRINOTECAN
- MITOMYCIN C
- PACLITAXEL
- VINBLASTINE
- VINCRIFINE

### MISCELLANEOUS
*(white cards)*
- ANGIOSTATIN
- AMSACRINE
- ARSENIC TRIOXIDE
- L-ASPARAGINASE
- BORTEZOMIB
- CARBOPLATIN
- CISPLATIN
- ERLOTINIB
- Gefitinib
- HYDROXYUREA
- IMATINIB
- PENTOSTATIN
- PROCARBAZINE
- THALIDOMIDE
- TRETINOIN

### ANTIMETABOLITES
- AZATHIOPRINE
- 5-FLUOROURACIL
- 6-THIOGUANINE
- 6-MECAPTOPURINE
- CYTARABINE (ARA-C)
- GEMCITABINE
- METHOTREXATE

### IMMUNOTHERAPY
- ALEMTUZUMAB
- AMINOGLUTETHIMIDE
- BEVACIZUMAB
- CETUXIMAB
- CYCLOSPORINE
- DEXAMETHASONE
- DENILEUKIN DIFTITOX
- EDRECOLOMAB
- GEMTUZUMAB
- IBRITUMOMAB
- INTERFERON α
- INTERLEUKIN 2
- INTERLEUKIN-12
- PREDNISONE
- RITUXIMAB
- TACROLIMUS (FK506)
- TOSITUMOMAB
- TRASTUZUMAB
- TUMOUR NECROSIS FACTOR α

### HORMONES and RELATED AGENTS
- Aminoglutethimide
- Exemestane
- Flutamide
- Goserelin
- Leuprolide
- Tamoxifen

### SUPPORTING AGENTS
- ALLOPURINOL
- ERYTHROPOIETIN
- FILGRASTIM
- INTERLEUKIN 11
- LEUCOVORIN
- MESNA
- SARGRAMOSTIM (GM-CSF)
REVIEW OF NUCLEOTIDE BIOCHEMISTRY

1. FOLATE BIOCHEMISTRY (METHOTREXATE)
   A. Conversion of folate to dihydrofolate and dihydrofolate to tetrahydrofolate is catalyzed by dihydrofolate reductase (DHFR).
   B. Two steps in the conversion of 5-phosphoribosylamine to IMP (purine synthesis) use tetrahydrofolate as a carbon donor.
   C. Tetrahydrofolate is also involved in the generation of dTMP from dUMP (pyrimidine synthesis) – this reaction is catalyzed by thymidylate synthase (see 2A below).

2. PYRIMIDINE SYNTHESIS (5-FLUOROURACIL)
   A. The rate limiting step in DNA synthesis is the conversion of UMP to TMP, which is catalyzed by thymidylate synthase.
   B. Conversion of UMP to UDP is catalyzed by pyrimidine monophosphate kinase; this reaction is important in the development of resistance to 5-FU.
   C. One step in the degradation of thymidine nucleotides is catalyzed by dihydropyrimidine dehydrogenase; an inherited deficiency of this enzyme leads to greatly increased sensitivity to 5-FU.

3. PURINE SYNTHESIS (6-MP, 6-TG, PENTOSTATIN)
   A. De novo purine synthesis begins with the conversion of ribose-5-phosphate to 5-phosphoribosyl-1-pyrophosphate (PRPP), a reaction catalyzed by purine nucleoside phosphorylase (PNP). The first committed step in purine synthesis is the formation of 5-phosphoribosylamine via the enzyme PRPP glutamyl amidotransferase.
   B. IMP and GMP can also be created by via the “salvage pathway” whereby PRPP is combined with hypoxanthine or guanine bases (including 6-MP and 6-TG) by the actions of hypoxanthine-guanine phosphoribosyl transferase (HGPRT).
   C. 6-MP and 6-TG (and their naturally occurring analogues) inhibit guanylyl kinase, preventing the conversion of GMP to GDP.
   D. One route for the degradation of adenosine nucleotides is conversion of AMP back into IMP, a reaction that is catalyzed by adenosine deaminase. This enzyme is inhibited by PENTOSTATIN, which alters the balance of nucleoside diphosphates and leads to a decrease in the activity of ribonucleotide reductase (see 4 below).
   E. One route for the degradation of purine nucleotides (and 6-MP and 6-TG) occurs via conversion of IMP to uric acid. Two steps in that process, conversion of hypoxanthine to xanthine and xanthine to uric acid, are catalyzed by the enzyme xanthine oxidase. This enzyme is inhibited by ALLOPURINOL.

4. CONVERSION OF RIBONUCLEOTIDES TO DEOXYRIBONUCLEOTIDES (HYDROXYUREA)
   This reaction is catalyzed by ribonucleotide reductase.
DRUGS THAT PREVENT DNA SYNTHESIS

Antimetabolites are analogues of folic acid, pyrimidines or purines that interfere with key enzymes used during DNA synthesis. These agents are cell cycle specific (CCS), as their effects occur during S phase. A common mechanism for the development of resistance to these agents is modification of the target enzymes.

