Overview of Cancer Therapies

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Goals of Cancer Therapy

- Prevention
- Cure
- Control
- Palliation

Biotherapy & Targeted Therapies

Action of Antineoplastic Drugs

- Alter cellular activity during one or more phases of cell cycle
- Affects *both* normal & malignant cells
Biotherapy

- Use of agents:
  - Derived from biologic sources
  - That affect biologic responses.
- Therapy that capitalizes on the use of natural body proteins and their functions to fight cancer.

Types of Biologic Agents

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colony stimulating factors</td>
<td>Stimulate reproduction of hematopoietic cells</td>
<td>Erythropoietin (Aranesp) Pegfilgrastim (Neulasta) Interferon α, interferon γ</td>
</tr>
<tr>
<td>Interferons</td>
<td>Inhibit viral replication; immunomodulating</td>
<td>Interferon α, interferon γ</td>
</tr>
<tr>
<td>Interleukins</td>
<td>Promote proliferation, differentiation and recruitment of immune cells</td>
<td>Aldesleukin, Oprelvekin</td>
</tr>
<tr>
<td>Miscellaneous BRM</td>
<td>Various</td>
<td>Lenalidomide, Pomalidomide, Thalidomide</td>
</tr>
</tbody>
</table>

Hematopoietic Growth Factors

- Stimulates the differentiation, proliferation, maturation, and functioning of hematopoietic cells.
- **Erythropoietic stimulating agents:**
  - Stimulate red blood cell production
- **Granulocyte colony stimulating factors (G-CSF)**
  - Regulates production of neutrophils
- **Granulocyte macrophage colony stimulating factor (GM-CSF)**
  - Regulates differentiation neutrophils, monocytes, macrophages & dendritic cells

Interferons

- Actions:
  - Antiviral (inhibit viral replication)
  - Antiproliferative (prevent proliferation of tumor cells)
  - Immunomodulatory (modulate immune response of host)
- Side Effects:
  - Fever, chills, headache, N/V, diarrhea, fatigue, depression, anorexia, confusion, myelosuppression, injection site erythema
Interleukins

- Stimulate activation of immune cells (T and B cells, NK cells, LAK cells, tumor-infiltrating lymphocytes).
- Side Effects:
  - Fever, chills, headache, N/V, diarrhea, myelosuppression, cardiac changes, capillary leak syndrome

Biotherapies

- Monoclonal antibodies
- Small molecules
  - Tyrosine kinase inhibitors or activators
- Growth factors
  - Epidermal (EGF)
  - Vascular Endothelial (VEGF)
- Angiogenesis and antiangiogenic agents

Targeted Therapies

- Cellular growth, function, & apoptosis are regulated by complex network of biochemical & molecular signals
- Referred to as “cell signaling”
- “Signal transduction” is generation of a signal from either
  - Outside the cell (growth factors and growth factor receptors)
  - Inside the cell (tyrosine kinase inhibitors)
- Produces signaling cascade that travels down a pathway to the cell nucleus
Monoclonal Antibodies

- Antibodies cloned from a single antibody
  - Recognize and bind to only one tumor associated antigen
- Highly specific proteins

**Mechanisms of Action:**

- Rituximab (Rituxan®) CD20 Non-Hodgkin's Lymphoma
- Trastuzumab (Herceptin®) HER2 Breast
- Bevacizumab (Avastin®) VEGF Multiple types (colorectal, NSCLC, etc)
- Cetuximab (Erbitux®) HER1/EGFR Colorectal cancer, Head & neck cancer
- Panitumumab (Vectibix®) EGFR Colorectal cancer

**Method of Action:**

- Monoclonal Antibodies vs Small Molecule Inhibitors

- No dimerization
- No signal transduction
- Receptor internalization

- TGF-β MABs
- No phosphorylation

- TKI

- No signal transduction
Tyrosine Kinases

- Responsible for receptor signaling
- Targeted therapies directed to specific targets along signaling pathway
- Moderate, control and/or kill cancer cells
- Small molecules
- Primarily oral therapies
- May develop resistance

