The Basics of Cancer Immunotherapy

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Disclosures

No real or apparent conflicts of interest to report.
Why do we care about cancer?
10,600 people die of cancer each week!
Cancer Statistics

2014 Leading Causes of Death in U.S.

Heart Disease: 614,348
Malignant Neoplasms: 591,699
Chronic Low Respiratory Disease: 147,101
Unintentional Injury: 136,053
Cerebrovascular: 133,103
Alzheimer’s Disease: 133,103
Diabetes Mellitus: 126,654
Influenza & Pneumonia: 93,541
Cancer: 48,146
Nephritis: 42,773
Suicide: 76,488

Source: www.cdc.gov
Cancer Statistics 2015

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>232,340</td>
<td>28%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>110,110</td>
<td>14%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
<td>69,140</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>49,560</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>45,310</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>32,140</td>
<td>5%</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>37,600</td>
<td>31,630</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>24,720</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27,880</td>
<td>22,480</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>22,240</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>854,790</strong></td>
<td><strong>805,500</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,260</td>
<td>72,220</td>
<td>28%</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,720</td>
<td>39,620</td>
<td>10%</td>
</tr>
<tr>
<td>Colorectum</td>
<td>26,300</td>
<td>24,530</td>
<td>9%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>19,480</td>
<td>18,980</td>
<td>6%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>14,890</td>
<td>14,030</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,660</td>
<td>10,060</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,220</td>
<td>8,430</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,820</td>
<td>8,190</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>10,590</td>
<td>6,780</td>
<td>3%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,780</td>
<td>6,150</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>306,920</strong></td>
<td><strong>273,430</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

*Estimates are rounded to the nearest 10 and exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Source: www.cancer.org
Objectives

• Introduction to the immune system
• Interaction between cancer and the immune System
• Immunotherapy
  o Principles of Immunotherapy
  o Classes of Immunotherapy
  o Disease specific treatments
• Nursing implications
• Outline the challenges and the future of immunotherapy
Immune System Overview

- Nonspecific
  - First line of defense
  - WBCs (Natural Killer cells, Neutrophils)
  - Activation of adaptive response

- Specific
  - Adapts specifically to diverse stimuli
  - B-cell antibody production
  - T-cell stimulation
  - Memory functions
Immune System and Cancer

- Tumor cells express specific antigens
- **Antigen presenting cells (APC)** → ingest tumor antigens
- **B cells** → produce antibodies against tumor antigens
- **T cells** → recognize and destroy tumor cells
- **Natural killer cells** → generating proteins that stimulate the immune system AND producing killing molecules
Tumor Immunology

1. Dendritic cell captures tumor antigen.
2. Tumor antigen presented to resting T cell in lymph node.
3. Activated T cell undergoes clonal expansion and secretes cytokines.

Slide credit: clinicaloptions.com
Role of the Immune System in Cancer and Cancer Prevention

- Evade checkpoints and cell signals to stop growing or die (apoptosis)
- Form its own blood vessels for a source of food and energy (angiogenesis)
- Invade other tissues and spread throughout the body
- Evade the immune system and avoid destruction
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
Principles of Immunotherapy

- Immunotherapy is a treatment of disease by inducing, enhancing, or suppressing an immune response.
- Immuno-oncology uses immunotherapy to target the immune system to fight cancer.
- Cellular therapy is a treatment in which cellular material is injected into a patient.
- Immunotherapy works by:
  1. Stopping/slowing the growth of cancer cells
  2. Stopping cancer from spreading to other parts of the body
  3. Helping the immune system recognize cancer cells and increase its effectiveness at eliminating cancer.
Benefits of Immunotherapy

• Modalities of cancer treatment: Surgery, radiation, chemotherapy, AND immunotherapy

• Why immunotherapy?
  o **POWERFUL**: Attacks anywhere in the body
  o **SPECIFIC**: Trained to recognize only cancer
  o **MEMORY**: Remembers cancer cells to fight them later
  o **UNIVERSAL**: Can be used to treat most cancers

• Many kinds of cancer immunotherapies
History of Immunotherapy

1976: BCG vaccine for bladder cancer

1863: Connection between immunotherapy and cancer recognized

1976: BCG vaccine for bladder cancer

1985: Interferon first approved for hairy cell leukemia

1992: IL-2 approved for RCC

2008: First cancer vaccine approved for RCC

2010: Sipuleucel-T approved for prostate cancer

2014-2015: PD-1 inhibitors approved for melanoma, squamous NSCLC

2015: First oncolytic virus approved for melanoma

2011: CTLA-4 inhibitor approved for melanoma

2016: PD-1 inhibitor approved for CHL
PD-L1 inhibitor approved for UC

1990: GVL effect recognized as basis of allo-HSCT efficacy; DLI induces CML remissions

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1796: First use of immunotherapy, Jenner smallpox vaccine

1863: Connection between immunotherapy and cancer recognized

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Classes of Immunotherapy

- Monoclonal Antibodies
- Vaccines
- Cytokines
- Adoptive T-Cell Transfer
- Checkpoint Inhibitors

