Cancer Chemotherapy

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Polyfunctional Alkylating Agents

• Not cell cycle-specific.
• Work by transferring alkyl groups to various cellular constituents, mainly to DNA, leading to cell death.
• They also interact with sulfhydryl, amino, hydroxyl, carboxyl and phosphate groups of other cellular nucleophiles.
• DNA interactions can occur on a single strand or on both strands through cross-linking, i.e. bifunctional with two reactive groups.
Polyfunctional Alkylating Agents

• Can cause acquired resistance and cross resistance, but not with nitrosureas.
• Direct vesicant effects.
• Nausea and vomiting.
Polyfunctional Alkylation Agents

- Cyclophosphamide.
- Mechlorethamine.
- Chlorambucil.
- Melphalan.
- Thiotepa.
- Busulphan.
- Nitrosureas
Polyfunctional Alkylating Agents

• **Nitrosureas:**
  • Carmustine (BCNU).
  • Lomustine (CCNU).
  • Semustine (methyl-CCNU).
  • Streptozocin; for insulin-secreting islet cell carcinoma, also to induce diabetes in experimental animals.
  • Not cross-resistant with other alkylating agents.
  • Highly lipid soluble.
Polyfunctional Alkylating Agents

• Platinum analogs:

  • Cisplatin:
    • Kills cells in all stages.
    • Binds DNA and inhibits synthesis and function.
    • Nephrotoxic, hydration is necessary.
    • Solid tumors.
<table>
<thead>
<tr>
<th>Alkylation Agent</th>
<th>Single-Agent Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechlorethamine (nitrogen mustard)</td>
<td>0.4 mg/kg IV in single or divided doses</td>
<td>Nausea and vomiting</td>
<td>Moderate depression of peripheral blood count; excessive doses produce severe bone marrow depression with leukopenia, thrombocytopenia, and bleeding; alopecia and hemorrhagic cystitis occasionally occur with cyclophosphamide; cystitis can be prevented with adequate hydration; busulfan is associated with skin pigmentation, pulmonary fibrosis, and adrenal insufficiency</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>0.1–0.2 mg/kg/d orally; 6–12 mg/d</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>3.5–5 mg/kg/d orally for 10 days; 1 g/m² IV as single dose</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg/d orally for 4 days every 4–6 weeks</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Thiopeta (triethyleneethio-phosphoramide)</td>
<td>0.2 mg/kg IV for 5 days</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>2–8 mg/d orally; 150–250 mg/course</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Carmustine (BCNU)</td>
<td>200 mg/m² IV every 6 weeks</td>
<td>Nausea and vomiting</td>
<td>Leukopenia, thrombocytopenia, and rarely hepatitis</td>
</tr>
<tr>
<td>Lomustine (CCNU)</td>
<td>150 mg/m² orally every 6 weeks</td>
<td>Nausea and vomiting</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Altretamine</td>
<td>10 mg/kg/d for 21 days</td>
<td>Nausea and vomiting</td>
<td>Leukopenia, thrombocytopenia, and peripheral neuropathy</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>150 mg/m² orally for 5 days every 28 days</td>
<td>Nausea and vomiting, headache and fatigue</td>
<td>Leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>50–200 mg/d orally</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression, central nervous system depression, leukemogenic</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>300 mg/m² daily IV for 5 days</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20 mg/m²/d IV for 5 days or 50–70 mg/m² as single dose every 3 weeks</td>
<td>Nausea and vomiting</td>
<td>Nephrotoxicity, peripheral sensory neuropathy, ototoxicity, nerve dysfunction</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 5–7 mg x min/mL</td>
<td>Nausea and vomiting</td>
<td>Myelosuppression; rarely: peripheral neuropathy, renal toxicity, and hepatic dysfunction</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m² IV every 3 weeks or 85 mg/m² IV every 2 weeks</td>
<td>Nausea and vomiting, laryngopharyngeal dysesthesias</td>
<td>Peripheral sensory neuropathy, diarrhea, myelosuppression, and renal toxicity</td>
</tr>
</tbody>
</table>
Antimetabolites

• Utilize quantitative differences in metabolism of cancer cells from normal cells, that render them susceptible to a number of structural analogs.