Other intracellular pathways

- Mammalian target of rapamycin (mTOR) kinase inhibition
  - Temsirolimus
  - RCC
- BRAFV600E mutations
  - Vemurafenib
  - Melanoma

Small Molecule Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Disease</th>
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</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Tyrosine kinase inhibitor of EGFR and HER2</td>
<td>Breast cancer</td>
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<tr>
<td>(Tykerb®)</td>
<td></td>
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</tr>
<tr>
<td>Erlotinib</td>
<td>Tyrosine kinase inhibitor of EGFR</td>
<td>NSCLC</td>
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<tr>
<td>(Tarceva®)</td>
<td></td>
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<tr>
<td>Nilotinib</td>
<td>BCR-ABL kinase</td>
<td>CML</td>
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<tr>
<td>(Tasigna®)</td>
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<tr>
<td>Sorafenib</td>
<td>Multikinase inhibitor</td>
<td>HCC</td>
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<tr>
<td>(Nexavar®)</td>
<td></td>
<td>RCC</td>
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<tr>
<td>Ruxolitinib</td>
<td>Inhibits JAK 1 and 2</td>
<td>Myelofibrosis</td>
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<tr>
<td>(Jakafi®)</td>
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<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Multiple Myeloma</td>
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<tr>
<td>(Velcade®)</td>
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<td>Mantle cell lymphoma</td>
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</tbody>
</table>
Antiangiogenesis Agents

- Action: Target the neovascularature of tumors to halt their growth, prevent tumor invasion, and preclude metastatic spread.
- Examples:
  - Bevacizumab (Avastin®)
  - Thalidomide (Thalomid®)
  - Lenalidomide (Revlimid®)

Angiogenesis

Biotherapy Summary

- Agents
  - Derived from biologic sources or
  - That affect biologic responses
- Mechanisms of action
  - Vary depending on classification of agents
  - Directed towards identifiable molecular targets on tumor cells

The family of a client want to know the differences between molecular kinase inhibitors from the monoclonal antibodies the client had previously. What are the key differences?

1. Monoclonal antibodies are smaller than kinase inhibitors and have less of a potential for immune system activation.
2. The kinase inhibitors are larger molecules that have less likelihood for drug-drug interactions.
3. Monoclonal antibodies are smaller molecules with a much longer half-life.
4. The kinase inhibitors are oral agents with shorter half-lives and have a greater potential for drug-drug interactions that require monitoring.
Which of the following options apply to targeted therapies that have been approved for use in cancer therapy?

(Select all that apply)

1. Rituximab is a chimeric agent and trastuzumab is a humanized agent thus work together when used in breast cancer.
2. Adverse events of antiangiogenesis agents include bleeding, hypertension and proteinuria.
3. They can play a role in the inhibition of the intracellular tyrosine kinase domain of the VEGF receptor.
4. The mTOR agents target rapamycin pathways thus regulating cell survival, proliferation and growth.
5. They are primarily used as conjugated agents attached to a chemotherapy drug or other agent or toxin.

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**Types of Immunotherapy**

| Adoptive cell transfer | Autologous mononuclear cells activated/expanded in culture
| Immunotoxin | Directs cytotoxic action of a virus to a specific cell type
| Immune Checkpoint Inhibitors | Target PD-1 on T cell
| | Target PD-L1
| | Target CTLA-4

| Example | Provenge (prostate)
| | Yescarte (lymphoma)
| | Kymriah (ALL)
| | Denileukin Diftux (c Tcell lymphoma)
| | TVEC (melanoma)
| | Pembrolizumab
| | Nivolumab
| | Avolumab
| | Durolumab
| | Ipilimumab (melanoma)

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**Immune Checkpoint inhibitors**