All classes either 1) boost an immune response OR 2) enable the immune system to recognize and fight the tumor.
Monoclonal Antibodies

- Monoclonal antibodies (mAb) are designed to target tumor-specific antigens
- Passive but specific
- Improve response rates
- Derive from human antibodies, animal antibodies, or a combination of the two
- mAbs work in a variety of ways:
  - Flag cancer cells for destruction
  - Block growth cells and receptors
  - Deliver other anticancer agents to the tumor site
- Examples: rituximab, trastuzumab, bevacizumab
mAb Infusion Reactions

- Tolerated better than chemo
- Affect any organ system
- Administer slowly
- Premeds lessen the severity of reactions
- Usually most severe with first dose

**Table 3. Signs and Symptoms of Hypersensitivity Reactions**

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>CLINICAL MANIFESTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Chest pain, palpitations, hypotension, hypertension, tachycardia, bradycardia, arrhythmia, edema, ischemia or infarction, cardiac arrest</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Headache (throbbing in nature), dizziness, confusion, loss of consciousness</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash, pruritus, urticaria, flushing, local or diffuse erythema, conjunctival erythema and tearing, angioedema</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Rigors, diaphoresis, fever, generalized feeling of warmth</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, metallic taste, diarrhea, abdominal cramping and bloating</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Incontinence, uterine cramping or pelvic pain, renal impairment</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgias, myalgias, fatigue, tumor pain, hypotonia</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Anxiety, sense of impending doom</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cough, dyspnea, nasal congestion, rhinitis, sneezing, hoarseness, tachypnea, wheezing, chest tightness, hypoxemia, bronchospasm, reduced pulmonary expiratory flow, oropharyngeal or laryngeal edema, stridor, pulmonary infiltrates, cyanosis, acute respiratory distress syndrome</td>
</tr>
</tbody>
</table>
Vaccines

- **Cancer vaccines:**
  - Educate immune system to target cancer
  - Trigger an immune response against a patient’s cancer

- **Two types of vaccines:**
  - **Preventative** = prevent cancer
    - Vaccines against viruses, i.e. Gardasil
  - **Therapeutic** = treat cancer
    - Autologous: Patient’s own cancer cells
    - Allogeneic: Many different cancer cells

National Cancer Institute, 2011
Sipuleucel-T Vaccine

Di Lorenzo, et al., Nature Reviews Clinical Oncology, Sept 2011
Vaccine Side Effects

- Side effects mimic other vaccines:
  - Injection site pain, redness, swelling, warmth, itchiness, and rash
  - Fever
  - Chills
  - Weakness
  - Dizziness
  - Nausea and vomiting
  - Muscle aches
  - Fatigue
  - Headache
Cytokine Therapy

• Nonspecific immune stimulation (especially T cells)
• “Interleukins” and “Tumor Necrosis Factor”
• Interleukin-2 (IL-2):
  o T cell growth factor
  o Cytokines bind to T cell → T cells proliferate → continued cytokine production → immune activation
  o FDA approved in 1992 for metastatic renal cell carcinoma and metastatic melanoma
  o Durable response
  o Administer in controlled setting
Cytokine Therapy SE

- **Viscous side effect profile:**
  - Fevers, malaise
  - Headache
  - Arthralgias
  - Rash
  - Flushing
  - N/V/D
  - Cardiac arrhythmias
  - Hypotension
  - Capillary leak syndrome
Adoptive T-Cell Transfer

- TCells collected from patient → engineered to recognize tumor antigens → reinfused
- CAR-Tcell therapy = a type of T-cell transfer therapy
  - Leukemia, lymphoma most promising
  - Other trials in myeloma, melanoma, and neuroblastoma
  - Not FDA approved, only in clinical trials
What is CAR-T cell therapy?

- **Chimeric Antigen Receptor T**cell therapy
- Chimeric means two different things joined together
  - CAR is the joining of an antibody and a t-cell receptor
- T cells are modified to express receptors specific to a patient’s cancer, CD19 best studied
- Total number of patients treated is small, results are promising
- CAR-T cells should be able to provide long-lasting remissions
Cytokine Release Syndrome (CRS)

- Cytokines are chemical messengers produced by cells
- T cell proliferation and activation → release of cytokines
- Biomarkers: IL-6, IL-10, IFN-γ, CRP
- Mild flu-like symptoms to shock to multi-organ failure
- Usually within 5 days of 1st infusion
- Required observation for CRS is protocol dependent
- Correlation between the development of CRS and the response to therapy
# Symptoms of CRS

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypotension</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures</td>
</tr>
</tbody>
</table>
Checkpoint Inhibitors

- Common immune checkpoints:
  - Programmed cell death protein 1 (PD-1)
  - Programmed death ligand 1 (PD-L1)
  - Cytotoxic T lymphocyte-associated protein 4 (CTLA-4)

