Drugs Affecting the Immune System: Antineoplastic

Mildred Gonzales, MSN, RN, OCN
mgonzales@dhs.lacounty.gov

Terminology

• Oncology
  ▫ Branch of medicine concerned with the study of malignancy – development, diagnosis, treatment, and prevention

• Antineoplastic
  ▫ Pertaining to a substance, procedure, or measure that prevents proliferation of cells
    • Antineoplastic drugs or cytotoxic therapy are pharmaceutical agents often used to destroy cancer cells

Cell Cycle Time

G0 = resting phase, cells are not in the process of cellular division
G1 = relatively dormant with some RNA and protein synthesized
S = DNA is synthesized; RNA and protein synthesis continue
G2 = some RNA synthesized
M = mitosis (cellular division)
Key Points

• Cancers arise from a single abnormal cell that multiplies and grows
• As abnormal cells continue to divide, they lose more of their original characteristics
  ▫ Anaplasia: Loss of cellular differentiation & organization
  ▫ Autonomy: Allows them to grow in an uninhibited way
  ▫ Metastasis: Ability to travel to other sites of the body
  ▫ Angiogenesis: Ability to grow new blood vessels to feed the tumor

Cancer chemotherapy

• Use of chemicals to kill cancer cells by interfering with cell replication
  ▫ Guided by specific protocols
• Usually given in cycles
• Factors that play a major role in the response of cancer cells to anticancer drugs
  ▫ Growth fraction
  ▫ Doubling time
• Anticancer drugs — more effective against neoplastic cells that have high growth fraction

Antineoplastic or Anticancer Drugs

• Treat malignancies by directly killing tumor cells
  ▫ Damage the DNA
  ▫ Inhibit the synthesis of new DNA strands to stop the cell from replicating
  ▫ Stop mitosis
• Destroy cancer cells by inhibiting cell division but also affect normal cells particularly the rapidly multiplying cells or cells that replace themselves quickly and causing side effects
Cancer Chemotherapy

- Cell-cycle specific (CCS) agents
  - Also called “cell-cycle dependent drugs”
  - Exert their influence during a specific phase of the cell cycle
  - Most effective against rapidly growing cancer cells
  - Include: antimetabolites and mitotic inhibitors

Cancer Chemotherapy, cont.

- Cell-cycle nonspecific drugs (CCNS)
  - Also called “cell-cycle independent drug”
  - Act during any phase of the cell cycle
  - Include: alkylating drugs, anti-tumor antibiotics, hormones

Use of Combination Chemotherapy Drugs

- Combined use of CCS & CCNS drugs maximize cell death – synergistic effect
- Able to kill cells in all phases of the cell cycle especially cells that multiply rapidly & go through the cell cycle quickly
- Decrease drug resistance and increase destruction of cancer cells
  - Example: Cyclophosphamide, Doxorubicin, & Fluorouracil are used in breast & prostate cancer
Drug Resistance

Causes of multidrug resistance (MDR)

- Cell mutation
- Natural resistance
- Gene amplification
- Ability to repair DNA damage

Specific Classes of Chemotherapy Drugs

- Alkylating agents
- Antimetabolites
- Antitumor antibiotics
- Plant alkaloids (Mitotic inhibitors)
- Miscellaneous chemotherapy agents

Alkylating Agents

- CCNS category, but most effective against cells in the G0 phase
- Useful in the Tx of slow-growing cancers, which may have cells in the resting phase such as:
  - Lymphomas, leukemias, multiple myeloma, & solid tumors in breast, ovary, uterus, bladder, stomach
- Mechanism of action
  - Inhibit DNA synthesis by binding to and damaging the DNA itself.
Alkylating Agents

- Pharmacokinetics
  - Degree of absorption varies
  - Metabolized and sometimes activated in the liver
  - Excreted in the urine
- Contraindications and Cautions
  - Pregnancy and lactation
  - Known allergy
  - Bone marrow suppression
  - Suppressed renal or hepatic function
- Dosing for each alkylating agent is specific for each treatment regimen

Alkylating Agents, cont.

- Adverse effects: N/V, hemorrhagic cystitis, bone marrow suppression, alopecia, secondary malignancies, and sterility
- Major dose-limiting toxicities occur in:
  - Hematopoietic system
  - Urinary systems

Prototype: Cytoxan (cyclophosphamide)

- Pharmacokinetics
  - Well absorbed from GI tract
  - Moderately protein-bound
  - Metabolized in the liver
  - < 50% is excreted unchanged in the urine
- Onset of action: 2 to 3 hrs
- Therapeutic effect may take several days
Cytoxan, cont.

