INTRODUCTION TO CANCER THERAPY AND IMMUNOMODULATORS

Ma. Stephanie Fay S. Cagayan, M.D., Ph.D
Department of Pharmacology, UP College of Medicine
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I. Introduction

Modern cancer treatment incorporates three primary therapeutic approaches: surgery, chemotherapy, and radiation therapy, either individually or in combination. Effective utilization of any of these treatments necessitates a thorough comprehension of its underlying principles.

Within the realm of pharmacological intervention for neoplastic conditions, there exists a variety of drug classes. In addition to cytotoxic agents, the arsenal now includes small-molecule kinase inhibitors, monoclonal antibodies, cancer vaccines, adaptive cell therapies, and various other pharmaceutical agents.

Immunomodulators, a subset of drugs, possess the capacity to modulate immune function by either activating or suppressing it. These drugs find extensive utility in various medical fields, such as the management of autoimmune diseases. Notably, within the domain of cancer therapy, these agents offer innovative options for combating malignancies.

This educational module seeks to introduce medical and healthcare professional students to the fundamental principles governing the use of chemotherapeutic agents as a modality for treating malignancies, while also examining the distinct characteristics of prototype antineoplastic agents.

II. Learning Objectives:

1. Understand the cell cycle and its regulatory checkpoints
2. Relate the different mechanism of action of cytotoxic agents with their targets in the context of the cell cycle
3. Know the concept of immune surveillance
4. Describe the tumor microenvironment and the role it plays in cancer
5. Identify cellular kinetics in tumors
6. Describe the function of the different immunomodulators particularly those used in cancer therapy

III. Key Concepts and Outline of the Topic

I. Introduction
   a. Cancer and its Origins
   b. Treatment Modalities in Cancer
II. Systemic Therapy
   a. Cytotoxics
   b. Hormones
   c. Miscellaneous
III. Immunotherapy
   a. Immunomodulators
   b. Types of Immunotherapies
   c. What is not considered immunotherapy?
IV. Mechanisms of resistance to anticancer drugs
V. Nursing Implications

IV. Reading references:

1. Katzung. Basic and Clinical Pharmacology, 15th ed. Chapter 54: Cancer Chemotherapy
2. Harvey and Champe. Lippincott's Illustrated Reviews Pharmacology, 4th ed., Chapter 3

I. INTRODUCTION:

A. Cancer and Its Origin

- Cancer is a collective term for a group of more than 100 unique diseases throughout the body
- Primarily characterized by unchecked growth and dysregulation of cell division
- Malignant cancers: growing and spreading (metastasis) throughout the body beside normal cells

- Hallmarks of Cancer:
  i. Unlimiting multiplication
  ii. Escaping from growth suppressors
  iii. Promoting invasion and metastasis
  iv. Resisting apoptosis
  v. Stimulating angiogenesis
  vi. Maintaining proliferative signaling
  vii. Elimination of cell energy limitation
  viii. Evading immune destruction
  ix. Genome instability and mutation
  x. Tumor enhanced inflammation

- General Characteristics of Cancer Cells

  i. Uncontrolled Proliferation - not dividing more rapidly, but lose mechanisms that regulate cell division
     - In Burkitt's lymphoma, doubling time is 24 hours, while breast cancer doubles in 3 months
     - Due to aberrant growth signals and expression of telomerase to escape senescence
  ii. Dedifferentiation and loss of function
     - The more poorly differentiated a tumor, the more primitive and aggressive it is
  iii. Invasiveness
     - Cancers are able to thrive in places outside of normal growth
  iv. Metastasis
     - Secondary tumors grow in different sites from the original site

B. Treatment Modalities in Cancer

- Locally-directed treatment
  i. Surgery
  ii. Radiation Therapy

- Systemic Treatment
  i. Chemotherapy-attacks cells that are rapidly dividing to reduce the size of tumor and will also affect normal cells

- Treatment Schedules
  i. Combination chemotherapy can increase cytotoxicity of drugs but also their toxicities
  ii. Chemotherapy may be given thru:
     - Large doses intermittently i.e. 2-3-week intervals to allow recovery between cycles

- Smaller doses more frequently (dose-dense regimens) allow more frequent exposure of tumor to treatment at the cost of higher toxicity