General Categories

I. Drugs that prevent nucleotide synthesis (antimetabolites)

II. Inhibitors of DNA synthesizing enzymes:
   CYTARABINE, GEMCITABINE, HYDROXYUREA, PENTOSTATIN

I. ANTIMITABOLITES

Types

1. Folic acid analogues: METHOTREXATE, LEUCOVORIN (used for rescue)

2. Pyrimidine analogues: 5-FLUOROURACIL (5-FU), CYTARABINE, GEMCITABINE

3. Purine analogues: ALLOPURINOL (supporting agent), AZATHIOPRINE, 6-MERCAPTOPURINE, 6-THIOGUANINE, PENTOSTATIN

1. Folic acid analogs:
   METHOTREXATE, LEUCOVORIN

Mechanisms of Action

♦ MTX must have glutamates added - this poly-G/MTX mix more potently binds to DHFR and also prevents MTX from leaving cell (because it is so big)

♦ tumor cells are more capable of polyglutamating MTX \(\rightarrow\) selective toxicity (important re. LEUCOVORIN rescue)
MTX is an inhibitor of *dihydrofolate reductase (DHFR)* and the folate-dependent enzymes of purine and thymidylate synthesis in all species – net result:

1. inhibits DNA synthesis by blocking purine synthesis and deoxythymidylate synthesis (the rate limiting step)
2. prevents catabolism of methionine, histidine, serine and glycine and prevents interconversion of serine and glycine
3. inhibits choline degradation

**Pharmacokinetics**

- uses specific transporters to enter cells
- crosses the blood brain barrier poorly – can be given intrathecally
- readily absorbed from GI tract
- 50% bound to plasma proteins
- 40-90% excreted unchanged in urine (no metabolism) via a combination of glomerular filtration and active tubular secretion → drugs that decrease renal blood flow, are nephrotoxic, or are weak acids can delay excretion and lead to severe myelosuppression (the dose limiting toxicity) – must administer with bicarbonate to maintain urine pH above 6.5

**Resistance**

- changes in target enzymes
  1. production of DHFR with a decreased affinity
  2. increased concentrations of intracellular DHFR
  3. decreased thymidylate synthase activity
- decreased drug accumulation due to impaired transport
Toxicity

♦ primary toxic effects are on bone marrow (danger of spontaneous hemorrhage or life-threatening infection) and GI epithelium

Acute: mucositis, myelosuppression and thrombocytopenia - reach their maximum in 5-10 days, and decrease rapidly thereafter

Delayed: 1. pneumonitis (cough, fever and interstitial infiltrate)
2. hepatic fibrosis
3. alopecia, dermatitis

♦ abortifacaent

LEUCOVORIN RESCUE

♦ administration of LEUCOVORIN along with high dose METHOTREXATE to rescue host tissues from the effects of the intense MTX therapy

♦ LEUCOVORIN provides the normal tissues with reduced folate which circumvents the inhibition of DHFR

♦ only normal cells are able to utilize the LEUCOVORIN, which may be due to differential reactivation of DHFR in normal vs. tumour cells (additional reason for selective toxicity)

♦ net result is that one can use higher dose of MTX \(\rightarrow\) enhanced formation of MTX/polyglutamates \(\rightarrow\):
  1. more antitumor action without increasing toxicity (selective protection for normal cells)
  2. decreased resistance - higher dose can convert resistant cells into susceptible cells (if mechanism of resistance involves inability to actively transport MTX into cell - higher doses result in higher extracellular concentrations which promote diffusion, decreasing dependence on active transport processes)
2. **Pyrimidine analogs**: 5-FLUOROURACIL (5-FU), CYTARABINE (cytosine arabinoside, araC), GEMCITABINE

### 5-FLUOROURACIL (5-FU)

5-FLUOROURACIL inhibits the biosynthesis of pyrimidine nucleotides by inhibiting *thymidylate synthase*, the enzyme that catalyzes the rate limiting step in DNA synthesis. This results in the "thymineless death" of rapidly growing cells.

**Mechanisms of Action**

- **5-FU** cannot be methylated by *thymidylate synthase*, causing sustained inhibition of the enzyme, and decreased production of dTMP.
- Also can mimic function so that **5-FU** is incorporated into DNA or RNA - has other cytotoxic actions including DNA strand breakage and a decrease in protein synthesis.
- Tends not to be particularly effective when given alone – synergistic with METHOTREXATE.
- **LEUCOVORIN** $\uparrow$ binding of 5-FU to thymidylate synthase $\rightarrow$ $\uparrow$ 5-FU $t_{1/2}$

![Thymidylate Synthase Diagram](image)

**Pharmacokinetics**

- 5-FU should be administered parenterally.
- Must be activated (similar to CYCLOPHOSPHAMIDE).
significant metabolic degradation occurs, particularly in liver, but also in many other tissues (inherited deficiency of dihydropyrimidine dehydrogenase leads to greatly increased drug sensitivity)

Resistance

- changes in target enzymes
  1. loss or decreased activity of activation enzymes
  2. decreased pyrimidine monophosphate kinase (decreased incorporation into RNA)
  3. increased expression of thymidylate synthase

Toxicity

- has a low therapeutic index
- primary toxic effects are on bone marrow

Acute: 1. myelosuppression maximal in 9-14 days
         2. anorexia and nausea (indications of sufficient dose!)

