Overview

- Cellular kinetics
- Tumor kinetics
- Principles of combination chemotherapy
- Dose intensity
- Overcoming chemo resistance
- Classes of agents/ dose/use
- Targeted agents
Cell Cycle

- **S** - Replication of DNA
- **G1** - Gap 1 (cell grows)
- **G2** - Gap 2 (cell prepares to divide)
- **M** - Mitosis (cell division)

Interphase:

- **G1**
- **S**
- **G2**

Mitotic Phase:

- **M**

Cells that cease division
Principles of chemotherapy

The mitosis stages

Daughter cells → Interphase → Prophase → Metaphase → Anaphase → Telophase
Electron micrograph of mitotic cell
Sites of action of cytotoxic agents

Cell cycle level

- **Antibiotics**
  - Site: $S$ (2-6h)

- **Antimetabolites**
  - Site: $G_2$ (2-32h)

- **Alkylating agents**
  - Site: $M$ (0.5-2h)

- **Vinca alkaloids**

- **Mitotic inhibitors**

- **Taxoids**

Cell cycle phases:
- $G_0$
- $G_1$ (2-$\infty$h)
- $S$ (2-6h)
- $G_2$ (2-32h)
- $M$ (0.5-2h)
Sites of action of cytotoxic agents

DNA synthesis

DNA transcription

DNA duplication

Intercalating agents

Antimetabolites

Alkylation agents

Mitosis

Spindle poisons

Cellular level
Sites of action of cytotoxic agents

- Purine Synthesis
- Pyrimidine Synthesis
- Ribonucleotides
- Deoxyribonucleotides
- DNA
- RNA
- Proteins
- Enzymes
- Microtubules
- Alkylating Agents
- Antibiotics
- L-Asparaginase
- Vinca Alkaloids
- Taxoids
## Cell cycle phase specific drugs

<table>
<thead>
<tr>
<th>S phase–dependent</th>
<th>M phase–dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Vinca alkaloids</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Vinblastine</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Vinorelbine</td>
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<tr>
<td>Floxuridine</td>
<td>Podophyllotoxins</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Teniposide</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Taxanes</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Docetaxel</td>
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<tr>
<td>Methotrexate</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Procarbazine</td>
<td>G₂ phase–dependent</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>Bleomycin</td>
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<tr>
<td></td>
<td>Irinotecan</td>
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<td></td>
<td>Mitoxantrone</td>
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<td>Topotecan</td>
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<tr>
<td></td>
<td>G₁ phase–dependent</td>
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<tr>
<td></td>
<td>Asparaginase</td>
</tr>
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<td></td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

*a Have greatest effects in S phase and possibly late G₂ phase; cell blockade or death, however, occurs in early mitosis.

Cytokinetics

- Malignancies have three cell types
  - Actively dividing
  - Resting but with potential to multiply
  - Non-dividing without potential to multiply

- Actively dividing are a small fraction, most drug sensitive, but same drugs are also affect other rapidly dividing cells like bone marrow and GI mucosa
Concept of tumor cell burden and relation to phases of treatment
Tumor cell burden and relation to response to treatment

- Leukemia line L1210 has growth fraction of 100%, doubling time is 12 hours
- $10^9$ cells if you inject 1 cell, in 19 days
- Or $10^5$ in 10 days, or $10^8$ in 5 days
- Time to death is time required to get to $10^9$ cells
- Increase in 2 days of life = 90% destruction of cells (1 log kill), decrease from $10^6$ to $10^5$
- 99.999% kill = 5 log kill doesn’t cure even in animals unless initial burden is $10^4$
Combination chemotherapy is necessary to achieve log kill where populations of tumor cells are not equally sensitive to a single drug.
Gompertzian growth kinetics

- Some tumors have fewer dividing cells when the tumors get larger and hence a slower growth rate
Alternating chemotherapy to overcome resistance may not be helpful
Principles of combination chemotherapy

- Provides maximal cell kill within the range of toxicity tolerated by the host for each drug
- Broader coverage of resistant cell lines in a heterogeneous tumor population
- Prevents or slows development of drug resistant cell lines
Drug selection for combination regimens

- Drugs known to be active as single agents should be selected for combinations. Preferentially, drugs that induce complete remissions should be included.
- Drugs with different mechanisms of action should be combined in order to allow for additive or synergistic effects on the tumor.
- Drugs with differing dose-limiting toxicities should be combined to allow each drug to be given at full or nearly full therapeutic doses.
- Drugs should be used in their optimal dose and schedule.
- Drugs should be given at consistent intervals. The treatment-free interval between cycles should be the shortest possible time for recovery of the most sensitive normal tissue.
- Drugs with different patterns of resistance should be combined to minimize cross-resistance.
Designing drug combinations

- FOLFOX is a commonly used regimen for colon cancer: 5-FU, oxaliplatin, folinic acid
- 5FU is an antimetabolite, structural analog of pyrimidine, most active in S phase
- FdUMP, the active phosphorylation form of 5-FU combines with methylene THF and thymidylate synthetase forming a stable complex which prevents the conversion of uridine to thymidine. The 6th carbon of FdUMP is bound covalently to the enzyme with the methylene group covalently linking to the 5-carbon of the nucleotide.
- Excess of folic acid by supplying sufficient amount of methylene THF increases the complex formation and, therefore, improves the efficacy of 5-FU given at the same dose.
Designing drug combinations

- Oxaliplatin is a heavy metal complex cell cycle non-specific drug that forms intra and interstrand DNA crosslinks and DNA adducts. Diarrhea, thrombocytopenia and neuropathy are side effects.
Designing drug combinations

- Four-drug CHOP combination for lymphoma (cyclophosphamide, hydroxydaunomycin, Oncovin, and prednisone). CHOP consists of intermittent doses of:
- Cyclophosphamide, an alkylating agent whose major toxicities are marrow suppression and bladder irritation
- Doxorubicin, an antibiotic with topoisomerase (DNA repair)-inhibiting and DNA-intercalating properties whose major toxicities are marrow suppression and cardiac toxicity at higher doses
- Vincristine, a vinca alkaloid with peripheral nerve toxicity, but very little bone marrow suppression
- Prednisone, a synthetic corticosteroid hormone with effects on glucose metabolism and bone matrix
Designing drug combinations

• Paclitaxel- cisplatin: vehicle of paclitaxel may reduce myelotoxicity of cisplatin. Give taxol before cis, as cis potentiates taxol toxicity if given first

• 5-FU-leukovorin: 5-Fu binding to Ts requires folate as a cofactor, increased folate may increase efficacy of 5-FU

• MOPP: (mechlorethamine/vincristine (Oncovin)/procarbazine/ prednisone),

• CMF: (cyclophosphamide/methotrexate/5-FU)

• CAF: (cyclophosphamide/doxorubicin (Adriamycin)/5-FU).
Combination therapy

• Rationale
• Improved survival (esophageal cancer 5-Fu/cis + Rt vs RT)
• Improved local control (Rectal cancer)
• Larynx sparing (cis+5Fu +RT vs surgery +RT)
• Avoid toxicity of chemotherapy with equal survival (CHOP +RT vs CHOP)
Aim of combination therapy

**INCREASED EFFICACY**

activity
- Different mechanisms of action
- Different mechanisms of resistance

safety
- Compatible side effects
Goals of chemotherapy

1. Induction in advanced disease
2. Adjunct to local methods
3. Primary treatment for local disease when local therapy alone is inadequate
4. Direct instillation into sanctuary sites
Chemotherapy as initial treatment

