REVIEW OF CHEMOTHERAPY PHARMACOLOGY

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Learning Objectives

1. Identify the mechanism of action of the major classes of chemotherapy and targeted agents.
2. Apply the dose modifications for antineoplastics in patients with renal and hepatic dysfunction.
3. Summarize the mechanisms of resistance associated with antineoplastics and targeted agents. Describe the strategies utilized to overcome these resistance mechanisms.
4. List the dose limiting toxicities as well as any unique toxicities of each antineoplastic agent or targeted agent.
5. Summarize the tumor growth hypotheses that have been used to model cancer cell death from antineoplastic therapy.
Which of the following regarding chemotherapy and the cell cycle are correct?

A. Cisplatin is non-cell phase specific and works best on resting cells
B. Topotecan would be best administered as a continuous infusion or on multiple days
C. Docetaxel’s MOA is in the early part of the M phase of the cell
D. Alkylation agents are cell-phase specific agents
DNA is Information

<table>
<thead>
<tr>
<th>DNA</th>
<th>ENGLISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, T, G, C</td>
<td>A to Z</td>
</tr>
<tr>
<td>Codon</td>
<td>Word</td>
</tr>
<tr>
<td>Gene</td>
<td>Sentence</td>
</tr>
<tr>
<td>Chromosome</td>
<td>Chapter</td>
</tr>
<tr>
<td>Genome</td>
<td>Book</td>
</tr>
</tbody>
</table>
The diagram illustrates the cell cycle, which is divided into the following phases:

- **G₀ (Resting)**: Cells are not actively growing or dividing.
- **G₁**: Synthesis of components needed for DNA synthesis.
- **S**: Synthesis of DNA.
- **G₂**: Synthesis of components needed for mitosis.
- **M**: Mitosis, the process of cell division.

The cycle is depicted as a continuous loop, indicating that cells can remain in any phase of the cycle indefinitely until a trigger event prompts progression.
Cell Cycle

Cell Cycle (Phase)
Nonspecific Agents
Alkylation Agents
- Chlorambucil
- Cyclophosphamide
- Bendamustine
- Busulfan
- Ifosfamide
- Mechlorethamine
- Melphalan
- Thiotapec

Antitumor Antibiotics
- Doxorubicin
- Daunorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone

Nitrosoureas
- Carmustine
- Lomustine
- Streptozocin

Miscellaneous
- Altretamine
- Carboplatin
- Cisplatin
- Dacarbazine
- Oxaliplatin
- Procarbazine

Antimetabolites
- Azacytidine
- Cladribine
- Cytarabine
- Decitabine
- Fluorouracil
- Floxuridine
- Fludarabine
- Gemcitabine
- Methotrexate
- Mercaptopurine
- Pemtrexed
- Pentostatin
- Thioguanine

Cell Cycle (Phase)
- $G_0$
- $G_1$
- $G_2$
- $S$
- M
Principles of Chemotherapy: Action Sites of Cytotoxic Agents

DNA synthesis

Cellular level

DNA synthesis

DNA transcription

DNA duplication

DNA transcription

DNA duplication

DNA synthesis

Antimetabolites

Alkylating agents

Intercalating agents

Mitosis

Spindle poisons
Non-Cell Phase Specific Agents

- Exert their cytotoxic effect throughout the cell cycle
  - Cell kill is proportional to dose
  - Alkylating agents
    - Nitrogen mustards, cyclophosphamide, cisplatin, carboplatin
  - Antitumor antibiotics
    - Doxorubicin, daunorubicin
Cell Phase Specific Agents

- Toxic to the proportion of cells in the part of the cell cycle in which the agent is active.
- Antimetabolites
  - Antifolates: Methotrexate
  - Pyrimidine antagonists
  - Purine analogs
- Plant Alkaloids
  - Vinca alkaloids
  - Epipodophyllotoxins
  - Camptothecins
  - Paclitaxel
Tumor growth kinetics

Chemotherapy of benefit

Source: DeCherney AH, Nathan L: Current Diagnosis & Treatment Obstetrics & Gynecology, 10th edition; http://www.accessmedicine.com
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The HER Family and Ligands

Activated EGFR-TK: A Pivotal Driver of Malignancy

P = phosphate group.

