Principles of Cancer Treatment

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Objectives

• Describe modalities and mechanism of action for the following cancer treatments
  – Chemotherapy
  – Biotherapy and Targeted Therapy
  – Surgery
  – Complementary and Alternative Medicine
• Discuss goals of treatment
• List potential side effects of cancer treatments

SURGERY

• Is the oldest form of cancer treatment
• Is precise and local
• Is a method of diagnosing and staging cancer
• May be curative alone
• May be used with other modalities
• May remove some or all of the primary tumor
• May be palliative in nature

Diagnosis and Pathologic Staging

- Biopsy method?
- Treatment is often based on biopsy results and tissue analysis
  - Determine extent of disease (staging)
  - Used for tumor markers and genetic testing

Goals of Cancer Surgery

- Preventative/Prophylactic
  - To prevent or reduce risk of cancer in high-risk patients
    - Esophageal resection with Barrett’s esophagus
    - Mastectomy and/or salpingo-oophorectomy with BRCA mutations
    - Thyroidectomy with suspicious/symptomatic nodules
  - Only used in high-risk patients after careful consultation with oncologist and genetic counselor/geneticist

Goals of Cancer Surgery

- Curative
  - To remove entire tumor; must have well-defined margins (encapsulated)

- Palliative
  - Used when cancer is not curable
    - Stent placement, GI/GU resection or alternative outlet

Goals of Cancer Surgery

- Debulking/Cytoreductive Surgery
  - Removal of unencapsulated tumor tissue
  - With or without intraoperative chemotherapy (HIPEC)
  - With or without intraoperative radiation therapy
  - Is essential in both cure and palliation goals


http://www.cancer.org/treatment/understandingyourdiagnosis/staging
Goals of Cancer Surgery

- How much disease do you remove?
- Changing goals mid-procedure?

Other “Surgery”

- Cryotherapy/Cryosurgery/Cryoablation
  - Cryoprobe inserted to desired site
  - Treat primary lesion (Renal/Prostate) or metastatic lesion

- Transarterial Chemo Embolization (TACE)
  - Chemotherapy-filled microspheres injected directly into tumor
  - Treat large volume lesions (often liver primary)

Nursing Role

- Preoperative teaching and care
- Post-operative care
  - Communication
  - Pain management
  - Prevention and Management of SE associated with surgery and cancer
- Continuous patient education and follow-up
- Psychosocial support is key

CHEMOTHERAPY
Chemotherapy

- Systemic therapy using a chemical substance
  - Frequently given in combination with other chemotherapy or non-chemotherapy drugs
  - Toxic to both normal and cancerous tissues
    - Can be a limiting factor in dosage/use
  - Many routes of administration available
  - Often given in specific sequences (cycles) to maximize response and minimize side effects

Goals of Chemotherapy

- Curative
  - intended to cure disease
- Palliative
  - used to control symptoms and improve quality of life
- Myeloablative
  - Obliterates bone marrow
  - Used before BMT
- Adjuvant
  - used after primary treatment
    - chemo after surgery or radiation
- Neoadjuvant
  - used before primary treatment
    - Chemo used to shrink a tumor before surgery

Mechanism of Action

Cell Cycle-Specific

- Exert an effect at a specific part of the cell cycle
- Work best when given in cycles or divided doses
- Most effective when patient kept on regular treatment schedule

Cell Cycle-Nonspecific

- Exert effects in all phases of cell cycle, including G0
- Cell kill is directly proportional to the amount of drug administered.
- Dose dependent—easier to delay treatment so that higher dose can be given

Chemotherapy Classification

Cell Cycle-Specific

- Antimetabolites
  - Plant alkaloids
    - Camptothecins
    - Epipodophyllotoxins
    - Taxanes
    - Vinca alkaloids
  - Miscellaneous

Cell Cycle-Nonspecific

- Alkylating agents
- Antitumor antibiotics
- Nitrosoureas

Alkylation Agents

- Cell cycle-nonspecific
- Interfere with DNA replication by breaking DNA helix strand
- Examples:
  - Carboplatin/Cisplatin
  - Cyclophosphamide
  - Oxaliplatin
  - Ifosfamide
  - Dacarbazine

Side Effects

- Myelosuppression is the most common and lethal dose-limiting toxicity
- Many agents are irritants/vesicants
- Secondary malignancies are possible with some agents