Delayed: 1. alopecia, dermatitis
         2. acute cerebellar syndrome (somnolence, ataxia of trunk or extremities, unsteady gait, slurred speech, nystagmus)
3. **Purine analogs:** ALLOPURINOL, AZATHIOPRINE, PENTOSTATIN, 6-MERCAPTOPURINE (6-MP), 6-THIOGUANINE (6-TG)

**Review of purine synthesis**

- **source of ribose is 5-phosphoribosyl-1-pyrophosphate (PRPP) — synthesis of PRPP is catalyzed by purine nucleoside phosphorylase (PNP)**
- **the first committed step in purine synthesis is the formation of 5-phosphoribosylamine via the enzyme PRPP glutamyl amidotransferase**
- **6-MP and 6-TG enter via the “salvage pathway” whereby PRPP reacts with hypoxanthine or guanine bases to form IMP or GMP respectively — this reaction is catalyzed by hypoxanthine-guanine phosphoribosyl transferase (HGPRT)**
- **GMP is converted to GDP by guanylyl kinase**
- **there are numerous negative feedback pathways — the most critical is the "pseudofeedback" inhibition of the first two steps in the purine biosynthetic pathway (ribose-5-phosphate → PRPP → 5-phosphoribosylamine)**

**Mechanisms of Action**

- **AZATHIOPRINE** is converted to **6-MERCAPTOPURINE**

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6-MERCAPTOPURINE and 6-THIOGUANINE must be activated by HGPRT to T-IMP and 6-thioGMP. T-IMP and 6-thioGMP are poor substrates for guanylyl kinase, therefore T-IMP and 6-thioGMP accumulate, causing "pseudofeedback inhibition" of purine nucleoside phosphorylase (PNP) and HGPRT.
♦ these alterations result in:
   1. inhibition of purine nucleotide interconversion,
   2. a decrease in intracellular levels of guanine nucleotides
      (inhibition of glycoprotein synthesis)
   3. interference with DNA and RNA synthesis
   4. incorporation or purinethiols into both DNA and RNA

Pharmacokinetics

6-MERCAPTOPURINE
♦ two metabolic pathways in liver:
   1. methylation and subsequent oxidation
      - the enzyme responsible (thiopurine methyltransferase) has no known natural
        function, and polymorphic inheritance; 15% of UK population has little or no
        enzyme activity, which causes increased toxicity
   2. xanthine oxidase oxides 6-MP to 5-thiouric acid, which is inactive
      → DOSE MUST BE ADJUSTED IF GIVEN WITH ALLOPURINOL

6-THIOGUANINE
♦ unlike 6-MP, it can be administered concurrently with ALLOPURINOL (not
  metabolized by xanthine oxidase)

Resistance
♦ changes in target enzymes
  1. loss or decreased activity of activation enzymes (particularly HGPRT)
  2. decreased ability to inhibit PNP and HGPRT
♦ decreased drug accumulation due to impaired transport
♦ increased inactivation due to increased rates of degradation of the drugs or their
  "activated" analogs
Toxicity

♦ principal toxic effect is bone marrow depression (develops more slowly than with METHOTREXATE)
♦ anorexia, nausea and vomiting occur in 25% of adults; less often in children

TUMOR LYSIS SYNDROME is caused by the sudden, rapid death of millions of cells --- particularly problematic in patients with leukemia or lymphoma. TLS results from the development of electrolyte and metabolic disturbances that can produce life-threatening complications if not managed appropriately.

ALLOPURINOL (a xanthine oxidase inhibitor) is frequently used during chemotherapy of hematologic cancers to prevent hyperuricemia due to tumor cell lysis. The nephrotoxicity and acute gout produced by excessive uric acid are prevented by co-administration ALLOPURINOL with any chemotherapeutic agent.

Simultaneous administration of ALLOPURINOL and 6-MERCAPTOPURINE results in excessive mercaptopurine toxicity (because 6-MP is also metabolized by xanthine oxidase) unless the dose of 6-MP is reduced to 25-30% of normal.

II. INHIBITORS OF DNA SYNTHESIZING ENZYMES

Types

1. Antimetabolites: CYTARABINE, GEMCITABINE, PENTOSTATIN

2. HYDROXYUREA

Mechanisms of Action

1. Antimetabolites:

PENTOSTATIN

♦ inhibits adenosine deaminase, which alters intracellular concentrations of adenosine-containing compounds → inhibits ribonucleotide reductase, which catalyzes the conversion of ribonucleotides to deoxyribonucleotides
**CYTARABINE** (arabinose analog of cytidine; also called cytosine arabinoside, AraC)

- activated by conversion to AraCMP then to AraCDP and AraCTP
- phosphorylated and competes with dCTP for incorporation into DNA
- once inserted into DNA, it blocks DNA elongation by inhibiting DNA polymerase
- also causes reiteration of DNA segments, increasing the probability of mutations
- induces terminal differentiation of leukemic cells