Alkylating Agents

- Nitrogen mustards
  - Chlorambucil, Cyclophosphamide, Ifosfamide, Melphalan, Mechlorethamine hydrochloride, bendamustine

- Nitrosoureas
  - Carmustine, Lomustine, Semustine, Streptozocin

- Alkyl sulfonates
  - Busulfan

- Ethylenimines
  - Thiotepa, Hexamethylmelamine

- Triazenes
  - Dacarbazine

- Platinum analogues
  - Cisplatin, Carboplatin, Oxaliplatin
Figure 55–5. Mechanism of alkylation of DNA guanine. A bis(chloroethyl)amine forms an ethyleneimmonium ion and a carbonium ion that react with a base such as N7 of guanine in DNA, producing an alkylated purine. Alkylation of a second guanine residue, through the illustrated mechanism, results in cross-linking of DNA strands.

Alkylation Agents MOA

A. Activation

B. Nucleophilic attack of unstable aziridine ring by electron donor

(-SH of protein, -N of protein or DNA base, =O of DNA base or phosphate)
Alkylating Agents MOA

Adapted from. Goodman and Gilman’s the pharmacological basis of therapeutics, 11 Edition: http://www.accesspharmacy.com
Additional Alkylators

Mechlorethamine

Cyclophosphamide

Ifosfamide

Mfi Phai An

Chlorambucil
Which of the following agents produce the greatest inhibition of myelocytic bone marrow cell proliferation?

A. Cyclophosphamide
B. Carboplatin
C. Docetaxel
D. Busulfan
E. All of the above are equally toxic
Metabolic Pathway of Alkylators

Temozolomide vs. Dacarbazine


ACCP/ASHP Oncology Pharmacy Preparatory Review Course

Platinum Analogues
Cisplatin Carboplatin Oxaliplatin

Platinum Analogues

Cisplatin

Carboplatin

Oxaliplatin
Platinum Crosslinks

Intrastrand Cross-link Lesion

Cisplatin or Carboplatin

Oxaliplatin
## Clinical differences

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myelosuppression</strong></td>
<td>/</td>
<td>//</td>
</tr>
<tr>
<td><strong>Nephrotoxicity</strong></td>
<td>//</td>
<td>x</td>
</tr>
<tr>
<td><strong>Otototoxic</strong></td>
<td>/</td>
<td>x</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>/</td>
<td>x</td>
</tr>
<tr>
<td><strong>Emetogenicity</strong></td>
<td>////</td>
<td>//</td>
</tr>
</tbody>
</table>

Which drug inhibits DNA topoisomerase II and causes DNA breakdown?

A. Methotrexate
B. Paclitaxel
C. Topotecan
D. Epirubicin
Molecular Function of Topoisomerase

DNA-Associated Topo I

Stabilized “Cleavable complex”

Interaction with Replication Fork

Double-Strand DNA break
Topoisomerase II inhibitors prevent the rejoining DNA.

1. Topoisomerase II inhibitor attaches to topo-II / DNA complex.

2. DNA strands are broken but rejoining does not occur.

3. DNA strand breaks result. Number of strand breaks correlates with cell death.
Anthracyclines

MOA

- Inhibits topoisomerase II.
  - This prevents the religation of DNA during DNA replication causing DNA strand breaks.

Dose reductions required in patients with hepatic impairment.