- Checkpoints: molecules on certain cells that need to be activated or inactivated to start the immune response
- **PD-1**
  - Checkpoint on T cells
  - Acts as off switch to keep T cells from attacking other cells by binding to PD-L1
- **CTLA-4**
  - Checkpoint on T cells
  - Acts as off switch to keep immune system in check
  - Anti-CTLA-4 agents stop immune system from turning off
Side effects

- Injection site reactions
- Hypersensitivity
- Infusion reactions
- Cytokine Release Syndrome
- Flu-like symptoms
- Symptoms more severe with CTLA-4 agents than the PD-1 or PD-L1

Definitions

- **Hypersensitivity**: Immune response triggered by an allergen. Allergic reactions and Anaphylaxis are forms of this. Usually occur within 5-30 minutes of exposure although some may be delayed

- **Cytokine Release Syndrome**: Infusion reaction related to release of cytokines from the cells targeted by the medication, e.g. lymphocytes. This occurs during the Biotherapy administration, but may be delayed with Immunotherapy administration, e.g. cytokine storm.

### Hypersensitivity & Anaphylaxis VS Cytokine-Release Syndrome

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<thead>
<tr>
<th>Hypersensitivity &amp; Anaphylaxis</th>
<th>Cytokine-release syndrome</th>
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<tr>
<td><strong>Hypersensitivity &amp; Anaphylaxis</strong></td>
<td><strong>Cytokine-release syndrome</strong></td>
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<tr>
<td>- Allergic reactions</td>
<td>- Commonly referred to as &quot;Infusion Reaction&quot;</td>
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<td>- Usually mediated by release of IgE</td>
<td>- Most frequently seen with MOABs</td>
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<td>- Triggered by therapeutic agent, the diluent or solution</td>
<td>- Related to release of cytokines from targeted cells and other recruited immune cells (e.g. lymphocytes)</td>
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<tr>
<td></td>
<td>- IL-2, Interferon, Tumor Necrosis Factor</td>
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### Clinical Manifestations

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Clinical Manifestations of CRS: Lab values

- Increased levels of TNFα, IFNγ, IL6, IL8 and complement levels
- Decrease in platelets, hemoglobin and calcium
- Increase in liver function tests, d-dimers, LDH, creatinine, uric acid and phosphorus
- Decrease in WBC

These changes may be related to cell death of targeted cells.
Theory behind Therapy

- **Autologous:**
  - Potentially lethal doses of chemotherapy/radiation therapy
  - Patient’s own stem cells “rescue” the ablated marrow
  - Cure is chemotherapy/radiation, stem cells are supportive care

- **Myeloablative Allogeneic:**
  - Potentially lethal doses of chemotherapy/radiation
  - Donor stem cell “rescue” of the ablated marrow and “re-set” of the immune system for a graft versus tumor effect
  - Cure is both chemotherapy/radiation and stem cell infusion

- **Nonmyeloablative Allogeneic:**
  - Lower doses of chemotherapy/radiation along with immunosuppression
  - Cure is the graft vs tumor effect, chemotherapy eliminates microscopic disease
  - Also called Mixed Chimerism, Mini or Reduced Intensity

Indications for BMT

- **Malignant diseases:**
  - Acute and Chronic Leukemia
  - Hodgkin’s Lymphoma and Non-Hodgkin’s lymphoma
  - Myelodysplastic Syndromes
  - Multiple Myeloma
  - Amyloidosis
  - Selected solid tumors
    - Renal cell
    - Germ cell
    - Primary CNS
    - Neuroblastoma

- **Non-malignant diseases:**
  - Hematologic Disorders (Aplastic Anemia, Fanconi’s Anemia, Sickle Cell, Thalassemia)
  - Congenital Immunodeficiencies (SCID, Wiskott Aldrich Syndrome)
  - Inborn Errors of Metabolism (Hurler’s Syndrome, Guacher Disease)
  - Autoimmune Diseases (Systemic Sclerosis, Multiple Sclerosis)