**GEMCITABINE**

- similar to **CYTARABINE**, except cytotoxicity is not confined to S phase (equally effective against confluent cells and cells in log-phase) – still considered to be cell cycle specific!
- influx into cells occurs via active nucleoside transporters
- sequentially phosphorylated to form dFdCMP, then to dFdCDP and dFdCTP
- many sites of action, including:
  1. inhibition of DNA polymerase (similar to **CYTARABINE**)
  2. inhibition of ribonucleotide reductase
  3. incorporation into DNA, leading to DNA strand termination – this step is resistant to DNA repair mechanisms, and is critical for inducing apoptosis

2. **HYDROXYUREA**

- inhibits ribonucleoside reductase
- synchronizes cells in a radiation-sensitive phase of the cell cycle (G₁)
- resistance is due to changes in target enzymes
  1. increased expression of ribonucleotide reductase
  2. acquisition of ribonucleotide reductases with decreased sensitivity
DRUGS THAT INTERFERE WITH PROTEIN FUNCTION

I. SIGNAL TRANSDUCTION INHIBITORS (STIs): ERLOTINIB, GEFITINIB, IMATINIB

♦ tyrosine kinases are important regulators of intracellular signal transduction pathways that are involved in development and multicellular communication – they phosphorylate tyrosine residues
♦ over 1000 different tyrosine kinases have been identified
♦ more than half of the known receptor protein tyrosine kinases have been found in either mutated or overexpressed forms that are associated with malignancies

<table>
<thead>
<tr>
<th>CANCER TYPE</th>
<th>TYROSINE KINASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Bcr-abl</td>
</tr>
<tr>
<td>GIST</td>
<td>c-kit</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HER2</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Src, Yes</td>
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<tr>
<td>Many; inc. glioblastoma</td>
<td>PDGF</td>
</tr>
<tr>
<td>Epithelial derived (e.g., lung, pancreas, head and neck, breast, prostate, colon, stomach, ovaries, and brain)</td>
<td>EGFR</td>
</tr>
<tr>
<td>Many</td>
<td>VEGF (angiogenesis)</td>
</tr>
</tbody>
</table>

Signal transduction inhibitors (STIs) have the potential to revolutionize cancer treatment. First generation tyrosine kinase inhibitors, such as IMATINIB, ERLOTINIB and GEFITINIB bind to the ATP-binding site (NOT the substrate binding site) and prevent phosphate transfer from ATP to the substrate tyrosine. STIs generally have fewer side effects than conventional therapies because they are targeted toward the specific defect of a particular cancer: IMATINIB to bcr-abl in CML, and ERLOTINIB and GEFITINIB to EGFR which is overexpressed in epithelial-derived cancers.
Mechanism of Action

**IMATINIB**
- competitive antagonist of the ATP-binding site of bcr-abl (the non-receptor tyrosine kinase whose activity is deregulated by the translocation of its gene from chromosome 9 to chromosome 22 in most patients with chronic myeloid leukemia)
- preferentially binds to the active form of bcr-abl fusion tyrosine kinase and not to either Ser/Thr-kinases or most other tyrosine kinases – a notable exception is c-kit which is unique to gastrointestinal stromal tumours
- also a weak antagonist of the platelet-derived growth factor (PDGF) receptor

**ERLOTINIB, GEFITINIB**
- competitive antagonists of the ATP-binding site of epithelial growth factor receptor (EGFR)-tyrosine kinase, which is overexpressed in a large number of epithelial-derived cancers – exact mechanism of action is still debated (for example, no studies have been performed that demonstrate a correlation between EGFR receptor expression and response to GEFITINIB)

**Pharmacokinetics**
- oral administration; good bioavailability – GEFITINIB is absorbed more slowly, and less completely than the others
- highly plasma protein bound
- metabolized in the liver (CYP3A4), and excreted in the feces

**Resistance**
- IMATINIB – mutation of ATP-binding site that prevents drug binding in the cancer cells, often due to further mutations of bcr/abl gene (heterogeneity of tumour)
Therapeutic Uses

♦ **IMATINIB** can induce a complete hematological response in 85-95% of patients in the chronic phase of CML; can delay death in 25% of patients in blast crisis (75% of these patients initially respond) – also effective in gastrointestinal stromal tumours expressing c-kit tyrosine kinase

<table>
<thead>
<tr>
<th>Era</th>
<th>Discovery</th>
<th>Drug Treatment</th>
<th>Strategy</th>
<th>Survival</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Disease</td>
<td>None</td>
<td></td>
<td>31 months</td>
<td>0%</td>
</tr>
<tr>
<td>1960</td>
<td>Ph chromosome</td>
<td>Busulfan, Hydroxyurea</td>
<td>Kill all rapidly dividing cells</td>
<td>35-67 months</td>
<td>42% hematologic</td>
</tr>
<tr>
<td>1980</td>
<td>Bcr-Abl gene</td>
<td>Interferon α</td>
<td>Decrease cell proliferation</td>
<td>55-89 months</td>
<td>20-30% cytogenic, 80% hematologic</td>
</tr>
<tr>
<td>2001</td>
<td>Tyrosine kinase inhibitor</td>
<td>Imatinib</td>
<td>Suppress defective enzyme in cancer cells</td>
<td>&gt;5 years</td>
<td>50-95 cytogenic%</td>
</tr>
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Bone marrow transplant is the only curative therapy (30-50%) (patients over 60 do not qualify and not all patients can find a donor → overall cure rate for BMT is under 15%)