- Decrease dose
  - by 50% if bilirubin levels 1.2-3.0 mg/dL and
  - by 75% for bilirubin > 3.0 mg/dL;
  - generally omitted if bilirubin > 5.0 mg/dL.
### Dosage Adjustment of Hepatic Impairment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anthracyclines</th>
<th>Capecitabine</th>
<th>Dasatinib</th>
<th>Docetaxel</th>
<th>Etoposide</th>
<th>Eribulin</th>
<th>Erlotinib</th>
<th>Imatinib</th>
<th>Ixabepilone</th>
</tr>
</thead>
</table>
|                | 1. Bilirubin 1.2 - 3.0 mg/dL  
2. Bilirubin 3.1 - 5.0 mg/dL  
3. Bilirubin > 5.0 mg/dL | 1. Baseline hepatic dysfunction  
2. If patients develop ≥ grade 3 elevations of bilirubin (> 3 x ULN) or AST/ALT (> 5 x ULN) | 1. Decrease dose 50%  
2. Decrease dose 75%  
3. Omit | 1. Do not give  
2. Do not give | 1. Bilirubin 1.5 - 3.0 mg/dL  
2. Bilirubin 3.1 - 5.0 mg/dL | 1. Decrease dose 50%  
2. Omit | 1. Patient baseline bilirubin > 3.0 mg/dL  
2. In patients with normal baseline values, if baseline bilirubin doubles or AST/ALT triples or base OR if bilirubin > 3 x ULN or AST/ALT > 5 x ULN | 1. Initial Bilirubin > 3 x ULN  
2. Bilirubin > 3 x ULN or AST/ALT > 5 x ULN during treatment | 1. As a monotherapy agent if AST or ALT >10 x ULN or bilirubin >3 x ULN  
2. In combination with capecitabine AST or ALT >2.5 x ULN or bilirubin >1 x ULN | 1. Consider 25% dose reduction  
2. Withhold until < 1.5 ULN and decrease dose when restarted  
3. Use with caution  
4. Hold and modify dose  
5. Contraindicated |
## Dosage Adjustment of Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hepatic Impairment</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Child-Pugh Class C hepatic dysfunction</td>
<td>Dose reduction to 750 mg/day</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1. Baseline hepatic dysfunction</td>
<td>1. Use caution if patients</td>
</tr>
<tr>
<td></td>
<td>2. If patients develop ≥ grade 2 elevations of bilirubin (&gt; 1.5 x ULN)</td>
<td>2. Hold until bilirubin ≤ 1.5 x ULN; consider dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>modification</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Use with caution in hepatic failure</td>
<td>1. If transaminase &lt; 10 upper normal limit and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bilirubin 1.26-2 upper normal limit, reduce to 135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg/m2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. If transaminase &lt; 10 upper normal limit and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bilirubin 2.01-5 upper normal limit, reduce to 90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg/m2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. If transaminase &gt; 10 upper normal limit or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bilirubin &gt; 5 upper normal limit, do not use</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Bilirubin &gt; 5 mg/dL or AST/ALT &gt; 3 x ULN</td>
<td>Avoid use if possible</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Not studied in severe hepatic impairment (Child-Pugh class C)</td>
<td>Use with extreme caution in patients with liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cancer and elevated bilirubin levels.</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Use with caution in hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>1. Bilirubin 1.5 - 3.0 mg/dL</td>
<td>1. Decrease dose 50%</td>
</tr>
<tr>
<td>Vincristine</td>
<td>2. Bilirubin 3.1 - 5.0 mg/dL</td>
<td>2. Decrease dose by 75%</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3. Bilirubin &gt; 5.0 mg/dL</td>
<td>3. Omit</td>
</tr>
</tbody>
</table>
Anthracyclines

- Toxicities
  - Potent vesicants. Apply cold ice pack and evaluate for antidote use (99% DMSO 1-2 ml applied to site every 6 hours for 7-14 days) or Totect®.
  - Dose limiting myelosuppression (primarily leukopenia), chronic cardiomyopathies. All patients should have a baseline MUGA done to evaluate potential cardiotoxicity.
  - Additional toxicities include:
    - dose dependent nausea and vomiting, alopecia, and radiation recall.
    - Turns urine red, need to counsel patients on this AE.
Anthracyclines

Doxorubicin

Daunorubicin

Epirubicin

(4-Epidoxorubicin)