II. **SYSTEMIC THERAPY**

A. Cytotoxics

1. Alkylating Agents
    a. Nitrogen Mustards
    b. Nitrosoureas
    c. Platinum Containing Compounds
2. Antimetabolites
    a. Folate Antagonists
    b. Pyrimidine Analogues
    c. Purine Analogues
3. Plant-derived Agents
    a. Vinca Alkaloids
    b. Taxanes
    c. Camptothecins
4. Anti-tumor Antibiotics
    a. Anthracyclines
    b. Datinomycin
    c. Bleomycin
    d. Mitomycin

1. <u>Alkylating Agents</u>

- Includes Nitrogen Mustards (chlorambucil, cyclophosphamide, mechlorethamine), Nitrosoureas (carmustine, lomustine), Platinum containing compounds (cisplatin, carboplatin, oxaliplatin) and other alkyl sulfonates (busulfan).
- Highly reactive compounds forming **covalent bonds** with electron-rich sites in nucleic acids and phosphates (alkylation), amino acids and proteins (carbamoylation)→ **Cross-linking of bases, abnormal base-pairing** and **DNA stand breakage**
- Cell cycle non-specific, meaning they can kill cells inside and outside the cell cycle (exert maximum cytotoxicity at late G1 and S phases)
- A/E: **dose-related** → occurs mainly in rapid growing tissues (Bone marrow, GIT, reproductive system)

A. Nitrogen Mustards

- Prototype drug: Cyclophosphamide
- Prodrug: activated by CYP450 hepatic oxidases
- Activated in the liver and converted further into cytotoxic active metabolites, phospharamide (anti-cancer) and acrolein
- Functions as cytotoxic and immunosuppressant
- Pharmacokinetics: Good absorption in oral, IM, IV route and excreted primarily via kidneys
- Clinical Use: leukemia, non-Hodgkin's lymphoma, breast and ovarian cancers, and neuroblastoma
- Adverse effects:
    - Nausea/Vomiting
    - Bone marrow depression
    - Hemorrhagic cystitis due to acrolein - metabolite normally produced by metabolism of cyclophosphamide.
    - Antidote: MESNA and NAC (acetylcysteine)

B. Nitrosoureas

- Prototype drug: Lomustine

- Lipid soluble agent, so easily crosses BBB
- used in **CNS tumors**
- Administered PO
- Because of lipid solubility, can have cumulative delayed myelosuppression which lowers the bioavailability of the drug
- Previously used in treatment of Hodgkin's Lymphoma but not so much anymore

C. Platinum Containing Compounds

- Prototype drug: Cisplatin
- Pharmacokinetics: Used intravenously, distributes to most tissues and cleared in unchanged form by the kidneys
- Clinical Use:
  Cisplatin/Carboplatin → Testicular, Bladder, Lung and Ovarian CA
  Oxaliplatin → advanced colon CA
- Adverse Effects:
  - Predominantly profound nausea - use of 5HT3 receptor antagonists necessary when administering drug
  - Renal toxicity - aggressive hydration and diuresis required when administering drug to prevent tubular damage
  - Neurologic toxicity - such as paresthesia of the feet and hands
  - Ototoxicity (high frequency hearing loss and tinnitus)
  - Low myelotoxicity

2. <u>Antimetabolites</u>

- Includes Folate Antagonists (methotrexate), Pyrimidine Analogues (fluorouracil, cytarabine, gemcitabine), Purine Analogues (mercaptopurine, thioguanine)
- CCS (Cell Cycle Specific) → **high cell specificity to S phase**
- In addition to their cytotoxic effects on neoplastic cells, the antimetabolites also have immunosuppressant actions.
- Antimetabolites are analogs of natural compounds that inhibit essential metabolic routes specifically **purine synthesis**.