♦ **ERLOTINIB** and **GEFITINIB** are approved for use in metastatic non-small cell lung cancer after failure of standard chemotherapies - in a Phase II trial of **GEFITINIB**, 19% of patients showed shrinkage, and in another 34% of patients the tumours were at least temporarily stabilized) - different populations experience varying efficacies (25% of NSCLC cases in Japan, but 10% of cases in the United States) → having the “right” mutation means the difference between a “cure” and no response
Toxicity

♦ relatively minor side effects (esp. compared to standard therapy): nausea, vomiting, hepatotoxicity, drug interactions

♦ IMATINIB can cause edema and muscle cramps

♦ GEFITINIB causes skin rashes and acne; also interstitial pneumonia (which can be fatal)

<table>
<thead>
<tr>
<th>Understanding of the genetic defect</th>
<th>IMATINIB (CML)</th>
<th>GEFITINIB (NSCLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneity of disease process among candidate patients (“likely responders”)</td>
<td>Yes, among patients in chronic phase</td>
<td>No</td>
</tr>
<tr>
<td>Uniqueness of drug target (molecular markers)</td>
<td>Only in cancer cells</td>
<td>In many normal and cancer cells</td>
</tr>
<tr>
<td>Large scale success</td>
<td>Yes</td>
<td>Not really (fails more often than it works)</td>
</tr>
</tbody>
</table>

II. PROTEOSOME INHIBITOR: BORTEZOMIB

Mechanism of Action

♦ reversible inhibitor of the 26S proteasome (a large protein complex that degrades ubiquitinated proteins, esp. misfolded proteins)

♦ the ubiquitin-proteasome pathway is involved in the regulation of the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells - inhibition of the 26S proteasome affects multiple signalling cascades within the cell, leading to cell death

♦ the nature of the specific signalling cascades that are affected may confer specificity of BORTEZOMIB for cancer vs. normal cells, and determine its effectiveness in one type of cancer vs. another

Therapeutic Uses

♦ multiple myeloma
Toxicity

- asthenia (fatigue, malaise and weakness) and pyrexia
- nausea and vomiting, diarrhea or constipation, decreased appetite (including anorexia)
- thrombocytopenia, neutropenia and/or anemia
- peripheral neuropathy

### III. L-ASPARAGINASE

Asparagine $\rightarrow$ Aspartate

**L-asparaginase**

- selective toxicity because some tumour cells lack *asparagine synthetase* (i.e., they require an exogenous source of L-asparagine for protein synthesis)
- used to treat childhood acute lymphocytic leukemia
- main side effects are *hypersensitivity reactions* (fever, chills, nausea vomiting, skin rash and urticaria) because ASPARAGINASE is isolated from bacteria
- usually used with other agents; sequence of drug administration is critical (e.g., if METHOTREXATE is given first, you have synergistic cytotoxicity; if L-ASPARAGINE is given first, the METHOTREXATE cytotoxicity is reduced as METHOTREXATE toxicity is dependent upon synthesis of the enzymes necessary for DNA synthesis)
HEMATOPOIETIC AGENTS (COLONY STIMULATING FACTORS)
ERYTHROPOIETIN, FILGRASTIM, INTERLEUKIN 11, SAGRAMOSTIM (GM-CSF), THROMBOPOIETIN

Bone marrow suppression is the dose-limiting complication of many antineoplastic drugs. Recombinant forms of several lineage-dependent colony stimulating factors have been developed. These factors activate specific progenitor cells, resulting in the production of: ERYTHROPOIETIN → red blood cells, FILGRASTIM (G-CSF) → neutrophils, SAGRAMOSTIM (GM-CSF) → granulocytes, eosinophils, basophils and monocytes and INTERLEUKIN 11 and THROMBOPOIETIN → platelets.
Mechanism of Action

♦ **ERYTHROPOIETIN** is the most important (but not sole) regulator of the proliferation of the committed red blood cell progenitors BFU-E and CFU-E

♦ **FILGRASTIM (G-CSF)** regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and functional activation

♦ **INTERLEUKIN 11** stimulates BFU-meg to increase platelet production

♦ the primary therapeutic effect of **SAGRAMOSTIM (GM-CSF)** is stimulation of myelopoiesis

♦ **THROMBOPOIETIN** regulates platelet production

Toxicity

♦ **FILGRASTIM**: mild to moderate bone pain

♦ **INTERLEUKIN-11**: side effects include mild to moderate generalized edema due to sodium retention, conjunctival infection, tachycardia and atrial fibrillation (especially in elderly or children) – doesn’t cause fever (unlike many other cytokines)

♦ **SAGRAMOSTIM**: higher doses are associated with bone pain, flulike symptoms, fever, diarrhea, dyspnea and rash – some patients are extremely sensitive, exhibiting flushing, hypotension, nausea, vomiting and dyspnea, and a fall in arterial oxygen saturation due to sequestration of granulocytes in the pulmonary circulation
DRUGS TARGETING THE IMMUNE SYSTEM