Idarubicin

(4-Demethoxydaunomycin)

Sites of Difference in activities
Etoposide (VP-16)

- **MOA:** Topoisomerase II inhibitor

- **Dosage and Administration:**
  - 50 to 200mg/m²/day IV for 3-5 days every 3 weeks
  - IV infusion should be infused over 30-60 minutes to avoid hypotension
  - Oral dose is 2x greater than the IV
Etoposide (VP-16)

- **Toxicities:**
  - Dose limiting myelosuppression
    - primarily leukopenia.
  - Additional toxicities include
    - nausea and vomiting (with oral dosing),
    - alopecia
Topo I Inhibitors Mechanism of Action

DNA-Associated Topo I

Stabilized “Cleavable complex”

Interaction with Replication Fork

Double-Strand DNA break
Antimicrotubules

Vinca Alkaloids

Tubulin

α

β

Taxanes

Microtubule
Dose reductions required in patients with hepatic impairment.

Decrease dose
- by 50% if bilirubin levels 1.5-3.0 mg/dL and
- by 75% for bilirubin > 3.0 mg/dL;
- generally omitted if bilirubin > 5.0 mg/dL.

Toxicities
- All vinca alkaloids are potent vesicants,
  - apply warm pack and administer hyaluronidase
# Vinca Alkaloids

<table>
<thead>
<tr>
<th>Vinblastine</th>
<th>Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dose limiting leukopenia, and thrombocytopenia.</td>
<td>• Dose-limiting neurologic toxicity, constipation, and paralytic ileus.</td>
</tr>
<tr>
<td>• Additional toxicities include: Neurologic toxicity, constipation, abdominal cramps (much less than vincristine)</td>
<td>• Rarely causes bone marrow suppression and SIADH</td>
</tr>
<tr>
<td></td>
<td>• In general, the maximum dose of vincristine is 2mg weekly</td>
</tr>
</tbody>
</table>
Paclitaxel & Docetaxel

- Paclitaxel
  - Dose limiting leukopenia
  - Additional toxicities include: Hypersensitivity reactions, alopecia, cardiac
  - Toxicity, peripheral neuropathies, and mucositis
Paclitaxel & Docetaxel

- Docetaxel
  - Dose limiting leukopenia
  - Additional toxicities include:
    - Peripheral edema, alopecia, peripheral
  - Neuropathies, and hypersensitivity reactions.
Paclitaxel & Docetaxel

- **Miscellaneous:**
  - Patients must receive premedication prior to receiving paclitaxel to decrease the incidence of hypersensitivity reactions.
  - Patients receive both pre and postmedication with docetaxel to prevent the fluid retention associated with use.
Epothilones:

EpoA and paclitaxel bound to beta-tubulin

Specifically and Uniquely Bind to Beta-Tubulin

- Thiazole side-chain occupies the region of binding site not occupied by taxanes
- Only 1 polar contact point (C7-OH) is shared with taxanes

Epothilone Differences Versus Taxanes

- 5-25 times more potent than paclitaxel *in vitro*
- Efficacy not impaired by Pg-protein expression
- Potential benefit with altered B-tubulin binding
  - Paclitaxel resistant Ala to Thr substitution at residue 364 sensitive to Epo
  - Epothilone resistance associated with substitutions at residues 274 or 282, as well as high class III B-tubulin expression

Eribulin

- Synthetic analog of the marine macrolide halichondrin B that inhibits tubulin polymerization
- Inhibits growth (but not shortening of microtubules)
- Approved for metastatic breast cancer after two agents (including taxane and anthracycline)
Eribulin

- Adverse effects appear to similar to vinblastine (neutropenia), with a decreased incidence of neuropathy compared to vincristine
- Requires dose adjustments based on hepatic and renal function
## Dosage adjustment in Renal impairment