A. Folate Antagonists

- Prototype drug: Methotrexate
- MOA: Interfere with thymidylate synthesis, **competitive antagonist of dihydrofolate reductase (DHFR)**
- formed **polyglutamate derivatives** of methotrexate → important for cytotoxic actions
- Pharmacokinetics: Oral & Parenteral. Well absorbed orally, and eliminated via kidneys
- Indications: Head & Neck cancers, Breast cancer, Primary CNS Lymphoma (PCNSL). Used as immunosuppressant for Rheumatoid Arthritis, Crohn's disease, and Psoriasis
- Poor lipid solubility, limited ability to cross BBB, so need high dose regimen for treatment of PCNSL
- Toxic effects:
  - Bone marrow depression
  - Toxic effects on skin and gastrointestinal mucosa (mucositis)
  - **High dose regimens may cause nephrotoxicity, necessitating folinic acid (Leucovorin) rescue**

B. Pyrimidine Analogues

- Prototype drug: Fluorouracil (5-FU)- one of the oldest, developed in the 1950's

- Converted to 5-fluoro-2′-deoxyuridine-5′-monophosphate (5-FdUMP)→ inhibits thymidylate synthase→ **THYMINELESS DEATH**
- Indication: Colorectal cancer (with oxaliplatin, related to cisplatin, and irinotecan)
- Pharmacokinetics: When given IV→ widely distributed including CSF and is eliminated by metabolism
- Adverse Effects: Myelsuppresion, GI distress, alopecia, **Hand-foot syndrome (Palmar-plantar erythrodysesthesia)**

C. Purine Analogues

- Includes Mercaptopurine(6-MP), Thioguanine (6-TG)
- Activated by hypoxanthine-guanine phosphoribosyltransferases (HGPRTases) to toxic nucleotides→ inhibit purine metabolism
- Pharmacokinetics: **Low oral bioavailability** due to first-pass metabolism by hepatic enzymes
  - 6-MP → oxidized by xanthine oxidase
- Clinical use: acute leukemias and chronic myeloid leukemia (CML)
- Adverse Effects: Bone marrow suppression, hepatotoxicity

3. <u>Plant-derived agents</u>

A. Vinca Alkaloids

- Prototype drugs: Vincristine, Vinblastine, Vindesine, Vinorelbine
- Derivatives of rose periwinkle plant
- Binds to tubulin→ inhibits assemble of microtubles→ block formation of mitotic spindle
- **M-phase specific** - act during mitosis
- Indications: lymphomas, sarcomas, CNS tumors
- Pharmacokinetics: given parenterally, penetrates most tissues (except CSF), and cleared via biliary excretion.
- Adverse effects:
  - Vinblastine and Venorelbine→ gastrointestinal distress, alopecia, and bone marrow suppression
  - Vincristine→ neurotoxicity (areflexia, peripheral neuritis, and paralytic ileus)
  - **vinCristine:** CNS (neurotoxicity)
  - **vinBlastine:** Bone Marrow (myelosuppression)

B. Taxanes

- Prototype drugs: Paclitaxel and Docetaxel
- taxanes that came from the bark of Taxus sp. or Pacific yew tree and similar to vinca alkaloids they bind to tubulin BUT unlike vinca alkaloids, they prevent microtubule disassembly into tubulin monomers
- **Binds to tubulin**→ promotes microtubule formation (assembly)→ prevents depolymerization of microtubules (disassembly)
- CCS →M phase
- Pharmacokinetics: given IV, Metabolized by CYP450; 80% excreted in feces
- Clinical Use: breast, ovarian, lung, gastroesophageal, prostate, bladder, and head and neck cancer
- Adverse effects:
  - Myelosuppression
  - Neurotoxicity
  - Fluid retention - particularly with Docetaxel
  - Hypersensitivity (requires pre-medications with steroids and antihistamines)

C. Camptothecins
- Camptothecins from bark of Camptotheca acuminata (also called the "cancer tree")
- Includes Irinotecan and Topotecan
- Inhibits Topoisomerase I → DNA Damage
- G1-S Phase specific
- Pharmacokinetics:
  - *Irinotecan:* prodrug, converted to active metabolite (SN-38) hepatically, eliminated through bile and feces
  - *Topotecan:* eliminated renally
- Both are administered IV
- Topotecan can also be administered PO
- Toxicity
- Diarrhea (more for Irinotecan)
- Acute (<24 hrs from administration): Due to cholinergic effect of the drug, can be treated with atropine; >24 hrs: Due to tissue damage induced by the drug, treat with loperamide
- Myelosuppression

4. <u>Anti-tumor antibiotics</u>
- Come from fungi *(Streptomyces)*
- Bind to DNA non-covalently via intercalation between specific bases and block synthesis of RNA and/or DNA
  - Generates free radicals→ DNA strand scission (Bleomycin, Anthracyclines)
  - Forms complexes with topoisomerase II (Anthracyclines)
- Generally, cell cycle non-specific except Bleomycin