- Neoadjuvant (before surgery to shrink the cancer eg. Breast cancer, rectal, esophageal cancer)
- Adjuvant (after surgery to prevent recurrence eg gastric, breast, lung cancer)
- Definitive (early stage but sensitive to chemotherapy- testicular cancer, lymphoma)
- Metastatic (advanced cancer to control growth i.e. palliative eg. most solid tumors)
- Local infusion (FUDR pump in liver, BCG bladder)
Endpoints in evaluating response

- RECIST criteria (Response Assessment In Solid Tumors) complete response, partial response, stable disease, symptomatic deterioration, progressive disease.
- WHO criteria (World Health Organization)
## RECIST vs WHO criteria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RECIST</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (LD is the longest diameter)</td>
<td><strong>Target lesions</strong> (change in sum of LDs, maximum 5 per organ up to 10 total [more than one organ])</td>
<td><strong>Measurable disease</strong> (change in the sum of the products of LDs and greatest perpendicular diameters, no maximum number of lesions specified)</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>Disappearance of all target lesions, confirmed at ≥ 4 weeks</td>
<td>Disappearance of all known disease, confirmed at ≥ 4 weeks</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>≥ 30% decrease from baseline, confirmed at ≥ 4 weeks</td>
<td>≥ 50% decrease from baseline, confirmed at ≥ 4 weeks</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>≥ 20% increase over smallest sum observed or appearance of new lesions</td>
<td>≥ 25% increase in one or more lesions or appearance of new lesions</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Neither PR nor PD criteria met</td>
<td>Neither PR nor PD criteria met (no change)</td>
</tr>
</tbody>
</table>

RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization
Other endpoints in evaluating response

- Quality of life
- Marrow tumor burden (leukemias, myeloma)
- Resectability (R0, R1, R2)
- Survival
- Progression free survival
- Time to treatment failure
Treatment decision

- Natural history of the particular patient's disease
- Type and severity of symptoms
- Current activity level (performance status) of the patient
- Age
- Likely response rate of this malignancy to available therapy
- Measurability of response to therapy
- Psychosocial aspects of the patient, including motivation for treatment, availability of support systems, and financial consequences of therapy for the patient and family
Treatment decision-contd

• Biologic characteristics of the neoplastic disease
• Pharmacology of the agents to be used
• Spectrum of drug effectiveness as determined through clinical trials and through currently available *in vitro* predictive tests
• Clinical condition of the patient, including nutrition, infections, hematologic status
Dose intensity

- DI = amount of drug delivered per unit time expressed as milligrams per square meter per week, regardless of schedule or route.
- Relative Dose intensity = the same but relative to a standard regimen.
- Example: Std: Drug A 80mg/m²/day = 560mg/m²/wk
- Test: Drug A 100mg/m²/day D1-14 every 28 days, = 350mg/m²/wk
- DI = 350/560 = 0.62
Dose dense therapy

Conclusions

Dose-dense sequential application of Epirubicin and Paclitaxel with G-CSF as preoperative treatment of primary breast cancer (>3cm or inflammatory) resulted in a significant increase in the rates of

1. Measurable response 66% vs 59%
2. Pathologic CR (pT0, pTis) 19% vs 10%
3. Histologically negative nodes 50% vs 41%
4. Breast conservation 61% vs 50%

Toxicities were comparable between treatment arms with no significant increase in Grade 3+ Toxicities
Adjuvant Cyclophosphamide, Methotrexate and Fluorouracil in Node-Positive Breast Cancer*

![Graphs showing relapse-free survival and overall survival over years after mastectomy.](image)

*Relapse-free survival (panel A) and overall survival (panel B) according to the percentage of the optimal dose administered.

Dose and timing (dose density)

Effect of chemotherapy dose intensity and density on tumor cell kill and regrowth between cycles
Overcoming chemotherapy resistance

- Variety of reasons for chemotherapy failure in cancer patients
- Anatomic
- Pharmacologic
- Physiologic
- Mutations
- Biochemical (increased repair, drug efflux, altered drug targets, altered gene expression)
Mechanisms of drug resistance

• ANATOMIC: local intra peritoneal, CNS penetration

• PHARMACOLOGIC: Absorption- most IV, few subcutaneous/IM or oral

• Distribution Activation/Inactivation:
  -Activation of the alkylating agent, cyclophosphamide, requires mixed-function oxidase system of the liver.
  -5-FU must be phosphorylated before it is active.
  -Inactivation of the purine analogue 6-mercaptopurine is by enzyme xanthine oxidase. Allopurinol inhibits this enzyme and is often used to prevent hyperuricemia hence 6-MP dose needs to be reduced.
Pharmacology

- Drugs requiring dose modification for liver dysfunction
  - Amsacrine
  - Daunorubicin
  - Doxorubicin
  - Epirubicin
  - Idarubicin
  - Mitoxantrone
  - Paclitaxel
  - Docetaxel
  - Vinblastine
  - Vincristine
  - Thiotepa
  - Irinotecan
# Pharmacology

- Drugs requiring dose modification for renal dysfunction
  - Methotrexate
  - Capecitabine
  - Cladribine
  - Fludarabine
  - Cisplatin
  - Carboplatin
  - Oxaliplatin
  - Cyclophosphamide
  - Ifosfamide
  - Etoposide
  - Hydroxyurea
  - Streptozocin
  - Topotecan
  - Bleomycin
Mechanisms of Resistance

• PHYSIOLOGIC:
  – Inaccessible compartment
  – Impaired blood supply: inadequate drug exposure and hypoxia
  – Cell cycle specificity of drugs
Apoptosis and mutations

- Role of intact P53 is to trigger apoptosis (programmed cell death) in response to DNA damage.
- In >50% of cancers mutated P53 is present
- This results in the loss of ability to induce apoptosis in response to chemotherapy and radiation
- Bcl-2 potent suppressor of apoptosis is mutated in certain leukemias and lymphomas and is a target for antisense Bcl-2 mRNA therapy
Gene mutations that correlate with response

- EGFR mutations have been reported to predict response, lack of these mutations = poor response
- Activating mutations in Kit and PDGFR genes shows to correlate with response to Gleevec
**Structure of KIT Receptor**

- Type III receptor tyrosine kinase
- Extracellular domain binds ligand: stem cell factor (SCF)
- Downstream effects of SCF binding to KIT are proliferative and antiapoptotic
- Intracellular domain has
  - 2 tyrosine kinase domains
  - Multiple autophosphorylation sites
Normal KIT Signaling

• The KIT kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation

• This activated substrate initiates a signaling cascade culminating in cell proliferation and survival

GIST: Identification of KIT Gain-of-Function Mutations

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

- KIT staining was positive in 46 of 49 GIST (94%)
- 5 of 6 GIST had mutations in KIT gene
- Mutant forms of KIT are constitutively active
- Proposed that GIST may originate from ICCs
- Studies in knock-in mice with KIT mutations
  - Demonstrated that constitutive KIT signaling is sufficient to induce GIST
  - Parallel with the pathology seen with familial KIT mutations, eg, mastocytosis
GIST: Mutation Status and Prognosis

**Most Patients With GIST Will Carry KIT or PDGFRA Mutations**

- **KIT**
  - Exon 9 (18.1%)
  - Exon 11 (66.9%)
  - Exon 12 (0.8%)
  - Exon 13 (1.6%)
  - Exon 17 (1.8%)
- **PDGFRA**
  - Exon 18 (3.9%)