<table>
<thead>
<tr>
<th>AGENT</th>
<th>ORGAN DYSFUNCTION</th>
<th>DOSE MODIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>1. CrCl = 30 - 60 mL/min&lt;br&gt;2. CrCl = 10 - 30 mL/min&lt;br&gt;3. CrCl &lt; 10 mL/min</td>
<td>1. 25% - 50% decrease&lt;br&gt;2. 25% - 50% decrease&lt;br&gt;3. 50% decrease</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1. CrCl = 30-50 mL/min&lt;br&gt;2. CrCl &lt; 30 mL/min</td>
<td>1. 25% decrease&lt;br&gt;2. Do not use</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Renal insufficiency</td>
<td>Total Dose = AUC X (CrCl + 25)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Use with caution in patients with CrCl &lt; 50 mL/min</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Renal Failure</td>
<td>Decrease dose 25%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Decrease in proportion to CrCl if 15 - 50 mL/min</td>
<td>Decrease dose 25%</td>
</tr>
<tr>
<td>Eribulin</td>
<td>CrCl 30-50 mL/min</td>
<td>Decrease dose to 1.1 mg/m²</td>
</tr>
<tr>
<td>Fludarabine PO</td>
<td>1. CrCl: 30-70 mL/min&lt;br&gt;2. CrCl &lt;30 mL/min</td>
<td>1. Administer 80% of dose&lt;br&gt;2. Administer 50% of dose</td>
</tr>
<tr>
<td>Fludarabine IV,</td>
<td>Use in caution in patients with CrCl &lt; 60 mL/min</td>
<td></td>
</tr>
<tr>
<td>hydroxyurea PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1. CrCl = 10-50 mL/min&lt;br&gt;2. CrCl = &lt; 10 mL/min</td>
<td>1. Decrease dose 25%&lt;br&gt;2. Decrease dose 50%</td>
</tr>
<tr>
<td>Imatinib</td>
<td>1. Mild impairment CrCl 40-59 mL/min&lt;br&gt;2. Moderate impairment CrCl 20-39 mL/min</td>
<td>1. Maximum recommended dose: 600 mg&lt;br&gt;2. Decrease recommended starting dose by 50%; dose may be increased as tolerated; maximum recommended dose: 400 mg</td>
</tr>
</tbody>
</table>
## Dosage adjustment in Renal impairment

<table>
<thead>
<tr>
<th>Medication</th>
<th>CrCl &lt; 60 ml/min</th>
<th>Initial dose modifications required that depend on the indication for use. Please refer to package insert for dose recommended based on disease state treated and actual CrCl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>CrCl &lt; 60 ml/min</td>
<td>Increase dose. Monitor levels closely in all patients receiving high-dose therapy (e.g. ≥ 150 mg/m2).</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Decrease in proportion to CrCl</td>
<td>Initial dose modifications required that depend on the indication for use. Please refer to package insert for dose recommended based on disease state treated and actual CrCl.</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Dose in proportion to CrCl</td>
<td>Decrease dose 50-75%</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>Renal Failure</td>
<td>Decrease dose 50-75%</td>
</tr>
<tr>
<td>Topotecan IV</td>
<td>1. CrCl 20-39 mL/min 2. CrCl &lt; 20 mL/min</td>
<td>1. Decrease dose 50% 2. Do not use</td>
</tr>
<tr>
<td>Topotecan PO</td>
<td>1. CrCl = 30-49 mL/min 2. CrCl &lt; 30 mL/min</td>
<td>1. Reduce dose to 1.8 mg/m²/day 2. Insufficient data available for dosing recommendation</td>
</tr>
</tbody>
</table>
Antimetabolites

Purines

1. Purine
2. Adenine
3. Guanine

Pyrimidines

1. Pyrimidine
2. Cytosine
3. Uracil
4. Thymine
Purine and Pyrimididine analogues

- Need purine bases—A, G
- Need pyrimidine bases—C, T (DNA) and C, U (RNA)
- Can build in two ways—de novo and salvage pathways
- All cells use both
  - Continuously dividing cancer cells favor de novo synthesis
  - many drugs are directed here in an attempt to provide selectivity over normal cells
Purine Analogues

- Mercaptopurine and thioguanine
  - These analogues are converted in the body to the ribonucleotide form, which incorporate in the DNA to prevent purine synthesis.