• The most vulnerable pathways are those of nucleotide and nucleic acid synthesis.
Antimetabolites

**Methotrexate (MTX):**

- Folic acid analog which binds to the active site of dihydrofolate reductase (DHFR), interfering with the synthesis of the reduced form that accepts one-carbon units.
- This will interrupt the *de novo* synthesis of thymidylate, purine nucleotides and the amino acids serine and methionine.
- This will interfere with the formation of DNA, RNA and key cellular proteins.
• Resistance to Methotrexate (MTX):
  • Decreased drug transport.
  • Decreased formation of cytotoxic MTX polyglutamate.
  • Synthesis of increased levels of DHFR through gene amplification.
  • Altered DHFR with reduced affinity for MTX.
  • Decreased accumulation of drug through activation of MDRP170 glycoprotein transporter.
• **Leukovorine Rescue:**
  • The administration of the reduced folate leukovorine (5-formyltetrahydrofolate) to reverse the effects and toxicity of MTX.
  • This will compete with methotrexate for DHFR
  • Usually indicated in high dose methotrexate therapy to rescue normal cells.
Antimetabolites

• **Purine Antagonists:**
  
  • **6-Thiopurines:**
    
    • 6-Mercaptopurine (6-MP).
    • 6-Thioguanine 6-TG).

  Inhibit several enzymes.

  6-MP metabolized by xanthine oxidase, so toxicity is enhanced by Allopurinol
Antimetabolites

• **Pyrimidine Antagonists:**
  • 5-Fluorouracil:
    • Most widely used agent in colorectal carcinoma, also stomach, breast, esophagus, liver, head and neck, and pancreas.
Table 55–3. Antimetabolites: Dosages and toxicities.

<table>
<thead>
<tr>
<th>Chemotherapeutic Agent</th>
<th>Single-Agent Dosage</th>
<th>Delayed Toxicity¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>1250 mg/m²/bid orally for 14 days followed by 1 week of rest. Repeat every 3 weeks.</td>
<td>Diarrhea, hand-and-foot syndrome, myelosuppression, nausea and vomiting</td>
</tr>
<tr>
<td>Cladribine</td>
<td>0.09 mg/kg/d for 7 days by continuous IV infusion in sterile saline</td>
<td>Myelosuppression, nausea and vomiting, and immunosuppression</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>100 mg/m²/d for 5–10 days, either by continuous IV infusion or SC every 8 hours.</td>
<td>Nausea and vomiting, bone marrow depression with leukopenia and thrombocytopenia, and cerebellar ataxia</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>25 mg/m²/d for 5 days every 28 days (administer IV over 30 minutes)</td>
<td>Myelosuppression, immunosuppression, fever, myalgias, and arthralgias</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>15 mg/kg/d IV for 5 days by 24-hour infusion; 15 mg/kg weekly IV</td>
<td>Nausea, mucositis, diarrhea, bone marrow depression, and neurotoxicity</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² IV weekly for up to 7 weeks followed by 1 week of rest</td>
<td>Nausea, vomiting, diarrhea, myelosuppression</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>2.5 mg/kg/d orally</td>
<td>Myelosuppression, immunosuppression, and hepatotoxicity</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>2.5–5 mg/d orally (Rheumatrex); 10 mg intrathecally (Folex) once or twice weekly</td>
<td>Mucositis, diarrhea, bone marrow depression with leukopenia and thrombocytopenia</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>500 mg/m² IV every 3 weeks</td>
<td>Myelosuppression, skin rash, mucositis, diarrhea, and fatigue</td>
</tr>
<tr>
<td>6-Thioguanine</td>
<td>2 mg/kg/d orally</td>
<td>Myelosuppression, immunosuppression, and hepatotoxicity</td>
</tr>
</tbody>
</table>

¹These drugs do not cause acute toxicity.
Plant Alkaloids

Vinblastine:

• Periwinkle plant *Vinca rosea*.

