Chemotherapeutics

Andrew Stolbach
Principles of Chemotherapy

- Cytotoxic therapy
  - Damage DNA
  - Interfere with formation of mitotic spindle
- Targeted therapy
  - Hormonal
  - Antibody
- Growth Factor inhibition
Focus Your Studying On:

• Class effects
• Unique Adverse effects
• Unique mechanisms
• Unique antidotes
Antineoplastic Drug Targets

- **6-MERCAPTOPURINE 6-THIOGUANINE**
  - Inhibit purine ring biosynthesis
  - Inhibit DNA synthesis

- **ALIMTA METHOTREXATE**
  - Inhibit dihydrofolate reduction, block thymidylate and purine synthesis

- **CAMPTOTHECINS ETOPOSIDE TENPOSIDE DAUNORUBICIN DOXORUBICIN**
  - Block topoisomerase function

- **PROTEIN TYROSINE KINASE INHIBITORS, ANTIBODIES**
  - Block activities of signaling pathways

- **HYDROXYUREA**
  - Inhibits ribonucleotide reductase

- **5-FLUOROURACIL**
  - Inhibits thymidylate synthesis

- **GEMCITABINE CYTARABINE FLUDARABINE 2-CHLORODEOXYADENOSINE CLOFARABINE**
  - Inhibits DNA synthesis

- **PLATINUM ANALOGS ALKYLATED AGENTS MITOMYCIN TEMOZOLOMIDE**
  - Form adducts with DNA

- **L-ASPARAGINASE**
  - Deaminates asparagine
  - Inhibits protein synthesis

- **EPOTHILONES TAXANES VINCA ALKALOIDS ESTRAMUSTINE**
  - Inhibit function of microtubules

- **ATRA ARSENIC TRIOXIDE HISTONE DEACETYLASE INHIBITORS**
  - Inducers of differentiation

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Antineoplastics and the Cell Cycle

S PHASE SPECIFIC DRUGS
- cytosine arabinoside
- hydroxyurea

S PHASE SELF-LIMITING
- 6-mercaptopurine
- methotrexate

M PHASE SPECIFIC DRUGS
- vincristine
- vinblastine
- paclitaxel

CELL CYCLE NON-SPECIFIC DRUG
- alkylation drugs
- nitrosoureas
- antitumor antibiotics
- procarbazine
- cisplatin
- dacarbazine

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Classification of Chemotherapeutics
Alkylation Agents

- Busulfan
- Chlorambucil
- Mustards
  - Chloramphenicol
  - Cyclophosphamide
  - Ifosfamide
  - Mechlorethamine
  - Melphalan
- Nitrosureas
  - Bendamustine
- Carmustine
- Platinoids
  - Carboplatin
  - Cisplatin
- Triazenes
  - Dacarbazine
  - Procarbazine
  - Temozolomide
Classification of Chemotherapeutics

Antibiotic:

- Anthracycline
  - Daunorubicin
  - Doxorubicin
  - Idarubicin
- Bleomycin
- Mithramycin
- Mitomycin
- Mitoxantrone
Platinoid Structures

Carboplatin

Cisplatin
Mustard Structures

MECHLORETHAMINE

CYCLOPHOSPHAMIDE

IFOSFAMIDE

MELPHALAN

CHLORAMBUCIL

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Classification of Chemotherapeutics

Antimetabolite:
- 5-FU
- Fludarabine
- Gemcitabine
- Mercaptopurine
- Vitarabine

Antifolate
- Methotrexate
- Pemetrexed

![Chemical structures of 5-FU and uracil](image)
Classification of Chemotherapeutics

Antimitotic:
- Taxanes
  - Docetaxel
  - Paclitaxel
- Topoisomerase inhibitors
  - Etoposide
  - Teniposide
  - Irinotecan

Vinca Alkaloids
- “Catharanthus roseus” or “Vinca rosea” derivatives
  - Vinblastine
  - Vincristine

Radionuclides
- $^{131}I$
- $^{89}Sr$ (Strontium 89)
- $^{153}Sm$ (Samarium 153)
Classification of Chemotherapeutics (continued)

<table>
<thead>
<tr>
<th>Estrogen Targeting</th>
<th>Anti-androgen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>Biclamutamide</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Flutamide</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Nilutamide</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Leuprolide</td>
</tr>
<tr>
<td>Toremifene</td>
<td></td>
</tr>
</tbody>
</table>
Classification of Chemotherapeutics (continued)