- Fludarabine (2-fluoro-ara-AMP):
  - The triphosphate form inhibits ribonucleotide reductase and DNA polymerase.

- Pentostatin (2’-deoxycoformycin) and cladrabine
  - Inhibits ribonucleotide reductase
Purine Analogues

- Increase risk of infection
  - Bacteria (Listeria, Staph, Strep)
  - Fungal (Candida, Aspergillus, Cryptococcus)
  - Viral (Herpes Zoster, Varicella, CMV)
  - Other (Pneumocystis carinii)
Metabolism of thiopurine

Hepatotoxic

Myelosuppression

Pancreatitis

Genotype-Guided 6-MP Dosing

TPMT*1 (wild type)

TPMT*2

TPMT*3A

TPMT*3B

TPMT*3C

Homozygous
10% of standard dose

Heterozygous
60% of standard dose

Standard dose

Pharmacogenomics 2002;3:89-98.
Phenotype-Guided 6-MP Dosing

Dose adjustment:

- High TPMT (> 65 U/mL): increase dose
- Intermediate TPMT (25-45 U/mL): decrease dose 20-50%
- Low or absence TPMT (< 25 U/mL): decrease dose 80-90%

Pyrimidine Analogues

- Gemcitabine and cytarabine
  - Triphosphorylated to active drug which inhibits DNA polymerase
- 5-FU and capecitabine
  - Inhibit thymidylate synthase
Cytarabine (Ara-C)

- Cytidine deaminase
  - Ara-U
- dCMP deaminase
  - Ara-U
  - Ara-UMP
- Deoxycytidine kinase
  - Ara-C
  - Ara-CMP
  - Ara-CDP
  - Ara-CTP
- dCMP kinase
- NDP kinase
Metabolism of Azacitidine and Decitabine

Methotrexate

- **Mechanism**
  - Inhibits DHFR that prevents the conversion of dihydrofolate (FH2) to tetrahydrofolate (FH4)

- **Toxicities**
  - Dose limiting leukopenia and thrombocytopenia.
  - Renal tubular necrosis seen with high dose therapy.
  - Vigorous hydration and alkylation of the urine necessary to decrease risk of kidney damage.

- **Additional toxicities include:**
  - Pulmonary pneumonitis, alopecia, and stomatitis and mucositis.
Methotrexate

- High dose therapy (500-12,000 mg/m²) require leucovorin rescue until MTX levels are less than 0.05 M (5 x 10⁻⁸ M)
- Provides a source of reduced folate
- Does not protect against renal toxicity (need bicarbonate)
Leucovorin

Diagram showing the metabolism of leucovorin, including the role of dihydrofolate reductase and thymidylate synthetase in the synthesis of purines and DNA.
Leucovoring Recue Nomogram

![Graph showing the effect of different doses of MTX on plasma MTX concentration over time. The x-axis represents time after start of MTX infusion (hrs), and the y-axis represents plasma MTX concentration (µM). There are four curves representing different doses: 1000 mg/m² q 6 hr, 100 mg/m² q 3 hr, 10 mg/m² q 3 hr, and 10 mg/m² q 6 hr. The curves show the decrease in plasma MTX concentration over time for each dose.]

- 1000 mg/m² q 6 hr: 10 µM
- 100 mg/m² q 3 hr: 5.0 µM
- 10 mg/m² q 3 hr: 0.5 µM
- 10 mg/m² q 6 hr: 0.1 µM
Glucarpidase (carboxypeptidase G2)
Pemetrexed MOA

TS = thymidylate synthase  
DHFR = dihydrofolate reductase  
GARFT = glycaminide ribonucleotide formyltransferase
Tamoxifen

- **Mechanism Of Action**: Anti-estrogen (in breast) that inhibits nuclear binding of the estrogen receptor, blocking estrogen stimulation of breast cancer cells.
- **Indication**: Tamoxifen main use is in the treatment of estrogen-receptor positive breast cancer.
- **Also approved for the prevention of breast cancer in women deemed to be at high risk**
Tamoxifen