A. Anthracyclines
- The anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone) intercalate between DNA base pairs, inhibit topoisomerase II, and generate free radicals; blocking the synthesis of RNA and DNA and cause DNA strand scission. Also, membrane disruption occurs.
- Pharmacokinetics: Doxorubicin and Daunorubicin are given IV, metabolized in the liver and products excreted through bile and urine
- Toxicity:
  - Potent vesicant
  - When it spills or extravasates when given, it can cause a lot of tissue necrosis
  - Patients can get anywhere from mild irritation to outright necrosis necessitating plastic surgery intervention
  - Be careful when administering
  - Dexrazoxane: only approved treatment to ameliorate extravasation of doxorubicin
- Nausea→ particularly when given with cyclophosphamide in breast cancer
- Myelotoxicity
- Cardiotoxicity
  - Primarily due to direct effect on Topoisomerase II and
  - through generation of free radicals
  - Cumulative lifetime dose: 400-450 mg/kg
  - Ex. for breast CA: for every cycle, give 60 mg/kg at 7cycles at most
  - Keep track of how much has already been given to avoid heart failure

B. Datinomycin

- Intercalates in the minor groove of DNA between adjacent G-C pairs and interferes with movement of RNA polymerase, preventing transcription
- Has a similar action and toxicity with anthracyclines (Topoisomerase II poison and intercalator) except cardiotoxicity
- Clinical use: Rhabdomyosarcoma, Wilm's tumor, Ewing's tumor, Kaposi sarcoma, ChorioCA
- Administered IV

C. Bleomycin
- Bleomycin is a mixture of glycopeptides that generates free radicals, which bind to DNA, cause strand breaks, and inhibit DNA synthesis. DNA fragmentation is due to oxidation of a DNA-bleomycin-FE(II) complex leading to chromosomal aberrations.
- **Most effective in G2 phase** and mitosis but also acts in cells in G_0 phase
- Clinical use: Hodgkin's Lymphoma (HL)
- Pharmacokinetics: **must be given parenterally.** It is inactivated by tissue aminopeptidases but some renal clearance of intact drug occurs
- Adverse effects:
  - Pulmonary fibrosis→ test patients before if they have any underlying pulmonary disease
  - Mucocutaneous reactions
  - Hyperpyrexia

D. Mitomycin
- Forms an alkylating agent that cross-links DNA
- Pharmacokinetics: given IV and is rapidly cleared by hepatic metabolism
- Clinical use: treatment of anal cancer with Fluorouracil and radiation therapy (Nigro protocol)
- Administered IV
- Adverse effects: severe myelosuppression, nephrotoxicity, pulmonary fibrosis

B. Hormones

1. Glucocorticoid (Prednisone and Dexamethasone)
   - Prednisone is the most commonly used glucocorticoid in cancer chemotherapy. It interferes with lymphoid proliferation and causes dissolution of lymphocytes (Lymphocytopenia).
   - Steroids are used as part of treatment regimen for certain lymphomas and leukemias
   - Adverse Effects: Cushingoid features, Na+ and water retention, osteoporosis, peptic ulcer
2. Estrogens: Diethylstilbestrol (DES) and Ethinyl estradiol
   - May be used in palliative care of prostate cancer
   - Prostate cancers are androgen-dependent
   - Not first choice
3. Progestins: Megestrol, Norehisterone, and Medroxyprogesterone
   - Clinical use: supportive care in the treatment of uterine cancers. Management of anorexia (low/no appetite) - Megestrol or Medroxyprogesterone.
4. Anti-Estrogen
   - Compounds that prevent the stimulation of transcription by the estrogen receptor complexes
   - Two main types:
     - Nonsteroidal antiestrogens (Selective Estrogen Receptor Modulator - SERMs)→Tamoxifen
     - Pure antiestrogens→Fulvestrant (also used in treatment of breast CA)
   - Estrogen receptors are found in different target tissues, and binding in different tissues induces different responses.