- Tyrosine Kinase Inhibitors
  - Axitinib
  - Dasatinib
  - Erlotinib (EGFR)
  - Gefitinib (EGFR)
  - Imatinib
  - Lapatanib (EGFR/Her2/neu)
  - Nilotinib
  - Pazopanib
  - Regorafenib
  - Vandetanib
  - Vemurafenib

## Classification of Chemotherapeutics (continued)

<table>
<thead>
<tr>
<th>Angiogenesis Inhibitors</th>
<th>Biologic Response Modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bevacizumab</td>
<td>• Aldesleukin</td>
</tr>
<tr>
<td>• Lenalidomide</td>
<td>• Interferon-Alpha</td>
</tr>
<tr>
<td>• Sorafenib</td>
<td></td>
</tr>
<tr>
<td>• Sunitinib</td>
<td></td>
</tr>
<tr>
<td>• Thalidomide</td>
<td></td>
</tr>
</tbody>
</table>
### Classification of Chemotherapeutics (continued)

#### Monoclonal Antibodies

- Alemtuzumab (CD52)
- Bevacizumab (VEGF-A)
- Brentuximab vedotin (CD30)
- Cetuximab (EGFR)
- Gemtuzumab ozogamicin (CD33)
- Ipilimumab (CTLA4)
- Ofotumumab (CD20)
- Panitumumab (EGFR)
- Pertuzumab (Her2Neu)
- Rituximab (CD20)
- Trastuzumab (Her2Neu)
- Tositumomab 1131 (CD20)
## Selected Neoplastic Treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Induction: Vincristine, prednisone, daunorubicin, asparaginase, IT methotrexate</td>
</tr>
<tr>
<td>AML</td>
<td>Cytarabine, daunarubicin or Cytarabine, idarubicin</td>
</tr>
<tr>
<td>CML</td>
<td>Imatinib or nilotinib or dasatanib</td>
</tr>
<tr>
<td>CLL</td>
<td>Fludarabine, cyclophosphamide, rituximab</td>
</tr>
<tr>
<td>Hairy Cell Leukemia</td>
<td>Cladribine</td>
</tr>
<tr>
<td>Hodgkins</td>
<td>Doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD)</td>
</tr>
<tr>
<td>Non-Hodgkins</td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab (R-CHOP)</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Bortezomib, dexamethasone, thalidomide/lenalidomide</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>Cisplatin, etoposide or paclitaxel, carboplatin</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>Cisplatin, etoposide</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Cisplatin, pemetrexed or carboplatin, pemetrexed</td>
</tr>
</tbody>
</table>
## Selected Neoplastic Treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck</td>
<td>Cisplatin, 5-FU or paclitaxel, carboplatin</td>
</tr>
<tr>
<td>Esophageal</td>
<td>Cisplatin, 5-FU or paclitaxel, carboplatin</td>
</tr>
<tr>
<td>Uterine</td>
<td>Hormone therapy or cisplatin, doxorubicin</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Paclitaxel, carboplatin or docetaxel, carboplatin</td>
</tr>
<tr>
<td>Cervical</td>
<td>Cisplatin, paclitaxel</td>
</tr>
<tr>
<td>Breast</td>
<td>Adjuvant (hormone responsive): Tamoxifen (premenopausal) aromatase inhibitor (postmenopausal) ; Adjuvant HER2+ Docetaxel, carboplatin, trastuzumab</td>
</tr>
<tr>
<td>Testicular</td>
<td>Cisplatin, etoposide</td>
</tr>
<tr>
<td>Renal</td>
<td>Sunitinib, or temsirolimus or bevacizumab</td>
</tr>
<tr>
<td>Bladder</td>
<td>Gemcitabine, cisplatin or methotrexate, vinblastine, doxorubicin, cisplatin</td>
</tr>
<tr>
<td>Prostate</td>
<td>Luteinizing hormone agonist with antiandrogen</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>131I or sorafenib</td>
</tr>
</tbody>
</table>
## Selected Neoplastic Treatment

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>Docetaxel, cisplatin, 5-FU</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Gemcitabine, cisplatin or gemcitabine, erlotonib</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>5-FU, leucovorin, oxaliplatin (FOLFOX) or 5-FU, leucovorin, irinotecan (FOLFIRI)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Ipilimumab or vemurafenib or IL-2</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td>Sorafenib</td>
</tr>
</tbody>
</table>
Alkylation Agents