- Toxicities:
  - Menopausal symptoms: Hot flashes, nausea, and vomiting. Additional toxicities include vaginal bleeding, bone pain, menstrual irregularities, headache, and depression.
  - Rare toxicities include retinal toxicity and thromboembolic disorders. Concomitant warfarin therapy may increase your risk of bleeding.
  - The risk of endometrial is approximately 3x the normal population.
Selective Versus Nonselective Aromatase Inhibition

Cholesterol

Multiple steps involving P-450 enzymes and production of steroid intermediates

- Aldosterone
- Cortisol
- Androstenedione

Testosterone

Aromatase

- Estrone
- Estradiol

Selective Inhibitors

Nonselective Inhibitors

Strategies for Therapeutically Targeting the Androgen Receptor
What are Targeted Therapies?

Therapies directed towards a specific target on cells that affects angiogenesis and cell cycle mechanisms

Main targets:
- Cell specific markers
- EGFR - Epidermal Growth Factor Receptor
- VEGF - Vascular Endothelial Growth Factor

Therapies
- Monoclonal Antibodies
- Tyrosine Kinase Inhibitors
Antibody Structure

- **Murine**: Fc
- **Chimeric**: Fc (Antigen Binding)
- **Humanized**: Fc, CDRs
- **Imunoconjugate**: Fc, Toxin (e.g., radiation)
- **Human**: Fc

Blue = Murine; Gray = Human
Mechanism of Action of Antibody
Nomenclature

|-mab = monoclonal antibody

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<tr>
<td>o</td>
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<td>u</td>
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<td>xi</td>
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- o = mouse
- e = hamster
- u = human
- i = primate
- xi = chimera
- a = rat
- zu = humanized
Which of the following monoclonal antibodies would be expected to cause the lowest incidence of human-antimouse antibodies (HAMA) reactions?

- A. Epratuzumab
- B. Cetuximab
- C. Bevacizumab
- D. Panitumumab
- E. Tositumomab
## Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>MOA</th>
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<tr>
<td>Alemtuzumab</td>
<td>CD-52 on lymphocytes</td>
<td>CDC and ADCC</td>
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<tr>
<td>Rituximab and ofatumumab</td>
<td>CD-20 on B-cells</td>
<td>ADCC, CDC, and apoptosis</td>
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<td>Ibritumomab and tositumomab</td>
<td>Same as rituximab</td>
<td>Same as rituximab plus radiation</td>
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<tr>
<td>Gemtuzumab</td>
<td>CD-33 on myeloid cells</td>
<td>Double stranded DNA breaks</td>
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Ofatumumab

- Human CD20 mAb Binds a small-loop epitope of CD20
- Effective CDC of cells with low CD20 expression, including CLL cells
- More effective in vitro CDC versus rituximab

Brentuximab Vedotin: Mechanism of Action

An antibody drug conjugate directed against the CD30 antigen on Hodgkin’s cells

Biological Activities of CTLA-4 Antibody Blockade

The HER Family and Ligands

Which of the following statements about tyrosine kinase inhibitors is true?

A. They are usually administered via intravenous infusion due to their molecular size.
B. They compete with a natural ligand for binding to their target receptor.
C. They work intracellularly and prevent signal transduction after the receptor has been activated.
D. They work intracellularly to prevent the dimerization of growth factor receptors.
Anti-HER Blocking Monoclonal Antibodies

Mutational Status and EGFR Response

[Diagram showing the interaction of ligand with EGFR and downstream signaling pathways involving PTEN, Akt, mTOR, STAT 3/5, Ras, Raf, MEK, and MAPK, leading to survival and proliferation.]
## TKIs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>MOA</th>
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<tbody>
<tr>
<td>Trastuzumab</td>
<td>Her-2 extracellular receptor</td>
<td>• Decrease in cell proliferation</td>
</tr>
<tr>
<td>Cetuximab and panitumumab</td>
<td>Her-1 [EGFR] extracellular receptor</td>
<td>• Induce apoptosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decrease angiogenesis</td>
</tr>
<tr>
<td>Erlotinib and gefitinib</td>
<td>Her-1 [EGFR] tyrosine kinase</td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Her-1 [EGFR] and Her-2 tyrosine Kinase</td>
<td>• As above but has activity after trastuzumab relapse</td>
</tr>
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Which best explains sunitinib’s mechanism of action?