- Drug interaction with Cytoxan (cyclophosphamide)
  - Allopurinol or Thiazide diuretics – exaggerate the bone marrow depression
  - Phenobarbital – increases the toxicity of Cytoxan
  - Warfarin & Aspirin – potentiated effects
  - Digoxin – decreased levels

- Adverse reactions
  - Hemorrhagic cystitis - due to accumulation of toxic metabolites in the bladder
  - Secondary neoplasm
  - Bone marrow suppression

List of more alkylating drugs in textbook

Antimetabolites

- Considered to be ‘S’ phase specific in the cell cycle
  - Exception: Fluorouracil (5-FU, Adrucil) & floxuridine (FUDR) – considered CCNS as well as CCS

- Therapeutic actions
  - Disrupt the metabolic processes and inhibit enzyme synthesis
  - Prevent normal cellular function

Antimetabolites, cont.

- Indications
  - Acute leukemia, breast cancer, head and neck cancer, lung cancer, osteosarcoma, non-Hodgkin’s lymphoma

- Often given in combination with other agents to help overcome drug-resistant tumors
Antimetabolites, cont.

- Contraindications and cautions
  - Pregnancy and lactation
  - Known allergy
  - Bone marrow suppression
  - Renal or hepatic dysfunction
  - Known GI ulcerations or ulcerative diseases

- Adverse effects:
  - Bone marrow suppression — may lead to life-threatening infections or bleeding
  - Stomatitis, N/V/D, alopecia, rash, hepatic & renal dysfunction, & photosensitivity
  - CNS effects — headache, drowsiness, dizziness

Antimetabolites

Prototype: 5-Fluorouracil (5-FU, Adrucil)

- Action: prevention of thymidine synthetase production, thus inhibiting DNA & RNA synthesis
  - Therapeutic uses: CA of breast, cervix, colon, liver, ovary, pancreas, stomach, rectum
- Adverse reaction — similar to other antimetabolites
  - Stomatitis — an early sign of toxicity & should be reported
- Drug interactions
  - Leucovorin calcium & Metronidazole - ↑ 5-FU toxicity
  - Thiazide diuretics - ↑ myelosuppression
Antitumor Antibiotics

• Inhibit protein and RNA synthesis and bind DNA, causing fragmentation

• Classified as CCNS drugs except for bleomycin (Blenoxane) which has its major effect on the ‘G2’ phase.

• Each antitumor antibiotic exhibits a unique side effect profile
  ▫ Doxorubicin has severe cardiotoxic side effects

• Common side effects with above agents: mucositis, nausea, & vomiting

Plant Alkaloids (Mitotic Inhibitors)

• CCS and block cell division at the ‘M’ phase of the cell cycle

• Adverse reactions
  ▫ Leukopenia, N/V/D, reversible alopecia
  ▫ Damage to peripheral nerve fibers causing reversible or irreversible neurotoxicity
  ▫ Others - loss of deep tendon reflexes, muscle weakness, joint pain, muscle weakness, bone marrow depression

Mitotic Inhibitor: Vincristine (Oncovin)

• Adverse reactions
  ▫ hypotension, sensory loss, visual disturbances, ileus, fever, severe local reaction with extravasation, hyponatremia

• Life-threatening:
  ▫ Intestinal necrosis, seizure, coma, acute bronchospasm, bone marrow depression

• Drug interactions:
  ▫ Decreases the effects of digoxin and phenytoin
Miscellaneous Cytotoxic Agents

- Category includes a number of antineoplastic agents in which the mechanism of action is unclear
- Used in combination with another anticancer drug
- Examples:
  - L-asparaginase (Elspar) – used in acute lymphocytic leukemia
  - Pegaspargase (Onicaspar) - used in acute lymphoblastic leukemia
- Major toxicity – hypersensitivity reactions
- Other adverse effects – nausea, hepatotoxicity, impaired pancreatic function, coagulopathy

Hormonal Agents

- Cytostatic – prevent the growth of the tumor instead of causing cell death
- Receptor-site specific or hormone specific to block the stimulation of growing cancer cells that are sensitive to the presence of that hormone
- Not considered biohazard agents – do not require special handling precautions
- Most are contraindicated in pregnancy
- Adverse effects – nausea, hot flashes

Hormonal Agents

- Corticosteroids (prednisone, dexamethasone)
  - Suppress the inflammatory process
  - Can help decrease cerebral edema caused by a malignant brain tumor
  - Some adverse effects: fluid retention, K+ loss, ↑ blood sugar, ↑ risk of infection, muscle weakness, euphoria
Hormonal Agents, cont.