**Overall mutation frequency: 92.9%**

**Table 2. Relationship Between Kinase Genotype, Response And Outcome During Imatinib Therapy**

<table>
<thead>
<tr>
<th></th>
<th>EORTC phase I/II (n=37)</th>
<th>B2222 Phase II (n=127)</th>
<th>EORTC-Austral-Asian Phase III (n=363)</th>
<th>Overall Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td><strong>KIT exon 11</strong></td>
<td>83% (24)</td>
<td>*83% (85)</td>
<td>*70% (248)</td>
<td>74% (378)</td>
</tr>
<tr>
<td><strong>KIT exon 9</strong></td>
<td>25% (4)</td>
<td>48% (23)</td>
<td>35% (58)</td>
<td>38% (85)</td>
</tr>
<tr>
<td>No mutation</td>
<td>33% (6)</td>
<td>0% (9)</td>
<td>25% (52)</td>
<td>22% (61)</td>
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<tr>
<td><strong>Progressive disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KIT exon 11</strong></td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>KIT exon 9</strong></td>
<td>0%</td>
<td>17%</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td>No mutation</td>
<td>33%</td>
<td>56%</td>
<td>19%</td>
<td>25%</td>
</tr>
</tbody>
</table>
GIST: KIT and PDGFRA Mutations Predict Overall Survival

Biochemical mechanisms of resistance

- Decreased drug uptake or increased export
- Decreased drug-activating enzymes
- Increased drug-inactivating enzymes
- Increased levels of the inhibited target enzyme
- Altered affinity of the target enzyme for the drug
- Increased DNA repair
- Increase in an alternative metabolic pathway bypassing the drug inhibition
Mechanisms of Resistance

• Genetic
  – Abnormal transport, either decreased uptake or increased efflux (MDR, MRP, MTX transport)
  – Increased or altered target gene product (DHFR)
  – Increased intracellular metabolism or decreased activation (uridine kinase deficiency)
  – Increased intracellular binding (glutathione)
  – Enhanced DNA repair (uvrABC)
P-glycoprotein MDR pump

• 1. Normal P-gp function in the plasma membrane of a cancer cell during chemotherapy.
• 2. Competitive inhibition of the P-glycoprotein transporter.
Metabolism of cytotoxic agents

Cyclophosphamide

4-KETOCYCLOPHOSPHAMIDE
CARBOXYPHOSPHAMIDE

4-OH CYCLOPHOSPHAMIDE
ALDOPHOSPHAMIDE

HEPATIC CYTOCHROMES P 450

ACTIVATION

INACTIVATION
ALDEHYDE
DEHYDROGENASE

ACROLEIN

TOXICITY

PHOSPHORAMIDE
MUSTARD

CYTOTOXICITY
Drug resistance

EXTRACELLULAR

PGP<sub>170</sub>

ATP

Drug

INTRACELLULAR

ATP

Drug

Plasma Membrane
Chemotherapy Agents

- Antimetabolites
- Alkylating Agents
- Atypical alkylators
- Plant Alkaloids
- Antitumor antibiotics
- Antitumor enzymes
- Immunotherapies
- Monoclonal Antibodies

- Aromatase Inhibitors
- Tyrosine kinase inhibitors
- Prostatic hormones
- Proteasome Inhibitors
- Antiangiogenics
Classification of cytotoxic agents

<table>
<thead>
<tr>
<th>Alkylation Agents</th>
<th>Anti-Metabolites</th>
<th>Mitotic Inhibitors</th>
<th>Antibiotics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Cytosine</td>
<td>Etoposide</td>
<td>Bleomycin</td>
<td>L-asparaginase</td>
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<tr>
<td>Carmustine</td>
<td>Arabinoside</td>
<td>Teniposide</td>
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<td>Cisplatin</td>
<td>Fluorouracil</td>
<td>Vincristine</td>
<td>Doxorubicin</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Mercaptopurine</td>
<td>Vindesine</td>
<td>Mitomycin-c</td>
<td></td>
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<tr>
<td>Ifosfamide</td>
<td>Methotrexate</td>
<td>Taxoids</td>
<td>Mitoxantrone</td>
<td></td>
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<tr>
<td>Melphalan</td>
<td></td>
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<td>Plicamycin</td>
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</tr>
</tbody>
</table>
Antimetabolites

- Structural analogs of naturally occurring metabolites involved in DNA and RNA synthesis.
- Compete with normal metabolites for catalytic or regulatory site of a key enzyme or by substituting for a metabolite normally incorporated in DNA or RNA.
- Most active in S phase (active in tumors where growth fraction is high).
- Non-linear dose response curve (more drug after a point doesn't kill more cells).
Antimetabolites

- Folate analogs (methotrexate, trimetrexate)
- Pyrimidine analogs (5-FU, FUdR, capecitabine, Cytarabine, gemcitabine)
- Purine analogues (6-Mercaptopurine, 6-Thioguanine, fludaribine)
- Adenosine analogues (Cladribine, pentostatin)
- Substituted urea (Hydroxyurea)
# Antimetabolites