• Inhibits tubulin polymerization, disrupting assembly of microtubules, which are important part of the cytoskeleton and the mitotic spindle.

• This effect results in mitotic arrest and death of the cell.
Plant Alkaloids

Vincristine:

• Similar actions but different clinical activities and toxicity.
• Pediatric tumors.
• Neurotoxicity
• Milder myelosuppression.
• SIADH
Antitumor Antibiotics

• Products of various strains of the soil microbe *Streptomyces*.
• Bind to DNA through intercalation between specific bases and block the synthesis of RNA, DNA or both, cause DNA strand scission and interference with cell replication.
Antitumor Antibiotics

** Anthracyclines:**

Daunorubicin.

Doxorubicin “ Adriamycin”

Idarubicin.

Epirubicin

- Very widely used.
- Inhibit topoisomerase II.
- Intercalate with DNA.
- Bind to membranes to alter fluidity and ion transport.
- Generate semiquinone and oxygen free radicals leading to cardiotoxicity.
Antitumor Antibiotics

Anthracyclines:
• IV.
• Metabolized and excreted through the liver.
• Given on every 3-week schedule.
• Or, as low-dose weekly,
• Or, 72-96 hour continuous infusion.
Antitumor Antibiotics

Anthracyclines:

• Important anticancer drugs.

• Cancers of breast, endometrium, ovary, testicles, thyroid, stomach, bladder, liver, lung, soft tissue sarcomas, in childhood cancers and in hematologic malignancies.
Antitumor Antibiotics

**Anthracyclines:**

- Myelosuppression.
- Mucositis, *sometimes is dose-limiting.*
- "Radiation Recall Reaction": a severe skin reaction that occurs when certain chemotherapy drugs are administered during or soon after radiation treatment.
Antitumor Antibiotics

• Cardiotoxicity:
  • Acute: first 2-3 days.
    • Arrhythmias and ECG changes, pericarditis and myocarditis.
  • Chronic: dose dependent.
    • Cardiomyopathy and heart failure.
    • Results from increased production of free radicals.
    • Reduced by weekly or continuous treatment.
    • Iron chelation treatment may reduce it.
Hormonal Agents

• **Estrogen Inhibitor:**
  • **Tamoxifen:**
    • Competitive partial agonist-inhibitor of estrogen and binds to estrogen receptor of estrogen-sensitive tumors.
    • Extremely useful for both early and metastatic breast carcinoma.
    • Also as chemopreventive agent in women at high risk.
    • Endometrial cancer.
    • Oral and very safe.
Hormonal Agents

• **Androgen Inhibitors:**
  - Flutamide.
  - Bicalutamide.
    - Are nonsteroidal antiandrogen agents.
    - Oral.
    - Used in combination with radiation therapy for early-stage prostate cancer and metastatic cancer.
Hormonal Agents

• **Gonadotropin-releasing Hormone Agonists:**
  - **Leuprolide.**
  - **Goserelin.**
    - Are synthetic peptide analogs.
    - Given as depot preparations leading to transient release of FSH and LH followed by marked inhibition.
    - Indicated for advanced prostate cancer.
    - Cause hot flushes, impotence and gynecomastia.
Hormonal Agents