Additional:

- Hemorrhagic cystitis
  - Ifosfamide
  - Cyclophosphamide
- Nephrotoxicity
  - Cisplatin
- Anaphylactic Reactions
  - Oxaliplatin, thiopeta, carboplatin

Common:

- Nausea/vomiting/diarrhea, decreased fertility, skin irritation, mucositis, alopecia, fatigue, neuropathy


Antitumor Antibiotics

- Cell cycle-nonspecific
- Bind with DNA; inhibits DNA/RNA synthesis
- Examples:
  - Bleomycin
  - Mitomycin
  - Mitoxantrone
  - Anthracyclines
    - Doxorubicin
    - Epirubicin
    - Idarubicin
    - Daunorubicin

Side Effects

- Myelosuppression is the most common dose limiting toxicity
- Many agents are vesicants
- Drugs are colored (not clear)
  - Teach patient that urine/sclera might be discolored after administration

Additional:

- Cardiotoxicity
  - Anthracyclines
    - Lifetime cumulative dose limits
- Pulmonary toxicity
  - Bleomycin
    - Test dose often used
- Radiation Recall
- Photosensitivity
- Nephro/hepatotoxicity

Common:

- Nausea/vomiting, alopecia, electrolyte imbalance, decreased fertility, PPE (hand-foot syndrome), mucositis

Nitrosoureas

- Cell cycle non-specific
- Interfere with DNA replication by breaking DNA helix
- Cross blood-brain barrier
- Examples:
  - Carmustine
  - Lomustine
  - Streptozocin

Side Effects

- Myelosuppression is the most common dose limiting toxicity
  - Also renal toxicity
- Delayed nadir: 4-6 weeks after treatment
- Agents can be irritating to veins if given rapidly

- Additional:
  - Nephrotoxicity
  - Hepatotoxicity
  - Pulmonary fibrosis
  - Lomustine
  - Altered glucose metabolism
    - streptozocin

- Common:
  - Nausea/vomiting, anorexia, impaired fertility

Antimetabolites

- Cell cycle-specific
- Act in S phase; inhibit DNA synthesis and/or repair.
- Given via many different routes
- Examples:
  - Capecitabine
  - Cytarabine
  - Fluorouracil
  - Gemcitabine
  - Methotrexate
  - Pemetrexed

Side Effects

- Major dose-limiting toxicity is myelosuppression
  - Also nephrotoxicity, hepatotoxicity, diarrhea, PPE, neurotoxicity, mucositis
- Dosing is highly variable depending on route and indication

- Additional:
  - Many agents are folic acid agonists or antagonists
    - Folic acid is either supplemented OR avoided!
  - Patients with hematologic malignancy may require hydration/allopurinol to prevent TLS

- Common:
  - Nausea/vomiting, alopecia, photosensitivity, constipation, fatigue, peripheral edema
Camptothecins

- Plant alkaloid
- Cell cycle specific
- Act in S phase; inhibits topoisomerase I, causing double-strand DNA changes
- Examples:
  - irinotecan
  - topotecan

Epipodophyllotoxins

- Plant alkaloid
- Cell cycle specific
- Act in G2 and S phase; interfere with topoisomerase II
- Examples
  - etoposide
  - teniposide

Side Effects

- Camptothecins:
  - Diarrhea is major dose-limiting toxicity
    - Early onset (within 24 hours) usually cholinergic
    - Treated with atropine

- Epipodophyllotoxins:
  - Myelosuppression
  - Hypersensitivity reactions
    - Secondary malignancy

Common Side Effects

- Additional:
  - Myelosuppression
  - Interstitial lung disease
    - Topotecan

- Common:
  - Nausea, vomiting, alopecia, anorexia, fatigue, mucositis

- Additional:
  - Hypersensitivity reactions
  - Secondary malignancy

- Common:
  - Nausea, vomiting, alopecia, anorexia,
Taxanes

- Plant alkaloid
- Cell cycle specific
- Act in G2 and M phases; inhibit cell division by stabilizing microtubules
- Examples:
  - cabazitaxel
  - docetaxel
  - paclitaxel

Side Effects

- Additional:
  - Use of in-line filter is required in some agents
  - paclitaxel
  - Consider dose adjustment or alternative agent in hepatic or renal dysfunction