A. Inhibits the tyrosine kinase activity of multiple receptors, such as VEGFR and PDGFR, involved in tumor growth and angiogenesis.

B. Competitive inhibitor of the VEGFR and PDGFR extracellular receptors involved in angiogenesis.

C. Competitive inhibitor of the EGFR and Her-2 receptor involved in tumor growth.

D. Inhibits the EGFR tyrosine kinase activity involved in tumor growth and angiogenesis.
Mechanism of Action of Current VEGF Inhibitors

Vendetanib

- **Mechanism Of Action:** Small-molecule inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and RET tyrosine kinases

- Mutations in RET proto-oncogene seen in the majority of medullary thyroid cancers

- 300 mg PO daily with or without food (decrease to 200 mg in patients with CrCl < 50ml/min); avoid in Childs-Pugh B or C Toxicities
Vendetanib

- Black box-QTc prolongation (Monitor EKG at baseline; 2 to 4 weeks and 8 to 12 weeks after starting; and every 3 months thereafter). Avoid in patients with hypocalcemia, hypokalemia, or hypomagnesemia
- CYP 3A4 substrate

Imatinib

- Indications:
  - Initial or salvage therapy for CML
  - Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)
Imatinib

- **Mechanism**
  - Inhibits the tyrosine kinase activity of Bcr-Abl
  - Inhibits c-Kit and platelet-derived growth factor receptor
- **Place in therapy:** CML, GIST
- **Inhibitor and substrate of CYP3A4**
Newer bcr-abl Inhibitors

- **Dasatinib**
  - Inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ
  - Binds to inactive and active conformations
  - 70 mg PO BID or 140 mg QD
  - CYP3A4 Inhibitor
  - Myelosuppression and pleural effusions are DLT
Newer bcr-abl Inhibitors

- Nilotinib
  - MOA similar to imatinib but binds to BCR-ABL 20-50 times more potent
  - Like imatinib binds to inactive bcr-abl conformations

A Simplified Illustration of BCR-ABL and Src Family Kinase Involvement in Oncogenic Signaling Pathways

Proteasome Inhibition by Bortezomib

mTOR Inhibitor Mechanism of Action

Crizotinib

- Inhibits multiple receptor tyrosine kinases
  - Anaplastic lymphoma kinase (ALK)
  - Hepatocyte growth factor receptor (HGFR, c-Met)
  - Recepteur d’Origine Nantais (RON)
Crizotinib

- Approved for locally advanced or metastatic NSCLC that is ALK-positive
- Companion diagnostic test designed to detect rearrangements of the ALK gene
ALK Fusion Oncogenes and Downstream Signaling Pathway

Vemurafenib

- BRAF kinase inhibitor
- Inhibits kinase activity of certain mutated forms of BRAF, including BRAF with V600E mutation (present in ~50% of melanomas)
- Not active against cells with wild-type BRAF

Dose
- 960 mg orally twice daily until disease progression
Activated EGFR-TK: A Pivotal Driver of Malignancy

P = phosphate group.

Vorinostat Mechanism of Action

Causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of cancer cells.

In which of the following cases would you either not dispense the chemotherapy or adjust the dose appropriately?

A. Daunorubicin-MUGA of 52%
B. Bendamustine-Bilirubin of 2.2mg/dL
C. Vinorelbine-CrCl of 32ml/min
D. Doxorubicin-Bilirubin of 1.9mg/dL
THANK YOU FOR YOUR ATTENTION