General Categories

I. Immunosuppressive agents
II. Immune system stimulants

I. IMMUNOSUPPRESSIVE AGENTS

<table>
<thead>
<tr>
<th>Cancer Chemotherapy</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Unstimulated</td>
</tr>
<tr>
<td>Cell Division</td>
<td>Random</td>
</tr>
<tr>
<td>Drug Administration</td>
<td>High dose, “pulse”</td>
</tr>
</tbody>
</table>

Types

1. Glucocorticoids:
   - AMINOLIGUTETHIMIDE,
   - DEXAMETHASONE,
   - PREDNISONE

2. Antibiotics: CYCLOSPORINE, TACROLIMUS (FK506)

Mechanisms of Action

1. GLUCOCORTICOID:
   - interfere with the cell cycle of activated lymphoid cells
   - most steroid-sensitive cancers have specific receptors for corticosteroids (e.g. prednisone-sensitive lymphomas)
   - PREDNISONE is used in the MOPP treatment for Hodgkin’s disease
2. ANTIBIOTICS

- bind to cytoplasmic proteins (CYCLOSPORINE to cyclophilin and TACROLIMUS to FK-binding protein)
- both agents inhibit calcineurin, which is necessary for activation of NFAT, a T cell-specific transcription factor that is involved in the synthesis of interleukins by activated T cells
- primary use as immunosuppressants during bone marrow transplants (BMT); somewhat successful in treating relapsed or refractory leukemias
II. IMMUNOSTIMULANTS

1. INTERLEUKINS

Mechanisms of Action

♦ increase proliferation of stem cells and megakaryocyte progenitor cells, leading to increased production of platelets

INTERLEUKIN 2 (IL-2)

♦ induces and expands a T-cell response cytolytic for tumour cells

♦ used either as a single agent or with adoptive cellular therapy using IL-2-stimulated autologous lymphocytes [“lymphokine-activated-killer” (LAK) cells]

Therapeutic Uses

♦ INTERLEUKIN 2 is approved for the treatment of metastatic renal cell carcinoma and malignant melanoma - it is being investigated for use in acute myelogenous leukemia in relapsed patients or following bone marrow transplantation

Pharmacokinetics

♦ either continuously infused or given as multiple intermittent doses due to its short half-life ($t_{1/2}^\alpha=13$ minutes; $t_{1/2}^\beta=85$ minutes)

Toxicity

♦ activation and expansion of lytic lymphocytes causes inflammation, vascular leak and secondary release of other cytokines (e.g. TNF, interferon)

♦ can cause hypotension (can be fatal), arrhythmias, peripheral edema, vomiting and diarrhea
2. INTERFERONS

Mechanism of Action
♦ secreted by leukocytes (mainly)
♦ bind to receptors found on all cell types and decrease cell proliferation
♦ may activate T cells
♦ INTERFERON α decreases production of the angiogenic protein FGF

Therapeutic Uses
♦ INTERFERON α is approved for hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma and Karposi’s sarcoma, and is in phase III clinical trials for treatment of hemangiomas in infants

Toxicity
♦ fever, myalgias, arthralgias, headache, fatigue, hypotension, myelosuppression, anorexia, confusion, depression, nephrotoxicity

3. TUMOR NECROSIS FACTOR α

Mechanism of Action
♦ similar to IL-1 in terms of action
♦ effects on many cell types (at least 17 different kinds)
♦ most important effect is enhanced binding of antigen-presenting cells to T helper cells
♦ may be released from macrophages
♦ induction by TNF is mediated through both interferon-dependent and -independent mechanisms
♦ may be more effective in patients who have previously received chemotherapy
Therapeutic Uses

- **TUMOR NECROSIS FACTOR α** is approved for use in malignant melanoma and soft tissue sarcoma of the extremities

Pharmacokinetics

- **intra-arterial administration** due to extremely short half-life and toxicity

Toxicity

- severe dose-limiting toxicity is **malaise and flu-like symptoms**, similar to those seen with Coley’s toxins

4. **ANTIBODIES and FUSION PROTEINS**

As molecular targets are identified that distinguish cancer cells from normal cells, monoclonal antibodies have been developed that can selectively recruit the immune system to destroy the cancer cells. Currently, antibodies have been designed that target CDs (CD20 in NHL, CD33 in AML, and CD52 in B-CLL), and cell surface proteins (HER2, 17-1A, VEGF, EGFR) that are overexpressed in specific cancers.