Class Effects

- **Myelosuppression**
  - Granulocyte nadir: 6-10 days
  - Recovery: 14-21 days

- **Hepatic venoocclusive disease**

- Mucosal toxicity

- Leukemogenesis

- Amenorrhea/Azoospermia
Alkylating Agents

Special Toxicities

- Busulfan (prolonged myelosuppression, seizures)
- Carmustine (pulmonary fibrosis)
- Cisplatin (ototoxicity, renal tubular tox → low K+, Mg++, Phos, Ca++)
- Ifosfamide (encephalopathy, cystitis)
- Meclorethamine: vesicant
- cyclophosphamide (cardiac, cystitis, renal tubular tox clinically similar to SIADH)
Antibiotics

Class Effects

• Myelosuppression

Special Toxicities

• Anthracyclines (cardiomyopathy, stomatitis)

• Bleomycin - Pulmonary fibrosis, BOOP

• Mitomycin C - HUS

• Mitoxantrone (cardiomyopathy, mucositis)
Anthracycline Cardiotoxicity

Acute (<24 hours)
- Dysrhythmias
- ECG changes
- Decreased EF
- Pericarditis
- Myocarditis

Late
- Dilated congestive cardiomyopathy
<table>
<thead>
<tr>
<th>Class Effects</th>
<th>Special Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myelosuppression</td>
<td>• 5-FU (hand-foot, cerebellar, <strong>coronary vasospasm</strong> with infusion)</td>
</tr>
<tr>
<td></td>
<td>• Acute methotrexate (nephrotoxicity, defective oogenesis/spermatogenesis, seizure)</td>
</tr>
<tr>
<td></td>
<td>• Chronic methotrexate (cirrhosis)</td>
</tr>
<tr>
<td></td>
<td>• Cytarabine (non-cardiogenic pulmonary edema, seizure, cerebellar)</td>
</tr>
</tbody>
</table>
Antimitotics*

Class Effects

• Myelosuppression
• Mucositis

Special Toxicities

• Cholinergic symptoms (irinotecan)
• GI perforation (paclitaxel-rare)
• Neuropathy (fludarabine, vincristine>vinblastine, paclitaxel)
• SIADH (Vincristine, vinblastine)

*Excluding colchicine
Colchicine
Autumn crocus (Colchicum autumnale)

Toxicity with therapeutic use:
Nephrogenic DI

• Acute Toxicity ("M-Phase arrest")
• Acute Fatal dose: ~ > 0.5 mg/kg

Phase I (10-24 h after ingestion):
• GI symptoms
• Phase II (1-7d after ingestion)
  • Multiorgan failure, sepsis

Treatment
• Aggressive GI contamination (charcoal, lavage)
• GM-CSF
## Radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Organ</th>
<th>Emission Type</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I</td>
<td>Thyroid</td>
<td>Beta, gamma</td>
<td>Thyroid, myelosuppression,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>emitter</td>
<td>secondary malignancies</td>
</tr>
<tr>
<td>$^{89}$Sr (Strontium 89)</td>
<td>Bone</td>
<td>Beta</td>
<td>myelosuppression</td>
</tr>
<tr>
<td>$^{153}$Sm (Samarium 153)</td>
<td>Bone</td>
<td>Beta, gamma</td>
<td>myelosuppression</td>
</tr>
</tbody>
</table>
Methotrexate

- Inhibits DHFR, TYMS
- Tri-phasic clearance, (2\textsuperscript{nd} phase- renal clearance, 3\textsuperscript{rd} phase tissue redistribution into plasma)
- Acidosis, renal failure, doses 100-1000mg/m\textsuperscript{2} associated with toxicity, folate deficiency
- Toxicity primarily dependent on DURATION of exposure
- Toxicity: Mucositis, hepatitis, renal failure, pancytopenia, seizures, hemiparesis, alopecia, oligospermia, hypersensitivity pneumonitis
Methotrexate (MTX)

MTX Inhibits
* Dihydro folate reductase (DHFR)
* Thymidylate synthetase (TYMS)