<table>
<thead>
<tr>
<th>Drug and Its uses&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosages</th>
<th>Toxicities&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Folate analog</strong></td>
<td></td>
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<tr>
<td><strong>Methotrexate</strong></td>
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</tr>
<tr>
<td><em>Breast, head and neck,</em></td>
<td>Numerous dosing schedules with combination therapy:</td>
<td><em>Mucositis, Gl ulceration (may produce hemorrhage or perforation), bone marrow depression, pulmonary fibrosis (previously irradiated area), nerve root irritation and convulsion (intrathecal), liver cirrhosis and osteoporosis (chronic therapy), renal damage (high dose), diarrhea, skin erythema</em></td>
</tr>
<tr>
<td><em>Gl, and lung cancers,</em></td>
<td>Low dose: 2.5-5.0 mg PO daily; or 5-25 mg/m&lt;sup&gt;2&lt;/sup&gt; PO, IM, IV twice weekly; or 50 mg/m&lt;sup&gt;2&lt;/sup&gt; IV every 2-3 wk</td>
<td></td>
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<tr>
<td><em>ALL, CNS leukemia (intrathecal), gestational trophoblastic tumors,</em></td>
<td>High dose: 1-12 g/m&lt;sup&gt;2&lt;/sup&gt; IV with leucovorin rescue every 1-3 wk</td>
<td></td>
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<tr>
<td><em>NHL (advanced stage),</em></td>
<td>Intrathecal: 5-10 mg/m&lt;sup&gt;2&lt;/sup&gt; (up to 15 mg) every 3-7 d</td>
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<tr>
<td><em>Burkitt’s lymphoma,</em></td>
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<tr>
<td><em>osteosarcoma,</em></td>
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<tr>
<td><em>mycosis fungoides</em></td>
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<tr>
<td>Adenosine analogs</td>
<td>Cladribine</td>
<td>Pentostatin</td>
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<tr>
<td><em>Hairy-cell leukemia,</em> NHL, mycosis fungoides, AML, CML, CLL</td>
<td>0.09 mg/kg/d (4 mg/m²/d) by continuous IV infusion for 7 consecutive days</td>
<td>Bone marrow depression, febrile episodes, rash, infections, septicemia</td>
</tr>
<tr>
<td><em>Hairy-cell leukemia,</em> ALL, CLL, lymphoblastic lymphoma, mycosis fungoides</td>
<td>4 mg/m² IV over 30 min every other week or for 3 consecutive weeks; give vigorous hydration before and after chemotherapy</td>
<td>Nephrotoxicity, CNS depression, bone marrow depression, nausea and vomiting, conjunctivitis</td>
</tr>
<tr>
<td>Purine analogs</td>
<td>Dosage and Administration</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Fludarabine</strong></td>
<td>25 mg/m²/d IV over 30 min for 5 d; repeat every 28 d</td>
<td>Bone marrow depression, nausea and vomiting, fever, malaise, pulmonary infiltrates, tumor lysis syndrome, CNS effects (high dose)</td>
</tr>
<tr>
<td><strong>Mercaptopurine</strong></td>
<td>1.5-2.5 mg/kg/d PO (100-200 mg in average adult) until response or toxic effects are seen; may increase dose to 5 mg/kg/d; adjust for maintenance dose; reduce dose by 50%-75% if given with allopurinol or if renal or hepatic insufficiency ensues</td>
<td>Bone marrow depression, nausea and vomiting, anorexia, diarrhea, cholestasis</td>
</tr>
<tr>
<td><strong>Thioguanine</strong></td>
<td>2 mg/kg/d PO until response or toxic effects are seen; may cautiously increase to 3 mg/kg/d</td>
<td>Bone marrow depression, liver damage, stomatitis</td>
</tr>
<tr>
<td><em>CLL, AML, NHL (low-grade)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>ALL, CML, AML</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug and Its uses</td>
<td>Dosages</td>
<td>Toxicities</td>
</tr>
<tr>
<td>---------------------------</td>
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<tr>
<td><strong>Pyrimidine analogs</strong></td>
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</tr>
<tr>
<td>Capecitabine</td>
<td>1,250 mg/m² bid PO with food (2 weeks on drug, 1 week of rest)</td>
<td>Diarrhea, stomatitis, nausea and vomiting, fatigue, hand-foot syndrome, bone marrow depression (minimal)</td>
</tr>
<tr>
<td>Breast cancer (relapsed), colorectal cancer, and other GI malignancies</td>
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</tr>
<tr>
<td>Cytarabine</td>
<td>AML induction: 100 mg/m²/d by continuous IV infusion on days 1-7; or 100 mg/m² IV every 12 h on days 1-7 Relapsed ALL: 3 g/m² IV over 1-3 h every 12 h for 4 doses</td>
<td>Bone marrow depression, nausea and vomiting, diarrhea, arachnoiditis (intrathecal), stomatitis, hepatic dysfunction, fever, conjunctivitis, confusion, somnolence, cerebellar toxicity</td>
</tr>
<tr>
<td>AML, ALL, CML, NHL, CNS leukemia (intrathecal)</td>
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</tr>
<tr>
<td>DepoCyt (liposomal cytarabine) CNS leukemia/lymphoma</td>
<td>Intrathecal: DepoCyt, 50 mg over 1-5 min every 14 d, with dexamethasone, 4 mg PO bid × 5 d</td>
<td></td>
</tr>
<tr>
<td>Floxuridine</td>
<td>0.1-0.6 mg/kg/d over several days via continuous arterial infusion supplying well-defined tumor; treatments given over 1-6 wk</td>
<td>Stomatitis and GI ulcers, bone marrow depression, abdominal pain, nausea and vomiting, diarrhea, liver dysfunction (transient)</td>
</tr>
<tr>
<td>GI adenocarcinomas metastatic to liver, including oral, pancreatic, biliary, colon, and hepatic cancers, and metastatic breast cancer</td>
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</tr>
<tr>
<td>Drug Name</td>
<td>Indications</td>
<td>Dosing Schedules</td>
</tr>
<tr>
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</tr>
<tr>
<td>Fluorouracil</td>
<td>Colon, rectal, stomach, pancreas, breast, head and neck, renal cell, prostate, and ovarian cancers, squamous cell carcinoma of esophagus, basal and squamous cell carcinoma of skin (topical), hepatic cancer (intra-arterial)</td>
<td>Numerous dosing schedules with combination therapy: Loading dose: 300-500 mg/m²; or 12 mg/kg IV daily for 3-5 d, followed by weekly maintenance Maintenance: 10-15 mg/kg IV weekly, as toxicity permits Infusion: 20-25 mg/kg by continuous IV infusion over 24 h daily for 4-5 d, every 4 wk</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Pancreatic cancer, lung, ovarian, breast, and bladder cancers</td>
<td>1,000 mg/m² IV over 30 min, once weekly for up to 7 weeks (or until toxicity necessitates reducing or withholding a dose), followed by 1 week of rest Subsequent cycles: Infusions once weekly for 3 consecutive weeks out of every 4 weeks</td>
</tr>
<tr>
<td>Substituted urea</td>
<td></td>
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</tr>
<tr>
<td>Hydroxyurea</td>
<td>CML, acute leukemia (emergent treatment), head and neck cancer, ovarian cancer, melanoma, essential thrombocytosis, polycythemia vera</td>
<td>Intermittent: 80 mg/kg PO every third day Continuous: 20-30 mg/kg PO daily</td>
</tr>
</tbody>
</table>

(See Table 5 for abbreviations)
Alkylating Agents

- *Dissociate* a positively charged, *electrophilic alkyl group* capable of attacking a negatively charged nucleophilic site on biologic molecules.
- Impair cell function by forming covalent bonds with amino, carboxyl, sulfhydryl and phosphate groups in DNA, RNA, proteins.
- Alter DNA structure and function and alter DNA base pairing, replication and transcription.
- Need cell proliferation to be active but not phase specific.
- Most agents must undergo a complex activation process.
- Resistance occurs by glutathione conjugation or enhanced DNA repair mechanisms.
Alkylating Agents

- Resistance to alkylating agents may be due to decreased uptake (melphalan), increased sulphydral proteins like glutathione (cyclophosphamide), enhanced DNA repair (nitrosoureas).
- Alkylating agents are **non cross resistant**.
- Multidrug resistance has **no** impact on these agents.
- Alkylating agents exert effects throughout cell cycle.
- Prolonged use results in infertility.
- Teratogenic and carcinogenic.
- (Most second malignancies are AML, with CTX risk of bladder CA)
Alkylating Agents

- Nitrogen mustard
- Melphalan
- Chlorambucil
- Cyclophosphamide, ifosfamide
- Busulfan
- Nitrosoureas (BCNU, CCNU)
- Thiotepa
Nitrogen mustards: vesicants, local tissue necrosis, pulmonary fibrosis, hemorrhagic cystitis

<table>
<thead>
<tr>
<th>Drug and Its uses&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosages</th>
<th>Toxicities&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nitrogen mustards</strong></td>
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<tr>
<td><em>Chlorambucil</em>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.1-0.2 mg/kg PO daily for 3-6 wk as required (usually 4-10 mg/d) or intermittent 0.4 mg/kg every 3-4 wk; increase by 0.1 mg/kg until control of disease or toxicity</td>
<td>Bone marrow depression, gonadal dysfunction, leukemia, hyperuricemia, pulmonary fibrosis</td>
</tr>
<tr>
<td><em>Cyclophosphamide</em>&lt;sup&gt;d&lt;/sup&gt;</td>
<td>40-50 mg/kg IV in divided doses over 2-5 d to start, followed by 10-15 mg/kg IV every 7-10 d; or 3-5 mg/kg IV twice weekly; or 1-5 mg/kg/d PO</td>
<td>Bone marrow depression, hemorrhagic cystitis, immunosuppression, alopecia, stomatitis, SIADH</td>
</tr>
</tbody>
</table>