Types and Therapeutic Uses

1. **Block CD52**: **ALEMTUZUMAB** (Campath) - B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with failed conventional therapy

2. **Block VEGF**: **BEVACIZUMAB** – discussed under antiangiogenesis

3. **Block EGFR**: **CETUXIMAB** (Erbitux) – colon cancer that has metastasized

4. **Block CD33**: **GEMTUZUMAB** (Mylotarg) - patients 60 years and older in first relapse with CD33-positive acute myeloid leukemia (AML) who are not considered candidates for cytotoxic chemotherapy

5. **Block CD20**: **RITUXIMAB** (Rituxan) and **TOSITUMOMAB** (Bexxar) - relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin’s lymphoma - **IBRITUMOMAB** (Zevalin) - first radiolabelled antibody approved! – relapsed or refractory low grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL), including patients with rituximab-refractory follicular NHL
6. **Block HER2 (ErbB2):** TRASTUZUMAB (Herceptin) - patients with metastatic breast cancer whose tumors overexpress the HER2 protein (combined with PACLITAXEL if they have not previously received chemotherapy)

7. **Block 17-1A** (cell-surface adhesion molecule that is expressed in a variety of tumors): EDECOLOMAB (Panorex) – colon cancer

8. **Target IL-2 receptors:** DENILEUKIN DIFTITOX (Ontak) is a fusion protein that has diphtheria toxin coupled to IL-2, with the goal of killing cells expressing IL-2 receptors (activated T lymphocytes, activated B lymphocytes and activated macrophages) – cutaneous T-cell lymphoma

**Pharmacokinetics**

- slow IV administration
- **long half-lives** - detectable at least 3-6 months after completion of treatment

**Toxicity**

Common to all:

1. hypersensitivity reactions (e.g., fever, muscle aches, headaches, rashes, anaphylaxis)
2. infections
3. unknown effects on immunization, carcinogenesis, mutagenesis, impairment of fertility, pregnancy, nursing infants (human IgG is secreted in milk)

<table>
<thead>
<tr>
<th>ALEMTUZUMAB</th>
<th>CETUXIMAB</th>
<th>GEMTUZUMAB</th>
<th>RITUXIMAB TIBRITUMOMAB, TOSITUMOMAB</th>
<th>TRASTUZUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>irregular heartbeat</td>
<td></td>
<td></td>
<td>cardiac arrhythmias</td>
<td>cardiac cardiotoxicity (ventricular dysfunction and CHF)</td>
</tr>
<tr>
<td>cough/tightness in chest/difficulty breathing</td>
<td>interstitial lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difficult urination</td>
<td>infusion reactions</td>
<td>seizures</td>
<td>tumour lysis syndrome</td>
<td>diarrhea</td>
</tr>
<tr>
<td>desquamation/rash</td>
<td>inability to speak</td>
<td></td>
<td></td>
<td>anemia, leukopenia</td>
</tr>
</tbody>
</table>
ANGIOGENESIS INHIBITORS

♦ all tissues (including tumors) secrete substances that promote or inhibit angiogenesis (the formation of new blood vessels) – more than 35 angiogenesis stimulators and 18 suppressors have been described so far

♦ once a group of cancer cells reaches a certain size (1–2 mm in diameter), it must develop a blood supply in order to grow because diffusion is no longer adequate to supply the cells with oxygen and nutrients and to take away wastes

♦ some tumors secrete substances that inhibit angiogenesis at other tumor sites, which leads to the clinical phenomenon whereby:

1. A patient has a primary tumor, and there is no evidence that the primary tumor has metastasized.

2. A surgeon removes the primary tumor.

3. Some weeks later, metastases of the tumor appear throughout the patient's body. The speed of their appearance indicates that they were present all along but too small to be detected (this is one of the justifications for chemotherapy as an adjunct to surgery for the treatment of solid cancers).

I. INTERFERON α

♦ decreases the production of the angiogenic protein FGF

II. INTERLEUKIN 12

♦ drives Th-cell differentiation throughout a T helper type 1 cell type of response, thus inducing interferon gamma (IFNγ) and favouring a switch from Ig to IgG2a

♦ some toxicity in humans has hampered its further development into clinical applications – being investigated for use in neuroblastoma, renal cell carcinoma, malignant melanoma, breast cancer when restricted to local administration

III. ANGIOSTATIN

♦ fragment of plasminogen that is normally secreted by tumors

♦ may be a prototype for a new class of agents with which to treat cancer
IV. BEVACIZUMAB

♦ monoclonal antibody directed against vascular endothelial growth factor (VEGF)

♦ approved (in combination with 5-FLUOROURACIL) for first-line treatment of patients with metastatic carcinoma of the colon or rectum – also being investigated in many other cancers (including NSCLC)

♦ can result in the development of gastrointestinal perforation and wound dehiscence (can be fatal)

♦ serious, and in some cases fatal, hemoptysis has occurred in patients with non-small cell lung cancer

V. THALIDOMIDE

**THALIDOMIDE** is a developmental toxin whose only approved use is in the treatment of Hansen’s disease, although it has significant off-label use in AIDS treatment and in multiple myeloma. **THALIDOMIDE** has significant teratogenic effects (especially phocomelia) in the children and grandchildren of women who take the drug while pregnant.