N5-formyl FH4 (Leucovorin)
Treatment of MTX Toxicity

- Leucovorin (dosing on following slide)
- IVFS
- Urinary Alkalinization
- Hemodialysis
- Thymidylate IV, carboxypeptidase
- Intrathecal MTX: CSF drainage/exchange
Leucovorin Dosing

• Routine “rescue” dosing
  • 10-25 mg/m\(^2\) IV/IM q 6 hours
  • 100 mg/m\(^2\) IV/IM q3 in renal compromise

• Methotrexate overdoses
  • Achieve equimolar leucovorin/MTX concentration but don’t wait for levels
  • 100 mg/m\(^2\) IV IV q3-6 is effective for most patients
  • DC infusion when MTX concentration is \(< 1 \times 10^{-8}\) mol/L and there is not bone marrow toxicity
Neurologic Adverse Effects (Excluding Neuropathy)

- AMS: cytarabine, ifosfamide, fludarabine, vincristine
- SZ: MTX (intrathecal $\rightarrow$ IV), busulfan, cytarabine
- Cerebellar ataxia: 5-FU, Cytarabine
- Cranial Nerves: vinca alkaloids
- Posterior leukoencephalopathy: Bortezomib
- Tinnitus, hearing loss, retinopathy: Cisplatin
- Unintentional intrathecal administration- CATASTROPHIC (vincristine)
Neurology Adverse Effects (Neuropathy)

- Bortezomib (peripheral)
- Brentuximab vedotin (peripheral neuropathy)
- Cytarabine (diffuse neurotoxicity)
- Docetaxel
- Fludarabine (diffuse neurotoxicity)
- Cisplatin>Carboplatin (peripheral)
- Ifosfamide
- Pertuzumab (peripheral)
- Thalidomide (peripheral)
- Vincristine>Vinblastine (peripheral, sensory-motor, ascending)
Renal/Electrolyte Adverse Effects

- Hemorrhagic cystitis: Cyclophosphamide, Ifosfamide
  **toxin= acrolein**
- Hemolytic Uremic Syndrome: Mitomycin
- Nephrogenic Diabetes Insipidus (DI): Colchicine
- “Nephrotoxicity”:
  - Azacitadine
  - Carboplatin
- Cisplatin (Distal tubular necrosis, low Mg++, low Ca++)
- Methotrexate
- Temsirolimus
- SIADH: Vincristine, vinblastine
- SIADH-Like: Cyclophosphamide, Ifosfamide
Cardiac Adverse Effects

• 5-FU
  —Coronary vasospasm (with infusion), cardiogenic shock

• Anthracycline abx (Danorubicin, Doxorubicin, Idarubicin), Mitoxantrone
  —Irreversible congestive cardiomyopathy
  —Immediate: dysrhythmia, pericarditis, myocarditis
Cardiac Adverse Effects

• Cyclophosphamide
  — Cardiomyopathy, hemorrhagic pericarditis

• Trastuzumab/Pertuzumab
  • Cardiomyopathy

• Tyrosine Kinase Inhibitors (imatinib, lapatanib, regorafinib)

• Vinca Alkaloids
  — Platelet aggregation
Pulmonary Adverse Effects

- **Bleomycin**: Pulmonary fibrosis, BOOP, nodular lesions
- **Busulfan**: alveolar-interstitial proteinosis
- **Carmustine**: Pulmonary fibrosis
- **Cyatarabine**: Mild-moderate ARDS
- **Methotrexate (MTX)**: hypersensativity pneumonitis, Hilar adenopathy
- **Mitomycin**: Pneumonitis, pulmonary fibrosis
- **Nitrosureas**: Upper lobe pulmonary fibrosis
- **Temsirolimus**: Interstitial lung disease
Pulmonary Adverse Effects
(Tyrosine kinase inhibitors and antibodies)

- Bortezomib
- Erlotinib
- Gefitinib
- Lapatinib
- Mitomycin
- Panitumumab
- Rituximab
- Traztuzumab
- Vendetanib
Mucositis

- 5FU
- Bleomycin
- Busulfan
- Daunorubicin
- Docetaxel
- Doxorubicin
- Everolimus
- Melphelan
- Mercaptopurine
- Methotrexate
- Mitomycin
- Mitoxantrone
- Paclitaxel
- Pemotrexed
- Regorafenib
- Sunitib
- Vinblastine
Hand-Foot Syndrome
(“Acral erythema,” “palmar-plantar erythrodysesthesia”)