<sup>a</sup>drug and indications

<sup>b</sup>toxicities
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Schedule</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estramustine</td>
<td>14 mg/kg/d PO in 3-4 equally divided doses; 300 mg/d IV for 3-4 wk, followed by 300-450 mg/wk IV over 3-8 wk</td>
<td>Bone marrow depression, ischemic heart disease, thromboembolism, thrombophlebitis gynecomastia, nausea and vomiting, hepatotoxicity</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1.2 g/m²/d via slow IV infusion for 5 consecutive days; repeat every 3 wk; give with mesna</td>
<td>Bone marrow depression, hemorrhagic cystitis, confusion, somnolence</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>0.4 mg/kg ideal body weight given as single dose or in divided doses of 0.1-0.2 mg/kg/d</td>
<td>Bone marrow depression, nausea and vomiting, local phlebitis, severe skin necrosis if extravasated, gonadal dysfunction</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Continuous therapy: 6 mg PO daily for 2-3 wk, no therapy for 2-4 wk, then maintenance with 2-4 mg PO daily Pulse: 10 mg/m² PO daily for 4 d every 4-6 wk</td>
<td>Bone marrow depression, anorexia, nausea and vomiting, gonadal testicular dysfunction, leukemia</td>
</tr>
<tr>
<td>Drug and Its uses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Dosages</td>
<td>Toxicities&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td><strong>Aziridine</strong></td>
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<tr>
<td>Thiotepa</td>
<td>IV: 0.3-0.4 mg/kg by rapid IV infusion Intravesical: 60 mg/60 mL sterile water instilled and retained in bladder for 2 h; repeat weekly for 4 wk Intracavitary: 0.6-0.8 mg/kg</td>
<td>Bone marrow depression, nausea and vomiting, mucositis, skin rashes</td>
</tr>
<tr>
<td>Ovarian, breast, and superficial bladder cancers, HD, CML, CLL, bronchogenic carcinoma, malignant effusions (intra-cavitary), BMT for refractory leukemia, lymphomas</td>
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<td></td>
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</tbody>
</table>

| **Alkyl sulfonate**            |         |                       |
| Busulfan                      | 2-8 mg PO daily for remission induction; adjust dosage to WBC count; 1-3 mg PO daily for maintenance; withhold induction if WBC count < 15,000/µL; resume therapy when WBC count > 50,000/µL | Bone marrow depression, pulmonary fibrosis, aplastic anemia, amenorrhea, gynecomastia, skin hyperpigmentation |
| CML, BMT for refractory leukemia, lymphomas |
Nitrosoureas: lipid soluble, high CNS penetration

<table>
<thead>
<tr>
<th>Nitrosoureas</th>
<th>Carmustine</th>
<th>Lomustine</th>
<th>Streptozocin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain tumor, multiple myeloma, HD, NHL, melanoma, BMT for refractory solid tumors and lymphomas</strong></td>
<td>150-200 mg/m² IV every 6-8 wk</td>
<td>130 mg/m² PO every 6 wk; adjust dose in combination chemotherapy</td>
<td>Daily: 500 mg/m² IV for 5 d every 6 wk until maximum benefit or toxicity Weekly: 1,000 mg/m² IV weekly for first 2 wk, then escalate dose to response or toxicity, not exceed a single dose of 1,500 mg/m²</td>
</tr>
<tr>
<td><strong>Gliadel wafers, Glioblastoma multiforme</strong></td>
<td>Up to 8 wafers placed in the brain cavity created by tumor removal</td>
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<tr>
<td><strong>Delayed bone marrow depression, nausea and vomiting, reversible hepatotoxicity, local phlebitis, pulmonary and renal damage (high dose)</strong></td>
<td></td>
<td>Delayed bone marrow depression, nausea and vomiting, reversible hepatotoxicity, pulmonary and renal damage, neurologic reactions, leukemia</td>
<td>Renal damage, nausea and vomiting, diarrhea, altered glucose metabolism, liver dysfunction</td>
</tr>
</tbody>
</table>

Count > 36,000/µL
### Platinum analogues

<table>
<thead>
<tr>
<th>Drug and Its uses</th>
<th>Dosages</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platinum complexes</strong></td>
<td></td>
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</tbody>
</table>
| Carboplatin | Single agent: 360 mg/m² IV every 4 wk  
Combination: 300 mg/m² IV every 4 wk  
Calvert formula:  
Total dose (mg) = Target AUC × (GFR + 25) | Bone marrow depression, nausea and vomiting, peripheral neuropathy, ototoxicity |
<p>| Ovarian cancer, endometrial, head and neck, lung, testicular, and breast cancers, relapsed acute leukemia, NHL | | |
| Cisplatin | 50 mg/m² IV or more every 3 wk; or 20 mg/m² IV daily for 4-5 d every 3-4 wk; give vigorous hydration before and after chemotherapy | Renal damage, nausea and vomiting, electrolyte disturbance, peripheral neuropathy, bone marrow depression, ototoxicity, radiosensitizer |
| Testicular, ovarian, bladder, uterine, cervical, and lung cancers, squamous cell cancer of the head and neck, sarcoma, NHL | | |
| Oxaliplatin | 85 mg/m² IV over 120 min on d 1 followed by infusional 5-FU and leucovorin on d 1-2, every 2 wk | Bone marrow depression, diarrhea, nausea and vomiting, neuropathies exacerbated by cold exposure, pharyngolaryngeal dysesthesia |
| Colorectal (second-line) | | |</p>
<table>
<thead>
<tr>
<th><strong>Nonclassic alkylators</strong></th>
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<tbody>
<tr>
<td><strong>Altretamine</strong></td>
<td></td>
</tr>
<tr>
<td><em>Ovarian, lung, breast,</em></td>
<td></td>
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<tr>
<td><em>and cervical cancers, NHL</em></td>
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<tr>
<td>4-12 mg/kg/d or 260 mg/m²,</td>
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<tr>
<td>PO divided in 3-4 doses for</td>
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<tr>
<td>14-21 d of a 28-d regimen</td>
<td>Nausea and vomiting,</td>
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<tr>
<td></td>
<td>bone marrow depression,</td>
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<tr>
<td></td>
<td>paresthesias, CNS toxicity</td>
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<tr>
<td><strong>Dacarbazine</strong></td>
<td></td>
</tr>
<tr>
<td><em>Malignant melanoma,</em></td>
<td></td>
</tr>
<tr>
<td><em>HD, soft-tissue sarcomas,</em></td>
<td></td>
</tr>
<tr>
<td><em>neuroblastoma</em></td>
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<tr>
<td><em>Melanoma:</em> 2.0-4.5 mg/kg/d</td>
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<tr>
<td><em>IV for 10 d every 4 wk; or</em></td>
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<td><em>250 mg/m²/d IV for 5 d</em></td>
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<tr>
<td><em>every 3 wk</em></td>
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<tr>
<td><em>HD:</em> 375 mg/m² IV on d 1,*</td>
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<tr>
<td><em>repeated every 15 d (single</em></td>
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<tr>
<td><em>agent); 150 mg/m²/d IV</em></td>
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<tr>
<td><em>for 5 d every 4 wk</em> (combination*</td>
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<tr>
<td><em>therapy)</em></td>
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<tr>
<td></td>
<td>Bone marrow depression,</td>
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<tr>
<td></td>
<td>nausea and vomiting,</td>
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<td></td>
<td>flulike syndrome,</td>
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<td></td>
<td>transient hepato-</td>
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<tr>
<td></td>
<td>toxicity, local irritation,</td>
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<tr>
<td></td>
<td>facial flushing, alopecia</td>
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<tr>
<td><strong>Procarbazine</strong></td>
<td></td>
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<tr>
<td><em>HD, NHL, brain tumors,</em></td>
<td></td>
</tr>
<tr>
<td><em>lung cancer</em></td>
<td></td>
</tr>
<tr>
<td><em>Single agent:</em> 4-6 mg/kg/d</td>
<td></td>
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<tr>
<td><em>PO until maximum</em></td>
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<tr>
<td><em>response</em></td>
<td></td>
</tr>
<tr>
<td><em>HD (MOPP):</em> 100 mg/m²/d*</td>
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<tr>
<td><em>PO for 14 d</em></td>
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<tr>
<td></td>
<td>Bone marrow depression,</td>
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<tr>
<td></td>
<td>nausea and vomiting,</td>
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<tr>
<td></td>
<td>lethargy, depression,</td>
</tr>
<tr>
<td></td>
<td>paresthesias, headache,</td>
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<tr>
<td></td>
<td>flulike symptoms</td>
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<tr>
<td><strong>Temozolomide</strong></td>
<td></td>
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<tr>
<td><em>Anaplastic astrocytoma</em></td>
<td></td>
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<tr>
<td><em>(relapsed), renal cell cancer,</em></td>
<td></td>
</tr>
<tr>
<td><em>(melanoma)</em></td>
<td></td>
</tr>
<tr>
<td>150 mg/m²/d PO</td>
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<tr>
<td>for 5 d every 28 d</td>
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<tr>
<td></td>
<td>Bone marrow depression,</td>
</tr>
<tr>
<td></td>
<td>nausea and vomiting</td>
</tr>
</tbody>
</table>
Natural products