**Mechanism of Action**

♦ reintroduced in 1998 (in the US) for use in erythema nodosum leprosum (ENL is characterized by painful skin nodules and nerve damage), a complication of Hansen’s disease

♦ in Hansen’s disease, works by suppressing immune and inflammatory reactions i.e., doesn’t function as an antibiotic – as soon as treatment is stopped, symptoms reappear

♦ unknown, complex mechanism of action - no toxic effect on cells of the immune system, but does alter the ratios of various types of immune cells and changes the expression of molecular markers on their surfaces
Specifically:

1. causes a shift in the pattern of T cell responses, favouring a Th2 response over a Th1 response (“more interleukins, less interferon and TNF”) – perhaps most effective anti-TNF agent known
2. antiangiogenesis and decreased cell movement (anti-metastatic?)
3. sedation and improved well being – prescribed as “wonder drug for prevention of morning sickness” – restores appetite and decreases wasting

Pharmacokinetics

♦ not very soluble in water and thus does not distribute rapidly through the body
♦ unstable at physiological pH
♦ breakdown products are rapidly excreted via the kidneys

Therapeutic Uses

♦ multiple myeloma (response rates 80% or better)
♦ active investigation in metastatic colon cancer, Kaposi’s sarcoma, brain, small cell lung and bone cancer

Toxicity

♦ relatively few side effects in adult males and non-pregnant females, other than peripheral neuropathy, loss of feeling and sensation in the extremities, nausea, constipation and rashes
♦ increased risk of deep vein thrombosis, particularly in multiple myeloma patients (most patients are placed on WARFARIN when thalidomide treatment is initiated)
♦ severe teratogenic effects occur 3-5 weeks postconception, in both children and grandchildren of thalidomide patients – defects include malformed intestines, hearing defects, absent ears, and/or ocular and renal anomalies – esp. phocomelia — it is estimated that 40% of thalidomide victims die within a year of birth - today there are approximately 5000 thalidomide survivors worldwide
DIFFERENTIATING AGENTS

TREINOIN, ARSENIC TRIOXIDE (ATO)

One hallmark of malignant transformation is differentiation block. Numerous chemicals --- including vitamin D and its analogues, retinoids (vitamin A derivatives such as TREINOIN), rexinoids (multifunctional nuclear retinoid X receptor ligands), benzamides and other inhibitors of histone deacetylase (HDAC) and inhibitors of DNA methylation --- can all induce tumour cell differentiation, ultimately leading to apoptosis.

♦ an example of differentiation block occurs due to the t(15;17) translocation in acute promyelocytic leukemia (APL) – this mutation directly confers the block by creating a fusion protein of portions of the retinoic acid receptor α and promyelocytic leukemia protein (PML-RARα)

♦ TREINOIN (all-trans retinoic acid; ATRA) activates the differentiation program and promotes degradation of the PML-RARα fusion gene - side effects include dry skin, reversible hepatic enzyme abnormalities, bone tenderness, hyperlipidemia and retinoic acid syndrome (fever, dyspnea, weight gain, pulmonary infiltrates and pleural or pericardial effusions)

♦ ARSENIC TRIOXIDE (ATO) is a heavy metal toxin that is a highly effective treatment for relapsed APL (complete responses in 85% of patients) – ATO is thought to work via induction of differentiation and promotion of apoptosis (although it has many other cytotoxic effects) – pharmacological doses are generally well tolerated, although arrhythmias due to prolongation of the QT interval and a leukocyte maturation syndrome similar to retinoic acid syndrome have been reported
STRATEGIES FOR CANCER CHEMOTHERAPY

I. COMBINATION CHEMOTHERAPY

PRINCIPLES OF COMBINATION DRUG SELECTION:
♦ active when used alone
♦ different mechanisms of action
♦ CCNS vs. CCS or active in different stages of cell cycle
♦ different toxicities

RESULT IN:
♦ decreased development of resistance
♦ synergistic effects
♦ decreased toxic effects

Examples of combination drug therapy:

1. Hodgkin’s disease:
   MOPP: mechlorethamine, Oncovin (vincristine), procarbazine and prednisone
   ABVD: Adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine

2. Non-Hodgkin’s lymphoma
   COP: cyclophosphamide, Oncovin (vincristine), and prednisone, with or without doxorubicin (COP-D or CHOP)

3. Testicular carcinoma:
   PVB: Platinol (cisplatin), vinblastine and bleomycin

4. Breast carcinoma:
   CMF: cyclophosphamide, methotrexate and 5-fluorouracil (with or without tamoxifen)
   FAC: 5-fluorouracil, Adriamycin (doxorubicin), cyclophosphamide

II. PULSE THERAPY

♦ Intermittent treatment with very high doses of a drug
♦ Allow hematologic and immunologic recovery between courses

Example: METHOTREXATE for the treatment of choriocarcinoma
III. RESCUE THERAPY

♦ Following administration of toxic doses of some chemotherapeutic agents, normal cells can be rescued by giving “antidotes”

♦ LEUCOVORIN can be used as a rescue during high dose treatment of METHOTREXATE – must monitor METHOTREXATE levels and maintain the output of alkaline urine, to prevent precipitation in renal tubules

IV. RECRUITMENT

♦ Use a CCNS drug to achieve a significant log kill (causing cancer cells in the Go phase to be recruited back into the cell cycle), then administer a CCS drug to kill dividing cells e.g., CMF for treatment of breast cancer

V. SYNCHRONY

♦ timing the drug combination in a way that produces a tumour cell kill that is greater than the additive effects of the individual agents e.g., use vinca alkaloids to kill cancer cells in M phase, then treat with another CCS drug (such as S phase-specific agent); also, cytarabine + anthracycline antibiotic in acute myelogenous leukemia