- 5FU
- Axitinib
- Lapatinib
- Doxorubicin
- Everolimus
- Melphalan
- Regorafinib
- Sorafenib
- Sunitinib
Tumor Lysis Syndrome

• Release of K+, Phos, uric acid into circulation

• Initiation of cytotoxic chemotheraphy in patients with high grade lymphoma or ALL

• Symptoms (due to metabolic abnormalities): n/v/d, hematuria, cramping, dysrhythmias

• Prevention

  • Hydration (alkalinize only in case of acidosis)

  • Uric acid inhibitors

• Treatment

  • Supportive, HD if indicated
Regulatory Laws

EPA Resource Conservation and Recovery Act 40 CFR

Regulation covers:

• Preparation equipment
• Delivery equipment
• Disposal (as hazardous waste)
Estrogen-Targeting Drugs

- Anastrozole (Aromatase inhibitor)
- Exemestane (Aromatase inhibitor)
- Fulvestrant (ER downregulator)
- Letrozole (Aromatase inhibitor)
- Tamoxifen (Estradiol competitive inhibitor)
- Toremifene (Estradiol competitive inhibitor)
Estrogen-Targeting Drugs

- Anastrozole (Aromatase inhibitor)
- Exemestane (Aromatase inhibitor)
- Fulvestrant (ER downregulator)
- Letrozole (Aromatase inhibitor)
- Tamoxifen (Estradiol competitive inhibitor)
- Toremifene (Estradiol competitive inhibitor)
Estrogen-Targeting Drugs
Toxicity

- All drugs
  - Vasomotor symptoms (hot flashes), hair loss vaginal atrophy
- Tamoxifen/Toremifine:
  - Endometrial cancer
  - Thromboembolic events
Tyrosine Kinase Inhibitors

Mechanism:

- Mutations that constitutively activate protein tyrosine kinases cause malignant transformation

Adverse effects

- Mild GI symptoms, edema, hepatotoxicity
- Axitinib
- Dysphonia, Hand-foot, Hypertension
Tyrosine Kinase Inhibitors

- Dasatanib
- Gefitinib
- Imatinib
- Lapatanib
- Nilotinib
- Pazopanib
- Regorafenib
Tyrosine Kinase Inhibitors

Edema

- Bosutinib
- Crizotinib
- Dasatinib
- Imatinib
- Nilotinib
Tyrosine Kinase Inhibitors

Hand foot

• Axitinib
• Lapatanib
• Regorafenib
• Sorafenib
• Sunitinib
Tyrosine Kinase Inhibitors

Hypertension

- Axitinib
- Pazopanib
- Regorafenib
- Sorafenib
- Sunitinib
- Vandetanib
Anti-Androgens

Class Effects
- Decreased libido
- Erectile dysfunction
- Hot flash (women)

Special Toxicities
- Enzalutamide (Edema)
- Flutamide (Hepatotoxicity)
- Nilutamide (Disulfiram reaction)
- Leuprolide (Thromboembolic events)
Angiogenesis Inhibitors

• Mechanism: Cancer cells secrete angiogenic factors that induce the formation of new blood vessels and guarantee the flow of nutrients to the tumor cells.

• VEGF- Inhibitors: Bevacizumab, sunitinib, sorafenib
  - Bleeding, arterial thromboembolic event, hypertension, GI perforation, congestive heart failure (bevacizumab only)

• Thalidomide, lenalidomide
  - Bone marrow suppression (lenalidomide)
  - Phocomelia (in fetus)
  - Sedation, constipation, peripheral neuropathy (thalidomide)
  - Thromboembolic events
Angiogenesis Inhibitors
Monoclonal Antibodies

Alemtuzumab (CD52)
- Myelosuppression, immunosuppression

Bevacizumab
- Thromboembolism, GI perforation

Brentuximab vedotin (CD30)
- Neuropathy
Monoclonal Antibodies

Cetuximab (EGFR)
  • Rash

Gemtuzumab ozogamicin (CD33)
  • Myelosuppression, hepatotoxicity
Monoclonal Antibodies

Ipilimumab (CTLA4)
  • Rash, neuropathy

Ofotumumab (CD20)
  • Myelosuppression

Pertuzumab (Her2Neu)
Monoclonal Antibodies

Rituximab (CD20)