- **Vinca alkaloids**
  - Vincristine
  - Vinblastine
  - Vindesine
  - Vinorelbine

- **Podophyllotoxins**
  - Etoposide

- **Taxanes**
  - Paclitaxel
  - Docetaxel

- **Camptothecins**
  - Irinotecan
  - Topotecan

- **Antitumor antibiotics**
  - Bleomycin
Topoisomerase Inhibitors

- **Topoisomerase I Inhibitors**
  - Irinotecan
  - Topotecan

- **Topoisomerase II inhibitors**
  - *Anthracyclines*
    - Doxorubicin
    - Epirubicin
    - Daunorubicin
    - Idarubicin
    - Mitoxantrone
  - *Epipodophylotoxins*
    - VP-16 Etoposide
<table>
<thead>
<tr>
<th>Drug and Its Uses&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosages</th>
<th>Toxicities&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antitumor Antibiotics</strong></td>
<td></td>
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<tr>
<td><strong>Bleomycin</strong></td>
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</tr>
<tr>
<td>Testicular cancer, HD, reticulum cell sarcoma, lymphosarcoma, squamous cell cancer of the head and neck, skin, cervix, vulva, and penis</td>
<td>10-20 U/m&lt;sup&gt;2&lt;/sup&gt; given IV, IM, or SC weekly or twice weekly; maximum total dose, 400 U; a 2-U test dose should be given because of a possible anaphylactoid reaction</td>
<td>Pneumonitis and pulmonary fibrosis, fever and allergic reactions, anaphylaxis, hyperpigmentation, Raynaud’s phenomenon, alopecia</td>
</tr>
<tr>
<td><strong>Dactinomycin</strong></td>
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<tr>
<td>Testicular cancer, gestational trophoblastic tumors, Wilms’ tumor, rhabdomyosarcoma, Ewing’s sarcoma</td>
<td>0.010-0.015 mg/kg IV daily for 5 d every 3 wk (usual adult dose, 0.5 mg), or 2 mg/m&lt;sup&gt;2&lt;/sup&gt; IV as a single dose every 3-4 wk</td>
<td>Stomatitis, bone marrow depression, anorexia, nausea and vomiting, diarrhea, alopecia, skin changes, anaphylactoid reaction</td>
</tr>
<tr>
<td><strong>Daunorubicin</strong></td>
<td>Remission induction: 30-45 mg/m&lt;sup&gt;2&lt;/sup&gt;/d IV for 3 d in combination therapy; total cumulative dose, 550 mg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Bone marrow depression, cardiotoxicity, alopecia, nausea and vomiting, diarrhea, stomatitis, fever, dermatitis at previously irradiated sites, red urine, anaphylactoid reaction</td>
</tr>
<tr>
<td>Drug</td>
<td>Uses</td>
<td>Dosage</td>
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</tr>
<tr>
<td>Doxorubicin</td>
<td>ALL, AML, breast, ovarian, bladder cancers, HD, NHL, SCLC, gastric cancer, sarcoma, Wilms’ tumor, neuroblastoma, thyroid cancer</td>
<td>60-90 mg/m² single IV injection every 21 d, 20-30 mg/m²/d IV for 3 d every 3-4 wk, or 20 mg/m² IV weekly; total cumulative dose of 550 mg/m²; reduce dose for liver dysfunction</td>
</tr>
<tr>
<td>Doxil</td>
<td>(liposomal doxorubicin) Ovarian cancer (refractory to paclitaxel- and platinum-based regimens), Kaposi’s sarcoma</td>
<td>50 mg/m² IV every 4 wk</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Breast cancer</td>
<td>100 mg/m² IV on day 1, or 60 mg/m² IV on days 1 and 8 in combination therapy</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>AML, CML (blast phase), ALL</td>
<td>12 mg/m²/d IV for 3 d every 3 wk in combination therapy</td>
</tr>
<tr>
<td>Drug and its uses(^a)</td>
<td>Dosages</td>
<td>Toxicities(^b)</td>
</tr>
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</tr>
<tr>
<td><strong>Mitoxantrone</strong></td>
<td>Remission induction: 12 mg/m²/d IV for 3 days, in combination with Ara-C</td>
<td>Bone marrow depression, cardiototoxicity, alopecia, stomatitis, nausea and vomiting, blue urine and sclera</td>
</tr>
<tr>
<td><em>AML, prostate, ALL, CML, breast and ovarian cancers</em></td>
<td></td>
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</tr>
<tr>
<td><strong>Mitomycin</strong></td>
<td>20 mg/m² IV every 6-8 wk as a single agent, or 5-10 mg/m² IV every 6 wk in combination therapy</td>
<td>Bone marrow depression (cumulative), nausea and vomiting, anorexia, alopecia, stomatitis, fever, pulmonary fibrosis</td>
</tr>
<tr>
<td><em>Gastric, colorectal, pancreatic adenocarcinomas, NSCLC, breast, uterine, cervical, and head and neck cancers</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Valrubicin</strong></td>
<td>800 mg IV once a week for 6 wk</td>
<td>Local bladder symptoms</td>
</tr>
<tr>
<td><em>Bladder</em></td>
<td></td>
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<tr>
<td><strong>Epipodophyllotoxins</strong></td>
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<tr>
<td><strong>Etoposide</strong></td>
<td><strong>Testicular</strong></td>
<td></td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>Testicular: 50-100 mg/m²/d IV for 5 d, or 100 mg/m²/d IV on days 1, 3, and 5</td>
<td></td>
</tr>
<tr>
<td>(refractory), SCLC,</td>
<td>Lung: 35-50 mg/m²/d IV for 5 d, or 100 mg/m²/d PO for 5 d</td>
<td></td>
</tr>
<tr>
<td>HD, NHL, AML, gestational</td>
<td>For both indications, given with combination therapy and repeated every 3-4 wk</td>
<td></td>
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<tr>
<td>trophoblastic tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Teniposide</strong></td>
<td><strong>Bone marrow depression</strong>, nausea and vomiting, diarrhea, fever, hypotension with rapid infusion, alopecia, rash</td>
<td></td>
</tr>
<tr>
<td>Relapsed ALL</td>
<td>ALL: 100 mg/m² once or twice weekly, or 20-60 mg/m²/d for 5 days in combination with Ara-C</td>
<td></td>
</tr>
<tr>
<td>in children, SCLC</td>
<td>Lung: 80-90 mg/m²/d for 5 days as a single agent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone marrow depression, nausea and vomiting, alopecia, hypotension with rapid infusion, increased liver enzymes</td>
<td></td>
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<tr>
<td>Microtubule agents</td>
<td>Docetaxel</td>
<td>Paclitaxel</td>
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</tr>
<tr>
<td><strong>Breast cancer (relapsed), lung, ovarian, pancreatic cancer, head and neck, esophagus, stomach, cervical, Kaposi’s sarcoma, uterine, prostate, and bladder</strong></td>
<td><strong>60-100 mg/m² IV over 1 hour every 21 days; or up to 42 mg/m² IV every week</strong></td>
<td><strong>135-175 mg/m² by IV infusion (ranging from 3-96 h) every 3 wk; or 80 mg/m² IV every week</strong></td>
</tr>
<tr>
<td><strong>Bone marrow depression, fluid retention, hypersensitivity reaction, paresthesias, rash, alopecia, myalgias</strong></td>
<td><strong>Bone marrow depression, peripheral neuropathy, alopecia, mucositis, anaphylaxis, dyspnea, myalgias</strong></td>
<td></td>
</tr>
<tr>
<td>Drug and Its uses</td>
<td>Dosages</td>
<td>Toxicities</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td><strong>Vinblastine</strong></td>
<td>4-12 mg/m² IV as a single agent every 1-2 wk; titrate dose to myelosuppression; adjust for hepatic insufficiency</td>
<td>Bone marrow depression, nausea and vomiting, ileus, alopecia, stomatitis, myalgias, vesication</td>
</tr>
<tr>
<td><em>HD, NHL, gestational trophoblastic tumors, testicular and breast cancers, mycosis fungoides, Kaposi’s sarcoma, histiocytosis X, bladder and renal cancers, NSCLC, CML (blast crisis)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vincloristine</strong></td>
<td>0.4-1.4 mg/m² IV weekly; maximum total dose, 2 mg/wk; reduce dose for hepatic insufficiency</td>
<td>Peripheral neuropathy, ileus, abdominal pain, SIADH, bone marrow depression (mild)</td>
</tr>
<tr>
<td><em>ALL, HD, NHL, rhabdomyosarcoma, neuroblastoma, Wilms’ tumor, multiple myeloma, sarcomas, breast cancer</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vinorelbine</strong></td>
<td>30 mg/m² IV over 10 min; repeat weekly</td>
<td>Peripheral neuropathy, bone marrow depression, nausea and vomiting, hepatic dysfunction</td>
</tr>
<tr>
<td><em>NSCLC, breast, ovarian, head and neck cancers, HD</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Camptothecin Analogs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Regimen</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irinotecan</strong></td>
<td>125 mg/m² IV over 90 min once weekly for 4 wk; then 2 weeks rest; or 350 mg/m² every 21 days</td>
<td>Bone marrow depression, diarrhea, nausea and vomiting anorexia, weight loss</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong>, lung, ovarian, and cervical cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Topotecan</strong></td>
<td>1.5 mg/m² IV over 30 min for 5 consecutive days at 21-d intervals</td>
<td>Bone marrow depression, fever, flu-like symptoms, nausea and vomiting</td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong> <em>(relapsed)</em>, <strong>SCLC</strong> <em>(relapsed)</em>, MDS, CMML</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Enzyme