- Common:
  - Hypersensitivity reactions
    - Premedicate with H2 antagonist, antihistamine, corticosteroid
  - Alopecia, facial flushing, fatigue, nausea, vomiting, myelosuppression, fluid retention


Vinca Alkaloids

- Plant alkaloid
- Cell cycle specific
- Act in G2 phase to block DNA production, and M phase to prevent cell division
- Examples:
  - Vinblastine
  - Vincristine
  - Vinorelbine

Side Effects

- Additional:
  - FATAL IF GIVEN INTRATHECALLY!
  - Nephrotoxicity
  - Hepatotoxicity

- Common:
  - Constipation, alopecia, nausea, vomiting

Miscellaneous Agents

• Cell cycle specific
• Have varied mechanisms of action
• Examples:
  – arsenic trioxide
  – hydroxyurea
  – vorinostat
  – asparaginase
  – procarbazine
  – ixabepilone

Side Effects

• Myelosuppression is most common dose-limiting toxicity
  • Also peripheral neuropathy
• Given by different routes, many PO

• Additional:
  – Alcohol should be avoided with procarbazine use
  • Antabuse-like reactions
  – Regular monitoring of labs and ECG needed with several agents
  – Asparaginase carries risk of anaphylactic reactions

• Common:
  – Nausea, vomiting, mucositis, hepatotoxicity, nephrotoxicity, fatigue, diarrhea

Routes of Administration

• Oral
• Intramuscular
• Subcutaneous
• Intravenous
• Intraperitoneal
• Intra-arterial
• Intrathecal
• Intrapleural
• Intravesicular

• Advantages and disadvantages for each route
• Additional care areas may administer by specialized route
  – Interventional radiology
  – Operating suite
• Review your institution’s policies and procedures

Combination Chemotherapy

• Many agents given in combination of two or more
• Different mechanisms of action maximizes cell kill
• Some agents have synergistic effects when utilized together
• Possible delayed drug resistance
Complications of Chemotherapy

- Hypersensitivity reaction
  - Often prevented by premedications
- Extravasation
  - Irritants
  - Vesicants
- Anaphylaxis
  - True allergic response
  - Can be a Code situation!
- Know your institutional policies!!

Summary

- Chemotherapy can be classified according to effect on cell cycle and pharmacologic class
- Each class has different mechanisms of action and side effect profiles
- Myelosuppression is the most lethal and most common side effect of chemotherapy

Biotherapy: NCI Definition

- N.: “Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases. It also is used to lessen certain side effects that may be caused by some cancer treatments.”
Biotherapy

- Alters the body’s immune system
- Enhances immune response
- Prevents metastasis of cancer cells
- Helps normal cells repair following treatment

- Used as both cancer treatment and supportive care
- Includes:
  - vaccines
  - interleukins
  - interferons
  - colony stimulating factors
  - targeted therapies

Biotherapy Potential

- Cure in the primary or adjuvant setting
- Improvement of overall response and disease-free survival when used with other therapies
- Stabilize/Control Disease
- Improve or maintain quality of life

Vaccines

- Two FDA approved for cancer prevention:
  - Hepatitis B
    - Can lead to hepatocellular carcinoma
  - Human Papillomavirus (HPV)
    - Gardasil protects against HPV types 6, 11, 16, 18
    - Cervarix protects against HPV types 16 and 18
- Vaccines for cancer treatment
  - Most are in experimental phases
  - Sipuleucel-T (Provenge) is the only vaccine approved by FDA (autologous cellular immunotherapy)

Interleukins

- Stimulates proliferation and recruitment of T, B, and NK cells to enhance tumor-fighting capabilities and immune response
- Used to treat renal cell carcinoma and metastatic melanoma
- Side effects include anaphylaxis, infusion reactions, flu-like symptoms, rash, edema, hepatic/renal/cardiac insufficiency
- Monitor fluid status: mimics septic shock
Colony-Stimulating Factors

- Stimulate erythropoiesis
  - Darbepoetin, Epoetin alfa
- Regulates production of neutrophils within bone marrow
  - Filgrastim, Pegfilgrastim
- Stimulates proliferation of neutrophils
  - Human G-CSF
- Side effects vary by drug
  - Allergic reaction, bone pain, hypertension

