*Funding for development of this activity was provided by an independent educational grant from Bristol-Myers Squibb.
Introduction to Immunotherapy
The Immune Response: Terminology

Immunity:
- The body’s ability to resist disease
- Ability of the body to respond to foreign substances (microbes and noninfectious molecules)

Immune system:
- Network (cells, proteins, tissues, organs and molecules) that works together to defend the body against attacks by foreign invaders.

Immune response:
- Coordinated reaction of cells and molecules of the immune system

(G. P. Dunn & Okada, 2015)
The Immune System: Self vs Non-Self

• The key to a functional immune system is the ability to distinguish between self and non-self.
  - Cells carry self marker molecules (SELF).
  - Cells carry markers that are not recognized as self (FOREIGN) → immune response

• Antigens trigger the immune response.
  - Microbe (e.g., virus)
  - Part of a microbe

Tumor antigens are recognized as foreign by the immune system and initiate an immune response.
Antigen-Specific: Adaptive

**Develops slowly and provides a more specialized defense against infections**

**Two types of adaptive response:**
- **Humoral immunity:** antibodies
- **Cell mediated:** T lymphocytes

Non-Specific: Innate

**Speed**

**Nonspecific**

**Limited duration**

**Lack immunologic memory**

**Inflammation is one of the first responses of innate immunity.**

**Enhances adaptive immune response through presentation of antigens**
Antibodies
Bind to antigens and mark cells for attack and destruction.

B Cells
Release antibodies to defend against threats.

CD8+ Killer T Cells
Seek out and destroy cancer cells.

Cytokines
Help immune cells communicate and coordinate the right response.

Natural Killer Cells
Identify and eliminate cells that fail to produce self-MHC class molecules.

Dendritic Cells
Digest foreign cells and present their proteins to immune cells for destruction.

CD4+ Helper T Cells
Send “signals” to other immune cells (B cells, CD8+ T cells) to make them more efficient.

Regulatory T Cells
Provide checks and balances to ensure the immune system doesn’t overreact.

Macrophages
Engulf and destroy harmful cells and present antigens to other immune cells.
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Images used with permission from the Cancer Research Institute.
Antibodies Bind to antigens and mark cells for attack and destruction.

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Immunotherapy Principles
Cancer cells are different than healthy cells.
Immunoediting: Cancer and Immunity

Cancer Progression

- Elimination
- Equilibrium
- Escape
The Cancer Immunity Cycle

1. Release of cancer cell antigens
2. Cancer antigen presentation
3. Priming and activating
4. Trafficking of T cells to tumor
5. Infiltration of T cells into tumor
6. Recognition of cancer by T cells
7. Killing of cancer cells

(Chen & Mellman, 2013)
Types of Immunotherapy
## Types of Immunotherapy

<table>
<thead>
<tr>
<th>Monoclonal Antibodies</th>
<th>Adoptive Cell Transfer</th>
<th>Checkpoint Inhibitors</th>
<th>Vaccines/Oncolytic Viruses</th>
<th>Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor-targeting mAbs</strong>&lt;br&gt;Boost immune stimulation pathways.</td>
<td><strong>Living immune cells modified to trigger an immune response</strong>&lt;br&gt;Immunomodulatory mAbs&lt;br&gt;De-suppress the immune response (“release the brakes”).&lt;br&gt;Harness memory cell function of the immune system to create sustained immunity.</td>
<td><strong>Interferons and interleukins</strong>&lt;br&gt;Set in motion a general immune response, activating a wide range of immune cells.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Monoclonal Antibody (mAb): Basic Structure
Monoclonal Antibodies: Function

Flag cancer cells for destruction.

Block growth signals and receptors.