| **Asparaginase** | 6,000 IU/m² IM 3 times weekly for 9 doses, or 100 IU/kg/d IV for 10 continuous days, starting on day 22 of treatment; usually given with vincristine and prednisone | **Allergic reactions** *(fever, chills skin rash, anaphylaxis)*, nausea and vomiting, anorexia, liver dysfunction, CNS depression, coagulopathy, hyperglycemia |
| **ALL**, **CML**, **AML**                                                                                                                                                           |

*(See Table 5 for abbreviations)*
Irinotecan

- **Mechanism of action**: converted to SN-38 by carboxylesterase; SN-38 binds to topoisomerase 1 and prevents ligation or promotes cleavage of single strand DNA.

- **Pharmacology**: conversion to SN-38 occurs in the liver, elimination of SN-38 is predominantly via hepatobiliary excretion.

- **Toxicity**: nausea, vomiting, diarrhea, cholinergic syndrome, myelosuppression.

- **Treatment**: antiemetics, loperamide.

- **Resistance**: decreased levels of topoisomerase 1.
Antitumor enzymes

• L-asparaginase derived from E-coli used in ALL

Immunotherapies

• Bacillus Calmette-Guerin (BCG) Tuberculosis vaccine found to generate inflammatory responses that are effective in readicating local bladder cancer after intravesical administration

• Interferon $\alpha$
  Has been shown to be active in melanoma, hairy cell leukemia, CML, NHL, renal cell carcinoma and multiple myeloma
Monoclonal antibodies

- Rituximab  CD20  B-cell NHL
- Trastuzumab  Her-2  Breast cancer
- Alemtuzumab  CD52  B-CLL
Aromatase inhibitors

- Anastrazole blocks conversion of adrenal androgens to estrogens.
- Letrozole blocks transformation of androstenedione and testosterone to estrogens.
- Exemestane is a false substrate for the aromatase enzyme
- Fulvestrant is a pure estrogen receptor antagonist given IM monthly
- All are used in postmenopausal hormone receptor positive breast cancer
Tyrosine kinase Inhibitors

- **Imatinib Mesylate (gleevec)**
  - TKI that inhibits BCR-ABL and thus signal transduction in CML. Also inhibits PDGFR and c-kit.
  - Orally absorbed
  - The liver is the predominant site of metabolism, with CYP3A4 being the main enzyme responsible
  - Used in CML, Ph+ ALL and malignant GIST tumors
  - Side effects: rash, diarrhea, fluid retention, fatigue
  - Mechanisms of resistance: Mutations in Bcr-abl gene
Tyrosine kinase Inhibitors

• Geftinib (Iressa) and Erlotinib (Tarceva)
• TKIs that inhibit TK phosphorylation associated with EGFR
• Orally absorbed
• Metabolism: In liver by CYP3A4
• Used in lung cancer
• Toxicity: rash, interstitial pneumonitis, diarrhea
• Resistance: Unknown
Agents used in prostate cancer

- LH/RH agonists: leuprolide acetate and goserelin acetate
- Antiandrogens: Flutamide
Proteasome inhibitors

- Bortezomib (velcade) is used in treatment of multiple myeloma
- Inhibits proteasomes, which are present in all cells and play an important role in degrading proteins important in cellular processes.
- Cancer cells are more susceptible to such inhibition resulting in apoptosis than normal cells.
- Side effects: nausea, fatigue, low platelets, peripheral neuropathy
Anti-angiogenics