Interferons

- Inhibit viral reproduction
- Immunomodulation
- Antiproliferative activity on tumor cells
- Used in treatment of hematologic malignancy, chronic hepatitis B and C, melanoma
- Side effects include flu-like symptoms, hypersensitivity reactions, hepatotoxicity, depression/suicidal ideation, renal insufficiency

Targeted Therapy

- Substantial growth in field in last 10 years
  - The first: Rituximab approved 1994
  - Within the last three years, 36 new oncology drugs received FDA approval
    - Most were targeted therapies
- Monoclonal antibodies (mAbs)
- Small Molecule Inhibitors

Monoclonal Antibodies

- Cell signaling directs cellular growth, function, and death
  - Done by biochemical or molecular messengers
    - Cytokines, enzymes, etc
    - Cancer cells have super signals
- Mechanism of action
  - Signal transduction
  - Generated inside or outside of the cell
  - Triggers a signaling cascade that directs the cell to do a specific activity
Monoclonal Antibodies

- **Mechanism of Action (Proposed)**
  1. Antibodies which target extracellular antigens on tumor cells
  2. NK cells recognize the antibody-covered tumor cell
  3. Cytotoxic proteins are released, killing the tumor cell
  
  **OR**
  1. Inhibit binding of growth factors to extracellular receptor

Monoclonal Antibodies in Action

**Rituximab**
- Targets the CD20+ extracellular antibodies on B lymphocytes
- Binds to receptors, recruiting NK cells
- Activates complement

**Bevacizumab**
- Targets vascular endothelial growth factor (VEGF)
- Prevents VEGF from binding to and inhibiting new vessel growth

Examples of mAbs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Source</th>
<th>Indication</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>rituximab</td>
<td>CD20</td>
<td>Chimeric</td>
<td>Non-Hodgkins Lymphoma</td>
<td>1994</td>
</tr>
<tr>
<td>trastuzumab</td>
<td>HER-2</td>
<td>Humanized</td>
<td>Breast, gastric cancer</td>
<td>1998</td>
</tr>
<tr>
<td>cetuximab</td>
<td>EGFR</td>
<td>Chimeric</td>
<td>HN, colorectal cancer</td>
<td>2004</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>VEGF</td>
<td>Humanized</td>
<td>Colorectal, GBM, NSCLC</td>
<td>2004</td>
</tr>
<tr>
<td>panitumumab</td>
<td>EGFR</td>
<td>Human</td>
<td>Colorectal cancer</td>
<td>2006</td>
</tr>
<tr>
<td>ofatumumab</td>
<td>CD20</td>
<td>Human</td>
<td>CLL</td>
<td>2009</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>CD30</td>
<td>Chimeric</td>
<td>HD, anaplastic lymphoma</td>
<td>2011</td>
</tr>
</tbody>
</table>

Side Effects

- Highly dependent on the cellular pathway being disrupted and agent administered
- Hypersensitivity reactions are possible
- Dermatologic toxicities can be severe (acneiform rash, PPE, dry/cracked skin, fissuring); can be dose-limiting
- Also cardiac dysfunction, hepatotoxicity, nausea, vomiting, hypertension, fatigue

Small Molecule Inhibitors

- **Mechanism of Action**
  - Act on signaling pathways that control tumor growth, proliferation, and invasion
  - Either moderate, control, and/or kill cancer cells
  - Most require chronic or long-term therapies

- **Tyrosine Kinase Inhibitors (TKIs)**
  - Erlotinib, Sorafenib, Sunitinib

- **Mammalian target of rapamycin (mTOR)**
  - Temsirolimus, everolimus

**Examples Small Molecule Inhibitors**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Indication</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib (Velcade)</td>
<td>26S proteasome</td>
<td>Multiple myeloma, mantle cell lymphoma</td>
<td>IV, SC</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR</td>
<td>NSCLC, pancreatic cancer</td>
<td>PO</td>
</tr>
<tr>
<td>Everolimus (Afinitor)</td>
<td>mTOR</td>
<td>Breast, renal cell</td>
<td>PO</td>
</tr>
<tr>
<td>Imatinib mesylate (Gleevec)</td>
<td>MCR-ABL</td>
<td>Ph+ CML</td>
<td>PO</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Multikinase inhibitor</td>
<td>Hepatocellular, renal cell carcinoma</td>
<td>PO</td>
</tr>
<tr>
<td>Temsirolimus (Torisel)</td>
<td>mTOR</td>
<td>Renal cell carcinoma</td>
<td>IV</td>
</tr>
</tbody>
</table>