    - For example, giving Tamoxifen, which inhibits estrogen production and controls breast CA, however, stimulates estrogen receptors in the uterus and may cause increased risk for uterine cancer.
    - After giving the drug, can produce an initial testosterone flare in men with prostate cancer à can make it seem like the prostate cancer is getting worse
    - Negative feedback occurs as the body is exposed to continuous amounts of the hormone
- Antagonists
    - Abarelix
    - Does not produce a testosterone flare

5. Anti-Androgen
    - Vital in the management of androgen-dependent prostate cancer
        - Given as part of medical castration
    - Used to manage the testosterone flare that follows GnRH agonists
    - Examples: Flutamide, Nilutamide Bicalutamide and Enzalutamide (only antiandrogen indicated for use in very advanced prostate cancer)

6. Somatostatin Analogues
    - Also known as growth hormone-inhibiting hormone (GHIH)
    - Somatostatin acts on the pancreatic D-type (delta) cell as an inhibitory hormone
    - Used to relieve symptoms of neuroendocrine tumors such as VIPoma, carcinoids and gastrinomas
    - Examples: Octreotide and Lanreotide
7. Gonadotropin-releasing hormone (GnRH Analog)
    - Examples: Leuprolide, Goserelin, Nafarelin
    - Clinicaluse: Prostate CA
    - Adverse Effects: bone pain, gynecomastia, hematuria, impotence, and testicular atrophy (Leuprolide)
8. Aromatase Inhibitors
    - Anastrozole and letrozole inhibit aromatase, the enzyme that catalyzes the conversion of androstenedione (an androgenic precursor) to estrone (an estrogenic hormone).
    - Clinical use: advanced breast CA
    - Adverse effects: nausea, diarrhea, hot flushes, bone and back pain, dyspnea, and peripheral edema

C. Miscellaneous

1. Protein Kinase Inhibitors (PKI)
    - Small molecules that inhibit kinase domain activity of target proteins (receptors with kinase domain). inhibits the tyrosine kinase activity of the protein product of the bcr-abl oncogene and c-kit by binding to the site where ATP is supposed to bind, so ATP cannot donate its phosphate to the substrate. Thus, signalling will not take place.
    - Used in treatment of cancers with specific driver mutations
    - Administered PO
    - Example: Imatinib (Glivec)
    - First PKI, developed in 2001
    - For treatment of chronic myelogenous leukemia (CML) with BCR-ABL fusion protein translocation
    - CR-ABL drives CML, always “on” and signaling growth
    - Binds to ATP-binding domain of BCR-ABL kinase, preventing downstream signaling

2. Monoclonal Antibodies
    - Example: Rituximab

- It targets CD-20 B-cell antigen and induces complement-mediated lysis, direct cytotoxicity, and induction of apoptosis
- Clinical use: Indolent B-cell lymphomas (CLL), autoimmune diseases
- A/E: hypersensitivity reactions (Fever, chills, nausea, headache) and myelosuppression

III. IMMUNOTHERAPY

A. Immunomodulators

- Blanket term referring to any drug that:
  - Moderate the immune response to a target
  - Mobilize the immune system
- Broadly categorized as:
  - Immunostimulants
    - Vaccines
    - Monoclonal antibodies
  - Immunosuppressants
    - Cyclosporin
    - Sirolimus
    - Tacrolimus
    - Methotrexate
    - Cyclophosphamide
    - Glucocorticoids

B. Types of Immunotherapy

- Role in Cancer
  - Activate the immune system, OR Prevent the deactivation of the immune system

1. Cytokines
   - Produced by immune cells as means of communication
   - May stimulate or suppress the immune system
   - In cancer therapy, we are interested in the activation of immune system against specific targets
   - Coordinate a robust response to an antigen to induce an immune response
   - Approved therapies: Interleukin-2, Interferon-α
   - Approved for: kidney cancer, melanoma
   - CAUTION: Non-specific and lead to generalized effect that can lead to very debilitating side effects, which may even need ICU.
2. Cancer Vaccines
   - Focused on stimulating the immune system to identify and destroy cancer that is already in the body
   - Specifically, CD8+ T cells to directly attack cancer cells
   - Types:
     - Dendritic cell vaccines
     - Peptide vaccines
     - Genetic vaccines
     - Immediate local effect at the site of injection (tumor cell lysis) + systemic effect to more effectively destroy the melanoma (tumor-specific immune response)
3. Monoclonal antibodies
   - Activate the immune system
   - Neutralize immunosuppressive mechanisms to prevent immune system deactivation
   - Example: Cetuximab