• Sex hormones or hormone-like agents
  ▫ Slow the growth of hormone-dependent tumors
  ▫ Estrogen therapy - palliative treatment used to decrease the progression of prostate cancer in men and slow the growth of breast cancer in women
    ▪ Examples: ethinyl estradiol (Estinyl); conjugated estrogens (Premarin)

Hormonal Agents, cont.

• Antiestrogens: tamoxifen (Nolvadex)
  ▫ Competes with estrogen for binding sites in target tissues, such as the breast
  ▫ Treat advanced breast cancer in premenopausal women
  ▫ Prevent tumor recurrence in both pre- and post-menopausal women
  ▫ Adverse effects - increase risk for endometrial cancer, thrombosis, hot flashes

Hormonal Agents, cont.

• Selective estrogen receptor modulators (SERMs)
  ▫ Act like antiestrogen but have fewer side effects
    ▪ Examples: raloxifene (Evista)
  ▫ Progestins - may be prescribed to treat breast cancer, endometrial cancer, and renal cancer
    ▫ Act by shrinking the cancer tissues
    ▪ Examples: megestrol acetate (Megace), medroxyprogesterone acetate (Depo-Provera)
Hormonal Agents, cont.

• Gonadotropin-Releasing Hormone Analogues (Leutinizing hormone-releasing hormone (LH-RH) agonists) e.g. leuprolide (Lupron)
  ◦ Suppress the secretion of follicle-stimulating hormone and luteinizing hormone from the pituitary gland
  ◦ Results in the suppression of testosterone, preventing it from stimulating the growth of prostate cancer cells

Anticancer drugs associated with second malignancies

• Second malignancies – acute leukemias, solid tumors
• Cause toxic damage through effects on DNA, mutations, & chromosomal damage
• Long-term survivors of chemotherapy have increased risk
• Alkylating agents - drugs most commonly implicated
  ◦ melphalan (Alkeran)
  ◦ cyclophosphamide (Cytoxan)

Cytoprotective drugs

• Cytoprotective drugs may be used to reduce toxicities
  ◦ IV or PO allopurinol (Zyloprim) – to reduce hyperuricemia
  ◦ Mesna (MESNEX) – often given with high-dose cyclophosphamide (cytoxan) to inactivate urotoxic metabolites in the bladder
Serious adverse effects of Cytotoxic Drugs

- Bone marrow depression
  - 1. **Low RBC count (anemia)**
  - Nursing measures
    - Assess for fatigue, SOB, VS & LOC changes, O2 sat
    - Plan rest periods for client
    - Assist with ADLs
    - Control pain, elevate HOB to facilitate breathing
    - Supplemental oxygen may be prescribed
    - Some patients may be prescribed FeSO4, erythropoietin, or blood transfusion of PRBCs

- Bone marrow depression, cont.
  - 2. **Low WBC count – leukopenia**
    - Low absolute neutrophil count (ANC) – neutropenia
    - Normal range = 1500 – 8000 cells/mm³
    - **What value is considered severe?** < 500
  - Nursing measures
    - Assess for localized infections. Usual S/S of infection may be absent or greatly reduced in neutropenic patients
    - Hand hygiene
    - Visitors with infections should take precautions
    - Monitor for increase or decrease in temperature
    - Fever, chills, URTI, sore throat should be reported to HCP
    - Colony-stimulating factors, e.g., filgrastim (Neupogen) may be administered

- Bone marrow depression, cont.
  - 3. **Low platelet count – thrombocytopenia**
  - Nursing measures
    - Petechiae, bruising, bleeding gums, & nosebleeds should be reported to HCP
    - Monitor platelet counts and bleeding time
    - Assess for occult blood in urine, stool, & emesis
    - Avoid medications that may promote bleeding
    - Avoid invasive procedures
    - Apply pressure to injection sites
    - Platelet transfusions may be needed
Other serious adverse effects

- Cardiotoxicity
  - Adriamycin: May cause ECG changes or CHF
  - Cytoxan: In very high doses
  - Herceptin: Cardiomyopathy
- Nephrotoxicity
  - 5-FU
  - Mutamycin

Other serious adverse effects, cont.