- Bevacizumab (Avastin)
- Monoclonal antibody that inhibits all forms of vascular endothelial growth factor (VEGF)
- Given IV
- Side effects: Bleeding, hypertension, thromboembolism
- Used in advanced colorectal, breast and lung
Liver tumor before treatment with anti-angiogenic
Post treatment
Sorafenib Targets Both Tumor-Cell Proliferation and Angiogenesis

Tumor cell

- EGF/HGF
- Autocrine loop
- Apoptosis
- EGFR/HGF
- PDGF
- VEGF
- Proliferation
- Survival
- Nucleus
- Sorafenib
- HIF-2
- NKDR

Endothelial cell or Pericyte

- PDGF-β
- Paracrine stimulation
- VEGF
- PDGFR-β
- Nucleus
- Sorafenib
- HIF-2
- NKDR

Angiogenesis: Differentiation, Proliferation, Migration, Tubule formation

Phase III SHARP Trial

Overall survival (Intention-to-treat)

Survival Probability

Hazard ratio (S:P): 0.69 (95% CI: 0.55, 0.88).

P=0.00058*

*O'Brien-Fleming threshold for statistical significance was P=0.0077.
ANTIANGIOGENIC THERAPY

DIRECT
(Endothelial cell dependent)
LOW risk of relapse or drug resistance
- e.g. Angiostatin
  - Endostatin
  - Vitaxin

INDIRECT
(Tumor cell dependent)
HIGH risk of relapse or drug resistance
- 1. VEGF receptor blockade
- 2. VEGF antibody
- 3. VEGF antisense

Conventional Chemotherapy
Multi-drug resistance

Toxicity to other organs
Some oncogenes or potential oncogenes which may drive tumor angiogenesis

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Angiogenic Protein</th>
<th>Inhibiting Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ras</td>
<td>VEGF</td>
<td>farnesyltransferase inhibitors</td>
</tr>
<tr>
<td>erbB2</td>
<td>VEGF</td>
<td>Herceptin</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>VEGF</td>
<td></td>
</tr>
<tr>
<td>receptor tyrosine kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGF</td>
<td>VEGF, bFGF, IL-8</td>
<td>C225 MAb to EGF receptor Iressa</td>
</tr>
<tr>
<td>receptor tyrosine kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcr-Abl</td>
<td>?? PDGF-R</td>
<td>STI571 (Glivec)</td>
</tr>
<tr>
<td>kinase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Toxicities of Chemotherapy

<table>
<thead>
<tr>
<th>Skin reaction</th>
<th>Mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Hepatic toxicity</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Sterility</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>Vascular toxicity</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>2nd malignancies</td>
</tr>
</tbody>
</table>
Toxicities, cont.

Skin

Erthematosus, macular/papular: Methotrexate, Ara-C
Hand-foot syndrome: 5-FU, adriamycin
Hyperpigmentation: 5-FU, busulfan, CPA
Radiation recall: Adriamycin, taxol
Photosensitivity: 5-FU, methotrexate

Alopecia

Anthracyclines, vincas, alkylating agents, etoposide, bleomycin, methotrexate, taxanes

Higher doses, and drugs in combination cause more alopecia
Toxicities, cont.

Nausea/Vomiting

Dependent on the agent:
(cisplatin > adriamycin > cyclophosphamide)

Dependent on schedule:
(bolus adriamycin > continuous infusion)

Dependent on analogue:
(cisplatin > carboplatin)
## Toxicities, cont.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Taxanes:</td>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Vincas:</td>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Cisplatin:</td>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td></td>
</tr>
<tr>
<td>Methotrexate:</td>
<td>Arachnoiditis and leukoencephalopathy</td>
</tr>
<tr>
<td>Ara-C:</td>
<td>Cerebellar syndrome</td>
</tr>
</tbody>
</table>
Toxicities

**Cardiac Toxicity - Anthracyclines**

Acute myocarditis
Subacute myocarditis
Chronic cardiomyopathy

Cumulative dose (2% at 240 mg/m$^2$, 45% at 1000 mg/m$^2$)
Schedule (bolus>continuous infusion)
Prior mediastinal radiotherapy
Uncontrolled hypertension
Age < 3 or > 70
Doxorubicin

- **Mechanism**: promotes free radical formation and induces topoisomerase II-dependent DNA fragmentation

- **Pharmacology**: hepatic metabolism to doxorubicinol and deoxyalglycones, eliminated in bile; no significant renal elimination

- **Toxicities**: Nausea, vomiting, mucositis, alopecia, myelosuppression, phlebitis, cardiac toxicity, secondary leukemias

- **Treatment**: antiemetics, dexrazoxane

- **Resistance**: increased drug efflux (MDR), decreased expression of topoisomerase II, increase in glutathione-dependent detoxification of peroxides
Toxicities, cont.

Bleomycin

Alkylating agents
Mitomycin-C
Methotrexate
Radiation therapy

Pulmonary Toxicity
Incidence of 3%
Dose related
Risk related to age
and use of high $F_{1}O_{2}$
Toxicities, cont.

**Mucositis and Diarrhea**
5-FU, methotrexate, adriamycin, etoposide
Dependent on schedule, dose and prior XRT

**Hepatic Toxicity**

Chemical hepatitis  
Ara-C, fludarabine, BCNU
VOD  
High dose alkylating agents
Cholestasis  
Intrahepatic FUdR
Fibrosis  
Methotrexate
Viral hepatitis  
Increase in activity with stopping chemotherapy
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Tubular Necrosis</td>
<td>Cisplatin, ifosfamide</td>
</tr>
<tr>
<td>Renal Tubular Acidosis</td>
<td>Ifosfamide, cisplatin</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Streptozocin</td>
</tr>
<tr>
<td>Hemolytic Uremic Syndrome</td>
<td>Mitomycin C, Gemcitabine</td>
</tr>
</tbody>
</table>
Toxicities, cont.

**Sterility**

Akylating agents > Antimetabolites

Older patient > younger patient

Higher dose > Lower dose

Incidence of premature menopause in women on adjuvant chemotherapy for breast cancer

CMF 60%

AC 30%
Toxicities, cont.

Second Malignancies
Chemotherapy is associated with an increased risk of hematologic malignancies within 5 years, while radiation therapy is associated with an increased risk of solid tumors over a lifetime.
High dose chemo with stem cell transplantation

- Hematologic malignancies treated this way when recurrent, aggressive types
- High dose chemotherapy completely destroys bone marrow, this allows a chance for cure with replacement of bone marrow with their own (autologous) or matched donated (allogeneic or cord blood) cells.
Thanks
The mitotic cycle with sites of action of certain phase-specific antitumor agents. $G_1 = \text{(Gap 1) resting phase}; G_2 = \text{(Gap 2) premitotic interval}; G_0 = \text{prolonged G1 or resting phase};$

$Vcr = \text{vincristine}; HN2 = \text{nitrogen mustard}.$
Sites of action of chemotherapy drugs
ONCOLOGY
Principles of chemotherapy

Side effects of chemotherapy

- Mucositis
- Nausea/vomiting
- Diarrhea
- Cystitis
- Sterility
- Myalgia
- Neuropathy

- Alopecia
- Pulmonary fibrosis
- Cardiotoxicity
- Local reaction
- Renal failure
- Myelosuppression
- Phlebitis