- Stevens Johnson Syndrome

Trastuzumab (Her2Neu)

- Cardiomyopathy

All Monoclonal antibodies

- Infusion reactions
mTor Inhibitors
(Everolimus, Temsirolimus)

- Mammalian target of rapamycin is a kinase in the PI3K family that regulates growth and proliferation

- Class Effects
  - Edema
  - Hyperglycemia
  - Myelosuppression
  - Pneumonitis
mTor Inhibitors
(Everolimus, Temsirolimus)

• Specific Effects
  • Everolimus
  • Temsirolimus- bowel perforation, nephrotoxicity

• CYP 3A4 interactions
Signal transduction: serine/threonine kinase BRAF

- B-RAF protein is an intracellular signal that affects growth and differentiation

- Vemurafenib, Dabrafenib
  - Rash, arthralgia
Proteasome Inhibitor

Bortezomib

- Neuropathy
- Posterior leukoencephalopathy (reversible)
- Thrombocytopenia
# Biologic Response Modifiers

<table>
<thead>
<tr>
<th>Aldesleukin (IL-2)</th>
<th>Interferon-alpha-2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypotension,</td>
<td>• Myelosuppression</td>
</tr>
<tr>
<td>• Capillary leak syndrome</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Lethargy/coma</td>
<td>• Hyperthyroidism</td>
</tr>
</tbody>
</table>
Arsenic Trioxide

- Edema
- Acute promyelocytic leukemia differentiation syndrome
- Fever, dyspnea, rash, pleural effusion
- Prolonged QT and complete AV block
Sipuleucel T

Patient’s WBC are incubated with a fusion protein consisting of

- Prostatic acid phosphatase (a prostate cancer antigen)
- GM-CSF

Cells are infused back into the patient

Toxicity

- Infusion reaction: Fever, chills, fatigue
Antidotes

- **Dexrazoxane**: Anthracycline ABX (Doxorubicin) cardiomyopathy: Iron chelator

- **Na Thiosulfate**: Cisplatin

- **MESNA** (2-mercaptoethane sulfonate sodium): cyclophosphamide inactivates acrolein to thioether

- **Methylene Blue**: Ifosfamide encephalopathy
Antidotes

- **Amifostine**: Cisplatin; activated intracellular by alkaline phosphatase, scavages free radicals

- **Folinic Acid**: MTX

- **Glutamic Acid**: Vincrisitine – prevention neuropathy

- **DDTC (diethyldithiocarbamate) /Disulfuram**: Cisplatin, also recall Ni, Ni Carbonyl
Antidotes

- **KI**: $^{131}$Iodine
- **Prussian Blue**: Thallium
- **DTPA**: Plutonium
- **G-CSF**: colchicine, most chemo agents
- **Pyridoxine**: Procarbazine (hydrazine)
Decontamination/Elimination

**AC:** Methotrexate, busulfan, melphalan

**MDAC:** colchicine

**Urinary Alkalization:** Methotrexate

**Plasmapharesis:** Cisplatin, Vincrisitine
Extravasation Antidotes

- **Dexrazoxane**: IV: Anthracyclines: limits free radicals

- **Dimethyl sulfoxide (DMSO)**: topical:
  Anthracyclines, Mitomycin: limits free radicals; compress- ICE

- **Sodium thiosulfate**: IV: Mechlorethamine: prevents tissue alkylation

- **Hyaluronidase**: SubQ: Vinca alkaloids, epipodophyllotoxins: degrades hyaluronic acid; compress- WARM
Transplant Principles

- Choose well-matched organs
- Choose multiple molecular targets in allograft response
  - Lower doses of multiple agent
- Intense immunosuppression for induction, lower doses for maintenance
- Maintain balance between drug toxicity and rejection
- Withdraw medications when toxicity exceed benefit
<table>
<thead>
<tr>
<th>DRUG</th>
<th>SITE OF ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Glucocorticoid response elements in DNA (regulate gene transcription)</td>
</tr>
<tr>
<td>Muromonab-CD3</td>
<td>T-cell receptor complex (blocks antigen recognition)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Calcineurin (inhibits phosphatase activity)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Calcineurin (inhibits phosphatase activity)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>DNA (false nucleotide incorporation)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td><em>Inosine</em> monophosphate dehydrogenase (inhibits activity)</td>
</tr>
<tr>
<td>Daclizumab, basiliximab</td>
<td>IL-2 receptor (block IL-2-mediated T-cell activation)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Protein kinase involved in cell-cycle progression (mTOR) (inhibits activity)</td>
</tr>
</tbody>
</table>