- Hepatotoxicity:
  - Cytoxan: In long term use
  - Adriamycin: Use with caution in patients with hepatic and renal impairment
- Neurotoxicity (Peripheral Neuropathy)

Managing Complications of Chemotherapy:

A. Extravasation: escape of a vesicant drug into surrounding tissues causing severe tissue damage or permanent damage to nerves, tendons, muscles, or loss of limbs
  - Usually occurs with peripheral access devices & seldom occurs when patients have central catheters
  - Continuous monitoring of the IV site is critical
  - Monitor for pain (may or may not be present), swelling, redness, & presence of vesicles on the skin
A. **Extravasation, cont.**

- If suspected, stop the IV infusion immediately but do not remove the IV line
- If possible aspirate the remaining drug or blood from the catheter
- Follow the procedure for giving the appropriate antidote according to facility policy
  - Typically given through the existing IV line or injected subQ around the infiltrated site
- Cover area with sterile, occlusive dressing if ordered
- Rest and elevate the affected extremity
- **PREVENTION** is the best approach.

B. **Chemotherapy-induced nausea and vomiting (CINV)**

- Among the most common and distressing symptoms experienced by clients receiving cancer treatment
- Can lead to reduction in effective drug therapy, physiologic alterations, ↓ QOL, and ↑ costs
- Antineoplastic drugs often stimulate the chemoreceptor trigger zone (CTZ) leading to N/V
- May be caused by irritation of GI tract, pain, anxiety
B. CINV, cont.

- **Types of CINV**
  - Acute
  - Delayed
  - Anticipatory
  - Breakthrough

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Within a few minutes to several hours of chemotherapy; ends within 24 h</td>
</tr>
<tr>
<td>Delayed</td>
<td>More than 24 h after chemotherapy; lasts several days (e.g., cyclophosphamide)</td>
</tr>
<tr>
<td>Anticipatory</td>
<td>Triggered by anything the patient associates with NV related to previous chemotherapy treatments, such as smell or taste</td>
</tr>
<tr>
<td>Breakthrough</td>
<td>Occurs even though preventive measures have been taken</td>
</tr>
</tbody>
</table>

CINV: chemotherapy-induced nausea and vomiting, NV: nausea and vomiting. Sources: References 1, 3, 4.

- Use of antiemetic agents in prophylaxis & Tx
  - **Highly emetogenic chemotherapy:**
    - EXAMPLE: ondansetron (Zofran)
  - **Low-risk for emetogenic chemotherapy**
    - EXAMPLE: metoclopramide (Reglan), or prochlorperazine (Compazine)
• Nurse's role in preventing & managing CINV – major focus is the effective improvement of nausea & vomiting and preservation of QOL

  ▪ Pre-treatment assessment and education
    • Patient and family expectations
    • Risk factors for CINV
    • Medication education – taking them on schedule
    • Self-care management strategies
    • Provide clear post-treatment instructions and contact numbers

  ▪ Supportive care
    • Minimize noise, stimulation, odors
    • Frequent mouth care is needed
    • Provide flat sodas and crackers
    • Hard candies
    • Ice chips

C. Oral Mucositis/Stomatitis

  • Ranges from mild to severe

  • Therapy often begins with good oral hygiene:
    A. Avoid ETOH
    B. Avoid Mouthwashes with ETOH
    C. Avoid harsh toothpastes
    D. Soft toothbrushes or sponge toothettes
C. **Oral Mucositis/Stomatitis, cont.**

- Assess for taste changes, tissue swelling, redness, pain, dry mouth, white patches

- Symptomatic treatment may include:
  1. Mouth rinses (Maalox, Lidocaine, Benadryl mix),
  2. Antifungal medications
  3. Pain meds

- Offer ice chips or ice pops to help relieve pain

- Assess intake & output

- Evaluate caloric needs
D. **Anorexia**

- Loss of appetite may be related to anemia, pain, fatigue, or bitter taste caused by some chemotherapy agents
- Provide small frequent meals high in calories and protein
- Plan for rest periods
- Address issues of pain control
- Hard candy or ice chips may help relieve bitter taste

E. **Diarrhea**

- Diarrhea may be caused by the following:
  - Other medications
  - Comorbid conditions
  - Enteral feedings

E. **Diarrhea, cont.**

- Assess normal bowel habits, monitor for F & E imbalances, I &O, and dehydration
- Antidiarrheal medications (e.g. Kaolin and Pectin)
- Small frequent meals & follow a low residue diet
- Avoid very hot or very cold foods
F. Alopecia