Stem Cell Sources

<table>
<thead>
<tr>
<th>Bone Marrow</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abundance of stem cells in BM</td>
<td>Anesthesia risk for donor</td>
</tr>
<tr>
<td></td>
<td>Lower rate of infections days +100 to +365</td>
<td>Post-operative pain for donor</td>
</tr>
</tbody>
</table>

| Peripheral Blood | Faster engraftment | Bone pain for donor |
|                 | Reduced treatment-related mortality | Slightly higher risk of GVHD |
|                 | Lower rate of infections to day +100 | |
|                 | More GVL effect than BM or UCB | |

| Umbilical Cord Blood | Readily available | Delayed engraftment |
|                     | Less risk of GVHD | Smaller “dose” of stem cells |
|                     | More “matches” | Slightly higher rate of early mortality |
|                     |                  | Cannot obtain more cells from donor |

Steps of BMT

- Evaluation
- Mobilization (Autologous Patients): GCSF +/- chemotherapy, then PBSC collection
- Conditioning: Chemotherapy +/- Total Body Irradiation (TBI)
- Pre-engraftment period
- Engraftment
- Recovery
- Long term side effects
Side effects: Conditioning related

- Acute
  - Nausea/vomiting/diarrhea
  - Pancytopenia
  - Infection
  - Mucositis
  - Alopecia
  - Hemorrhagic cystitis
  - Sinusoidal obstructive syndrome

- Long term
  - Pulmonary
    - Pulmonary fibrosis
    - Bronchiolitis Obliterans Organizing Pneumonia
  - Sterility
  - Decreased libido
  - Endocrine
    - Diabetes
    - Thyroid
  - Cardiac
    - Hypercholesteremia
    - CHF

Graft vs Host Disease: Donor immune system attacks host

- Acute:
  - One of most common complications of allogeneic BMT
  - Incidence is 30-70%
  - Major cause of morbidity and mortality after BMT
  - Involves Skin, Gut and/or Liver
  - Prevention: Immunosuppression
  - Treatment: Steroids

Side Effects: Graft vs Host Disease

- Chronic
  - Skin
  - Oral
  - Ocular
  - Genital
  - Lung
  - Joints/Fascia
  - Gut
  - Liver

- Treatment
  - Long Term
    - Immunosuppression
  - Steroids
  - Light therapy

A patient is going to receive a stem cell transplant. Awareness of which of the following would guide the nurse in providing the client and family with supportive information? (Select all that apply)

1. Syngeneic transplant, allows the client to receive stem cells from a perfect match and eliminates concern for rejection.
2. Allografting involves transplanting stem cells from a donor who is genetically different; thus the match is determined by blood typing.
3. In allografting, the coexisting of the donor and host stem cells in a mixed chimerism state can be beneficial.
4. Autografting carries the risk of reinfusing malignant cells; thus the cells must be treated before infusion.
5. When an appropriate donor cannot be found or allografting is determined to be too risky, autografting may be an option.
Common acute complications after HSCT are

1. Chronic graft vs host disease
2. Nausea, vomiting, and infection
3. Herpes varicella zoster infection
4. Impaired growth and development in children

Sources of hematopoietic stem cells for transplantation can be derived from:

1. Animal placenta and peripheral blood
2. Whole blood previously collected for blood transfusions
3. Bone marrow or blood circulating in the peripheral system of the donor
4. The blood cells pooled in the spleen of a donor

Bibliography


Resources

• American Cancer Society www.cancer.org, select “Treatment”
• Leukemia and Lymphoma Society, https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy
• National Cancer Institute www.cancer.gov, select “About Cancer > Cancer Topics”
• National Comprehensive Cancer Network www.nccn.org, select “NCCN Clinical Practice Guidelines in Oncology”
• National Marrow Donor Program www.marrow.org, select Physicians