**Aromatase Inhibitors:**

- **Aminoglutethimide:**
  - Nonsteroidal inhibitor of corticosteroid synthesis at the first step (cholesterol ---- pregnenolone).
  - Also inhibits extra-adrenal synthesis of estrone and estradiol.
  - Also; in body fat; inhibits aromatase enzyme that converts the adrenal androgen androstenedione to estrone.
  - Primarily used in metastatic breast carcinoma with significant estrogen or progesterone receptor expression.
  - Also effective in advanced prostate cancer.
  - Normally given with hydrocortisone
## Table 55–5. Hormonally active agents: Dosages and toxicities.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiandrogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>250 mg/tid orally</td>
<td>Mild nausea</td>
<td>Hot flushes, transient elevations in liver function tests</td>
</tr>
<tr>
<td><strong>Antiestrogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>20 mg/d orally</td>
<td>Transient flare of tumor symptoms</td>
<td>Menopausal symptoms, fluid retention and edema, thromboembolic events, increased incidence of endometrial hyperplasia and cancer</td>
</tr>
<tr>
<td><strong>Progestins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>40 mg orally 4 times daily</td>
<td>None</td>
<td>Fluid retention</td>
</tr>
<tr>
<td><strong>Adrenocorticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>40–200 mg/d orally</td>
<td>None</td>
<td>Fluid retention, hypertension, diabetes, increased susceptibility to infection, moon facies</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20–100 mg/d orally</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Gonadotropin-releasing hormone agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>3.6 mg SC monthly</td>
<td>Transient flare of tumor symptoms, pain at injection site</td>
<td>Hot flushes, impotence, gynecomastia</td>
</tr>
<tr>
<td>Leuprolide</td>
<td>7.5 mg SC monthly</td>
<td>Transient flare of tumor symptoms, pain at injection site</td>
<td>Hot flushes, impotence, gynecomastia</td>
</tr>
<tr>
<td><strong>Aromatase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglutethimide</td>
<td>250 mg orally twice daily and hydrocortisone 20 mg twice daily</td>
<td>Fatigue, mild nausea</td>
<td>Skin rash, adrenal insufficiency, myelosuppression</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>1 mg orally daily</td>
<td>Mild nausea, headache</td>
<td>Fatigue, hot flushes, arthralgias</td>
</tr>
<tr>
<td>Exemestane</td>
<td>25 mg orally daily</td>
<td>Mild nausea, headache</td>
<td>Fatigue, hot flushes</td>
</tr>
<tr>
<td>Letrozole</td>
<td>2.5 mg orally daily</td>
<td>Mild nausea, headache</td>
<td>Fatigue, hot flushes, arthralgias</td>
</tr>
</tbody>
</table>
Table 55-6. Miscellaneous anticancer drugs: Dosages and toxicities.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dosage</th>
<th>Acute Toxicity</th>
<th>Delayed Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>0.15 mg/kg/d IV for 60 days as induction therapy; 0.15 mg/kg/d IV for 5 days per week for a total of 5 weeks as consolidation therapy</td>
<td>Headache and lightheadedness</td>
<td>Fatigue, cardiac dysrhythmias, fever, dyspnea, fluid retention and weight gain</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>20,000 IU/m² daily IV for 5–10 days</td>
<td>Nausea, fever, and allergic reactions</td>
<td>Hepatotoxicity, mental depression, pancreatitis</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>5 mg/kg IV every 2 weeks</td>
<td>Hypertension, infusion reaction</td>
<td>Arterial thromboembolic events, gastrointestinal perforations, wound healing complications</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>400 mg/m² IV loading dose; 250 mg/m² IV weekly</td>
<td>Infusion reaction</td>
<td>Skin rash, interstitial lung disease</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>150 mg/d orally</td>
<td>Diarrhea</td>
<td>Skin rash, interstitial lung disease</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>250 mg/d orally</td>
<td>Hypertension, diarrhea</td>
<td>Skin rash, interstitial lung disease</td>
</tr>
<tr>
<td>Imatinib</td>
<td>400–600 mg/d orally</td>
<td>Nausea and vomiting</td>
<td>Fluid retention with ankle and periorbital edema, diarrhea, myalgias</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>300 mg/m² orally for 5 days</td>
<td>Nausea and vomiting</td>
<td>Bone marrow depression</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>10–12 mg/m² IV every 3–4 weeks</td>
<td>Nausea</td>
<td>Bone marrow depression, occasional cardiac toxicity, mild alopecia</td>
</tr>
<tr>
<td>Trastuzumab¹</td>
<td>4 mg/kg IV loading dose; 2 mg/kg/wk as maintenance</td>
<td>Nausea and vomiting, infusion-related hypersensitivity reaction</td>
<td>Cardiomyopathy, myelosuppression, pulmonary toxicity</td>
</tr>
</tbody>
</table>

¹This monoclonal antibody is described in Chapter 56: Immunopharmacology.