Checkpoint Inhibitors

Ribas, NEJM. 2012
Checkpoint Inhibitors: Patterns of Response

• Delayed clinical response: Therapy may take weeks to become apparent
• Pseudoprogression: Symptoms may get worse before they improve
• Infusion reactions and adverse events rare, but serious
• Adverse events typically present 6-12 weeks after therapy
Checkpoint Inhibitors: Immune-Related Adverse Events (irAE)

- Rash
- Pneumonitis
- Hepatitis
- Colitis
- Nephritis
- Myopathy

Endocrine:
- Hypophysitis
- Thyroiditis
- Adrenal insufficiency

Eyes:
- Uveitis
- Conjunctivitis
Patient Communication

- "Gas and brake pedal" analogy
  - Pressing the gas pedal = restoring T-cell activity and starting immune response against tumor
  - Brake pedal = immune checkpoint
  - Lifting the foot off the brake = enabling T cell-mediated immune response to continue

- "Removing muzzle off the dog" analogy
  - Muzzle = treating by checkpoint blockade
  - Dog = one’s immune system
Combination Therapy

• Goal: develop regimens of agents w/different MOA to outsmart resistance
• Immunotherapy + Chemotherapy $\rightarrow$ great promise
• Immunotherapy + XRT $\rightarrow$ synergistic effect
• Combination of immunotherapies:
  • CTLA-4 + PD1
Site-Specific Treatments
Prostate Cancer

- First indication for immunotherapy by FDA
- Prostate-associated tumor antigens:
  - PSA, PSMA, PAP, CTA
- Vaccines:
  - Sipuleucel-T
- Checkpoint inhibitors:
  - Many trials underway for PD-1, CTLA-4, and PDL-1
  - Delayed responses
- Adoptive T-cell Transfer:
  - NY-ESO-1
Lung Cancer

- Lung cancer cell’s down-regulate antigen presenting cells
- TAA associated for NSCLC: PD-1, MAGE-A3, NY-ESO-1, p53, MUC-1
- Monoclonal antibodies:
  - Bevacizumab and Ramucirumab
- Checkpoint Inhibitors:
  - Nivolumab and Pembrolizumab*
- Adoptive T-cell therapy:
  - NY-ESO-1
Leukemia

- Bleak survival rates
- **Monoclonal antibodies:**
  - Rituximab, ofatumumab, and obinutuzumab - CD20-positive CLL
  - Alemtuzumab - CD52-positive CLL
  - Blinatumomab – B-cell ALL
- **Adoptive T-cell therapy/ CAR-T cell therapy:**
  - One trial \(\Rightarrow\) 100% remissions in the pediatric group and 80%-90% remissions in the adult group.
  - Many companies are developing CAR T cells
Lymphoma

- mAbs have greatly benefited lymphoma treatment
- Monoclonal Antibodies:
  - Rituximab, Obinotuzumab – anti-CD20
  - Ibritumomab – mAB + XRT
  - Brentuximab – mAB + chemo
- Checkpoint Inhibitors:
  - Nivolumab
- Adoptive Cell Therapy/CAR-T Cell:
  - Targeting CD19 for lymphoma
Melanoma

- 4 immunotherapies have been FDA approved
- **Cytokines:**
  - IL-2
- **Checkpoint Inhibitors:**
  - Ipilimumab, pembrolizumab, nivolumab
  - Combination therapy – ipi + nivo approved
  - >25 trials for new drugs and combinations
- **Oncolytic Vaccines:**
  - Tamiologene laherparapvec (T-VEC, trade name Imlygic)
Renal Cell Carcinoma

- RCC tends to be chemo and XRT resistant
- Targeted therapies and immunotherapies are 1st line
- Checkpoint Inhibitors:
  - Nivolumab FDA approved
- Cytokines:
  - IL-2, INF-a
- Clinical trials:
  - Many checkpoint inhibitor combinations
  - Adoptive cell transfer, vaccines, and monoclonal antibodies
Nursing Implications

- Familiarize yourself with toxicity profile of each agent
- Observe patients closely and monitor vital signs frequently
- Vigilant supportive care (PRN meds)
- Know who to page
- Patient and caregiver education → report any symptoms ASAP
Patient Expectations

• Difference between MOA of chemo and immunotherapy
  o Chemotherapy designed to kill cancer
  o Immunotherapy designed to activate immune system to kill cancer
    • Does not directly act upon tumor cells
• Adverse events profile is different
• Provide written materials
  o Information about immunotherapy agent
  o Wallet card for PCP/ED
The Challenges

• Still learning about agents and implications
• Long-term success rates not fully understood
• Adverse events, frequency, and severity still being explored
• How long to treat?
• Urgent need:
  o Only 12 active immunotherapies approved
  o Only 3-6% of cancer patients participate in clinical trials
  o www.clinicaltrials.gov
The Future

• Clinical research in immunotherapy is rapidly increasing
• Combining treatment options
• Improving immune treatments
• Identifying people may benefit from immune treatments
• Cure????
Thank you.