IL, interleukin; mTOR, mammalian target of rapamycin.
Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Calcineurin-catalyzed dephosphorylation is required for T-Cell activation

Cyclosporine

- Nephrotoxicity
- Hypertension
- Hirsutism, Tremor, Hyperlipidemia

Tacrolimus

- Nephrotoxicity
- Neurotoxicity: Tremor, headache, motor disturbances.
Calcineurin inhibitors: CYP3A4 drug interactions

Increased Concentrations

- Allopurinol
- Bromocriptine
- CCB
- Colchicine
- Erythromycin
- Fluconazole
- Grapefruit juice
- Metoclopramide
- Protease inhibitors
Calcineurin inhibitors: CYP3A4 drug interactions

Decreased Concentrations

- Carbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- Octreotide
- St. John’s Wort
Sirolimus (Rapamycin)

Macrolide compound, CYP3A4

Inhibits IL-2/5, binds to kinase MTOR also known as FRAP, RAFT

Toxicity

- Hyperlipidemia
- Myelosuppression
- Stomatitis
- Slow wound healing
- Hepatic artery thrombosis (liver transplant)
Mycophenolate Mofetil (MMF)

- Blocks the inosine monophosphate pathway
  - B and T cells dependent on this pathway for proliferation
- No effect on cytokines
- Toxicity
  - Heme: Pure red cell aplasia, leukopenia
  - GI: N/V
- Combination with azathioprine or other antimetabolites can cause increased bone marrow suppression
# MMF drug interactions

<table>
<thead>
<tr>
<th>Increased Concentrations of MMF</th>
<th>Decreased Concentrations of MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acyclovir, ganciclovir</td>
<td>• Antacids: Al/Mg</td>
</tr>
<tr>
<td>• Probenecid</td>
<td>• Iron</td>
</tr>
<tr>
<td>• Salicylates</td>
<td>• Metronidazole</td>
</tr>
<tr>
<td>• Sirolimus</td>
<td>• Norfloxacin</td>
</tr>
<tr>
<td></td>
<td>• Rifampin</td>
</tr>
</tbody>
</table>
TNF-Alpha Inhibitors

(TNF is implicated in immune-mediated disease)

Drugs

• Adalimumab (RA, Crohn’s etc)

• Infliximab (RA, Crohn’s)

• Etanercept (RA, psoriatic arthritis, etc)
TNF-Alpha Inhibitors
(TNF is implicated in immune-mediated disease)

Adverse Effects

• All drugs: Immune-related disease
  • Infection
  • Lymphoma
  • Cardiomyopathy
  • Malignancy
  • Autoimmune disease induction
• Infliximab: Influsion reaction, SLE-like syndrome
TNF-alpha contraindications

- Latent TB or Hep B
- Chronic Heart failure
- Vaccinations with live organisms
Regulatory Laws

EPA Resource Conservation and Recovery Act 40 CFR

Regulates 9 anti-neoplastics:

- arsenic trioxide
- chlorambucil
- Cyclophosphamide
- daunomycin
- melphalan
- mitomycin c
- napthylamine mustard
- streptozocin
- uracil mustard
Question

A patient who received chemotherapy presents with pulmonary rales, lower extremity edema, and ejection fraction of 10%. Which drug is most likely responsible?

A) Cisplatin
B) Busulfan
C) Idarubicin
D) Temozolomide
<table>
<thead>
<tr>
<th>When I say</th>
<th>You say</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic cystitis</td>
<td>Cyclophosphamide, ifosfamide</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Cholinergic symptoms</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>Thyroid toxicity</td>
</tr>
<tr>
<td>Posterior leukoencephalopathy</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Catastrophic intrathecal administration</td>
<td>Vincristine</td>
</tr>
<tr>
<td>Infusion reaction and cardiomyopathy</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Doxorubicin cardiomyopathy “antidote”</td>
</tr>
<tr>
<td>Prolonged QT and AV block</td>
<td>Arsenic Trioxide</td>
</tr>
</tbody>
</table>
Focus Your Studying On:

• Class effects
• Unique Adverse effects
• Unique mechanisms
• Unique antidotes