- Used to treat cancers with overexpressed Epidermal Growth Factor Receptor (EGFR) in Colon, rectum, head & neck
- Cetuximab, an IgG, binds to EGFR (which is attached to a tumor cell)
- Induces direct effects that would ultimately lead to the cell dying (direct toxic effect)
- Induces inhibition of growth and inhibition of cytokine (paralyzes the tumor cell)
- Induces compliment mediated cytotoxicity through generation of membrane attack complex
- Activates Natural Killer (NK) cells to look for tumor cells and destroy them

4. Immunoconjugates
   - Smart Weapons: Chemotherapy + Radiotherapy
     - monoclonal antibody (which targets a specific cell type)
     - conjugated to a second agent (chemotherapy or radiotherapy)
     - delivers cytotoxic drug to specific target cells for less adverse effects
   - Ado-Trastuzumab Emtansine
     - for HER-2 enriched breast cancer
     - Trastuzumab (antibody) - target HER-2 positive breast cancer cells
     - Emtansine (chemotherapy) - tubulin inhibitor
   - Ibritumomab Tiuxetan
     - For lymphoma
     - Ibritumomab (antibody) - target CD20+ lymphoma cells
     - Tiuxetan (radioactive isotope)

5. Immune checkpoint inhibitors
   - Used to prevent the deactivation of the immune system
   - Sipuleucel-T
     - Prostate cancer vaccine
     - Harvest the APC of the patient (autologous)
     - "Teach" it to identify target through infusion of PAP (prostate
     - specific protein) attached to GM-CSF (granulocyte-macrophage colony-stimulating factor)
     - "Educated" APC proliferates and is reintroduced to the host "teach" immune system to attack the prostate cancer, via activation of T-cells
6. Adaptive cell therapies
   - Utilize modified effector cells (or lymphocytes) to treat tumors
   - Cells are primed outside of the body, then reinfused to attack the cancer living within
   - Examples:
     - Tumor infiltrating lymphocytes
     - TCR gene therapy
     - Chimeric antigen receptor T-cell (CAR-T)
       - Hailed by the American Society of Clinical Oncology as the advance of the year 2018
       - Patient's own T-cells are harvested and genetically modified in order to detect cancer proteins
         - When they are reinfused, they can target certain cells.
         - Afterwards, they stay in the body and stand guard
         - Initial treatment + surveillance
       - Possible benefit in:
         - Acute Lymphoblastic Leukemia (ALL)
         - Non-Hodgkin's Lymphoma
       - **CAUTION:** Cytokine release syndrome

- Potentially life-threatening
- Entire immune system is awakened by hyperactive immune cells
- Fever, respiratory failure, heart failure

7. Oncolytic viruses
    - Local therapy
    - **Viral vectors** are used to treat cancer through tumor regression
    - Viruses replicate in and kill established tumors
    - Dying tumor cells are more easily target for elimination by the immune system
    - Talimogene Laherparepvec
        - Modified Herpes Simplex Virus (HSV) type 1
        - Oncolytic virus for advanced melanoma
        - Looks for the melanoma to attack and destroy
            - Cells destroyed by the drug is highly immunogenic
            - Produce an immune response that allows the body to identify cancer cells and destroy them
    - T-cells are regulated by off switches
        - Certain receptors, when bound, tells the T-cell to stop functioning
        - Cancer hijacks these regulatory mechanisms
        - When T-cell identifies a tumor, instead of killing it, the T-cell is bound to the receptor and is turned off.
        - Examples of these receptors: CTLA4 and PD-1
    - Ipilimumab
        - Binds to CTLA4, which prevents cancer from binding to this receptor, thus preventing it from turning the T-cell off
        - First of its class, developed for the treatment of melanoma in 2011
    - Pembrolizumab, Nivolumab
        - Binds to PD-1, preventing cancer from turning off the T-cell
    - Atezolizumab
        - Binds to PD-L1, preventing cancer from turning off the T-cell
        - Allows the T-cell to do what it's meant to do - that is, kill cancer