**Side Effects**

- Very drug specific!
- Dermatologic toxicities
  - Rash, acneiform/maculopapular, itching, stomatitis (oral lesions)
  - Topical corticosteroids, oral antihistamines, oral corticosteroids
- Cardiac dysfunction
  - Edema, fluid retention, cardiomyopathy, decreased LVEF, QT prolongation, hypertension
- Miscellaneous
  - Electrolyte imbalances, hair color changes, hepatotoxicity, skin discoloration, bleeding

**Summary**

- Effect specific cellular markers/signals on both healthy and cancerous cells
  - Cancerous cells over-express tumor markers
- Infusion reactions are not uncommon in mAbs
- Many agents are PO
  - Patient education is important
  - Some agents cannot be crushed; know whether or not they can be taken with food
- Side effects are highly drug specific

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COMPLEMENTARY AND ALTERNATIVE (CAM) THERAPIES

CAM Therapies

• Any medical system, practice, or product that is not thought of as standard care
  — Complementary Medicine
    • A CAM therapy used along with standard medicine
  — Alternative Medicine
    • A CAM therapy used in place of standard treatments
  — Integrative Medicine
    • Combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness

Prevalence in the US

• Approximately 38% of adults and 12% of children use CAM
  — Most use is underreported
  — Use has risen significantly in recent years
  — Spans all cultural/ethnic backgrounds
• $33.9 BILLION spent in 2007 alone
  — Out-of-pocket visits, supplies, materials
• Some CAM practices are more regulated than others
  — Supplements/herbals are NOT FDA regulated

Types of CAM

• Alternative Medical Systems
  — Acupuncture, TCM, naturopathy
• Energy Therapies
  — Reiki, Qi Gong
• Exercise Therapies
  — Tai Chi, Yoga
• Manipulative and Body-based Methods
  — Chiropractic, therapeutic massage, osteopathy
• Mind-body Interventions
  — Aromatherapy, support groups, meditation
• Nutritional Therapeutics
  — Macrobiotic diet, vitamins
• Pharmacological and Biologic Treatments
  — herbals, hormones,
• Spiritual Therapies
  — Intercessory prayer, spiritual healing
Nursing Considerations

• Be aware of own attitudes, perceptions regarding CAM treatment
• Assess for CAM use with each patient
• Assist with finding evidence-based sources of information
  – ONS PEP
  – Natural Standard
• Support/empower patient choices

HAZARDOUS MEDICATIONS


Hazardous Medications

• Must meet one or more of these criteria:
  – Genotoxicity – causes DNA damage
  – Carcinogenicity – causes cancer development
  – Teratogenicity/developmental toxicity – fetal damage, loss
  – Reproductive toxicity – sterility, infertility
  – Organ toxicity – at low doses

Principles of Safe Handling

• Preparation in biologic safety cabinet (BSC) under laminar flow hood
• Safe handling techniques during storage, mixing, and transport
• Processes in place for labeling, administration, and disposal
• Personal Protective Equipment

Safe Handling Guidelines

- National Institute for Occupational Safety and Health (NIOSH) [www.niosh.com](http://www.niosh.com)
- Occupational Safety & Health Administration (OSHA)
  - [www.osha.gov](http://www.osha.gov)
- Oncology Nursing Society (ONS)
  - [www.ons.org](http://www.ons.org)
- American Society of Health-system Pharmacists (ASHP)
  - [www.ashp.org](http://www.ashp.org)
- Washington State Hazardous Drug Law (ESB 5994)
  - [http://www.lni.wa.gov/Safety/Topics/AtoZ/HazardousDrugs/](http://www.lni.wa.gov/Safety/Topics/AtoZ/HazardousDrugs/)
- Your own institutional policies and procedures

Washington State Law

- Passed in 2012 by state legislature
  - Requires all facilities that handle hazardous drugs to comply with NIOSH recommendations
    - List of hazardous drugs defined by NIOSH and formulary
  - Implemented in three stages:
    - January 1st, 2015—written hazardous drug control program implemented
    - July 1st 2015—provided employee training
    - January 1st, 2016—installed appropriate ventilated BSC
- Be aware of your facility-specific policy and procedure for hazardous medication handling

Questions?

- Thank you!!