- Not all chemotherapeutic agents cause hair loss
- Hair thinning, patchy baldness, or complete alopecia may occur, depending on the drug
- Hair on all areas of the body is affected; hair loss may be gradual or rapid

F. Alopecia, cont.

- Hair re-growth usually occurs once therapy is completed, texture may be changed
- Before therapy: Discuss potential hair loss and ways to address the problem
- Assess for body image changes/concerns
G. **Fatigue**

- Can have multiple causes: chemotherapy, sleep disturbances, emotional distress, depression, bone marrow depression, infection, pain, or electrolyte imbalances
- Plan ways to help client conserve energy
- Plan a well-balanced diet
- Encourage clients to participate in regular but not strenuous exercise
- Encourage stress reduction measures

H. **Hyperuricemia**

- Increased uric acid levels due to chemotherapy-induced cell destruction
- Can cause secondary gout and obstructive uropathy
- Monitor uric acid levels
- Allopurinol (Zyloprim) may be given as a prophylactic measure
- Encourage high fluid intake

I. **Infertility**

- Cancer treatments can cause infertility & premature ovarian failure
- Chemotherapy, radiation, & surgery can all affect the reproductive system
- If infertility occurs it may be permanent
- Pre-treatment counseling is advised
I. Infertility, cont.

- Encourage clients to discuss concerns about fertility with HCP before starting cancer treatment
- Encourage clients to discuss fertility-preserving options with HCP

Guidelines for Handling Cytotoxic Drugs

- Agencies in the US most often referred to for guidelines when handling antineoplastic agents:
  - National Institute for Occupational Safety and Health (NIOSH)
  - Occupational Safety and Health Administration (OSHA)
  - Oncology Nursing Society (ONS)
  - American Society of Health-System Pharmacists (ASHP)

Guidelines for Handling Cytotoxic Drugs

- Cytotoxic drugs are potentially hazardous to personnel and patients, and appropriate waste disposal is necessary
Guidelines for Handling Cytotoxic Drugs

• Education and training on the use of supplies & equipment to reduce exposure is the cornerstone
  - Health care professionals
  - Patients & their family

Reducing Exposures

• Cytotoxic drugs can be accidentally absorbed by inhalation, contact with skin or mucous membranes, and ingestion
  - Refer to agency policy and procedures
    - Most facilities mix these drugs under special environments in the pharmacy


Reducing Exposures

- Measures to reduce exposure:
  - Wash hands
  - Prepare drugs in a separate work area
  - Avoid hand-to-mouth or hand-to-eye contact
  - Use gown, mask, glove, face shield
  - Use powder-free gloves

Monitoring the effects of chemotherapy

- Performed at baseline, during, and after treatment
- Why monitor?
  - To determine optimal Tx options
  - To evaluate patient response
  - To monitor toxicity

Monitoring the effects of chemotherapy

- Five major body systems frequently monitored by laboratory tests:
  - Hematological
  - Hepatic
  - Renal
  - Cardiovascular
  - Pulmonary
Monitoring the effects of chemotherapy

- Hematologic system – CBC, CBC with differential
  - WBC, ANC, RBC, platelet, PT, PTT
- Hepatic system – LFTs
- Renal system – creatinine, BUN, electrolytes

Monitoring the effects of chemotherapy

- Cardiovascular system – ECG, echocardiography, cardiac enzymes
  - Anthracyclines (doxorubicin) widely known to be linked to cardiotoxicity
- Pulmonary system – PFTs
  - Bleomycin (Blenoxane) – most common cause of chemotherapy-associated pulmonary toxicity

Nursing Implications

- Monitor for oncologic emergencies
  - Infections
  - Allergic reactions
  - Renal, liver, cardiac, and pulmonary toxicities
  - Bleeding
  - Metabolic aberrations
  - Stomatitis with severe ulcerations
  - Bowel irritability with diarrhea
Education

• Client/family/caregiver education is critical. Teaching includes:
  ▫ Severe & often life-threatening side effects of chemotherapy drugs
  ▫ Common complications associated with chemotherapy, how these will be managed, and when to call their HCP
  ▫ Rectal temperature is not taken in patients who have low platelet counts
  ▫ Safe handling and disposal of chemotherapy agents
  ▫ Chemo drugs usually remain in the body for 48 to 72 hours after administration and is excreted in body fluids
    • Wear protective gloves when handling body fluids
    • Soiled linen from chemo spill: SPECIAL HANDLING