C. What is not considered immunotherapy?
- Not a cure-all
- Not a supplement
- Not side-effect free

IV. MECHANISMS OF RESISTANCE TO ANTICANCER DRUGS

1. Decreased accumulation of cytotoxic drugs
2. Decrease in uptake of drug by target cell
3. Insufficient activation of drug
4. Increase in inactivation of drug by target
5. Increased concentration of target enzyme
6. Decreased requirement for substrate
7. Rapid repair of drug-induced lesions
8. Altered activity of target
9. Mutations in various genes

V. CLINICAL IMPLICATIONS

Standard of Care Guidelines for Administering IV Chemotherapy:

Prior to Administration

- Patient assessment, confirm allergies, and evaluate any preexisting symptoms.
- Verify signed consent for treatment was obtained and signed by provider and patient.
- Monitor laboratory values and verify laboratory values within acceptable range for dosing.
- Take measures to prevent medication errors:
    - Perform independent double-check of original orders with a second chemotherapy-certified MD/RN.
    - Double check for accuracy of treatment regimen, chemotherapy agent, dose, calculations of body surface area, schedule, and route of administration.
- Recalculate chemotherapy doses independently for accuracy.
- Verify appropriate pre-medication and pre-hydration orders.
- Ensure patient education completed and address outstanding patient questions.

Administration

- Dual MD/nurse verification and sign off at the bedside:
- Compare original order to dispensed drug label at the bedside with another chemotherapy-certified RN and verify patient identity.
- Safe handling of hazardous medications; reduce exposure to self and others.
- Intravenous line management: insertion, evaluation, and assessment.
    - Check patency of IV site for brisk blood return immediately prior to connecting hazardous agent to the patient and as indicated during infusion.
    - Continuous monitoring for infiltration, phlebitis, extravasation, or infection.
- Continuous patient monitoring for acute/adverse drug effects and allergic reactions.
- Prompt recognition and management of hypersensitivity reactions.
- Safe handling and management of chemotherapy spills.

After Administration

- Flush IV line, ensure brisk blood return prior to removing peripheral IV device, flush/maintain vascular access device according to institution policy.
- Safe handling and disposal of hazardous waste according to institution policy.
- Document in medical record the medications given, patient education, and patient response, including any adverse events.
- Ensure patient has appropriate discharge instructions, anti-nausea medications, and education, and emergency contact information of physician's office in event of emergency.

Oral Chemotherapy: Key Teaching Points

General Safety Guidelines

- Keep cancer drugs in original packaging until used or placed within the daily pill box.
- Do not mix chemotherapy medications with other medications in the pill box. They should always remain separate from other medications.
- Perform hand hygiene (soap and water) before and after handling all medications.
- Do not let the medication come in contact with household surfaces (countertops, tables). If they do, clean the surface thoroughly to remove all traces of the drug.
- Store medications in a cool, dry place, away from excess heat or sunlight exposure.

Safe Medication Disposal

- Never discard cancer medications in household trash, place down the drain, or flush down the toilet.
- Ask your provider or pharmacist where to return unused and left-over medication.

- Empty pill bottles may be put in household trash. Do not recycle the bottles.
- Never reuse cancer medication pill bottle

Exposure to household contacts

- When possible, the patient should handle their medication themselves.
- If anyone other than the patient comes in contact with cancer pills, wash the affected area with soap and water immediately. If rash/skin changes occur, the patient should contact their provider.
- Caregivers should transfer the medication into a cup or spoon when handling the medication. If picking up the medication with their hand is unavoidable, wear disposable gloves to prevent any unnecessary exposure (i.e. absorption via the skin).
- If there is any contact with bodily fluids, household trash should be double-bagged.
- A small amount of medication may be present the patient's urine, stool, vomit, or blood.
    - Caregivers should wear disposable gloves when handling body fluids.
    - Items soiled with body fluids should be kept in plastic bags until washed.
    - These items should be washed separately from other laundry in hot water.
    - Pregnant women should not come in contact with medications or body fluids.
    - Low-pressure toilets should be double-flushed after each use by patients on oral cancer medications.
- The toilet lid should always be closed prior to flushing the toilet.
    - If any fluids splash from the toilet, the surface should be wiped down with disinfectant cleaner (wearing gloves).
    - Take precautions to ensure pets do not drink from the toilet.
- Gloves should never be re-used. Discard gloves in household trash after one use

Reference: 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology. (Neuss et al., 2016; Olsen et al., 2019).