Deliver other anticancer agents to the site of the tumor.
# Some Common Monoclonal Antibody Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism</th>
<th>Example Agents</th>
<th>Applications in Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20</td>
<td>Transmembrane protein that serves as a calcium channel implicated in activation, proliferation, and differentiation of B cells; present in the majority of B-cell NHLs and CLL; targeting CD20 leads to rapid cell lysis</td>
<td>rituximab, obinutuzumab, ofatumumab</td>
<td>NHL, CLL</td>
</tr>
<tr>
<td>CD22</td>
<td>Role in establishing a baseline level of B-cell inhibition; helps maintain homeostasis in humoral immunity; expressed in majority of B-cell ALL</td>
<td>inotuzumab, ozogamicin</td>
<td>ALL</td>
</tr>
<tr>
<td>HER2</td>
<td>Transmembrane receptor tyrosine kinase; overexpressed in some breast cancers</td>
<td>pertuzumab, trastuzumab</td>
<td>Breast</td>
</tr>
<tr>
<td>EGFR</td>
<td>Regulates epithelial tissue development; targeting can inhibit signaling pathways leading to cell lysis and induce an immune response against cells with binding receptors</td>
<td>cetuximab</td>
<td>Colorectal, lung</td>
</tr>
</tbody>
</table>
Vaccines in Cancer

- Tumor cell
- Cancer Vaccines
- Antigen
- Vector-based
- Dendritic
Oncolytic Viruses: Triggering the Immune Response

Normal cell

Virus infects but cannot replicate

Unharmed

Virus infects other tumor cells.

Tumor cell

Virus infects and replicates.

Released antigens promote anti-tumor immune response.

Tumor cell lysis causing release of viral particles and tumor antigens

(Chen & Mellman, 2013)
Checkpoint Inhibitor Therapy: Immune Checkpoints

• Immune checkpoints are a part of a healthy immune system.
• Regulate immune function and prevent overstimulation.
• Provide a mechanism for tumor cells to evade T-cell recognition.
• Blocking negative immune regulators (checkpoints) may give the human immune system the power to fight cancer.
Checkpoint Receptors in T-Cell Regulation
## Immune Checkpoint Inhibition Agents

### Cytotoxic T Lymphocyte Antigen 4 inhibition (CTLA-4)
- ipilimumab

### PD-1 inhibition
- nivolumab
- pembrolizumab
- cemiplimab-rwlc

### PD-L1 inhibition
- atezolizumab
- avelumab
- durvalumab
Impact of Modification of T-cell Activation: Immune-Related Adverse Events (irAEs)

“Immune-related toxicity can attack virtually every organ system.”
- John A. Thompson, MD
CAR T-Cell Therapy: Engineering a Patient’s Immune Cells to Fight Cancer

- Chimeric antigen receptor (CAR) T cells are genetically modified autologous T cells that are used to produce an anticancer effect.
  - Patient’s T cells are modified to target cancer cells.
  - Chimeric antigen receptor is constructed to bind with a target on the cancer cell.
  - CAR T cells may also include a molecule that stimulates the T cell to increase immune response.
- Currently, these cells are designed to target a single surface antigen.

<table>
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<th>Target</th>
<th>Drug</th>
<th>Clinical Application(s)</th>
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<tr>
<td>CD-19</td>
<td>Tisagenlecleucel</td>
<td>ALL, DLBCL</td>
</tr>
<tr>
<td>CD-19</td>
<td>Axicabtagene ciloleucel</td>
<td>B-cell lymphoma</td>
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CAR T-Cell Therapy

1. Remove blood from patient to get T cells
2. Make CAR T cells in the lab
3. Grow millions of CAR T cells
4. Infuse CAR T cells into patient
5. CAR T cells bind to cancer cells and kill them

Image from the National Cancer Institute
CAR T-Cell Therapy: Adverse Events

Neurologic Toxicity
(confusion, delirium, aphasia, seizure)

"On-target, off-tumor" Toxicity

Cytokine Release Syndrome
(fever, fatigue, hypertension/tachycardia, nausea, capillary leak, cardiac/renal/hepatic dysfunction)

CAR Anaphylaxis/Allergy
Immune responses to mouse-derived and/or recombinant proteins

(Anderson et al., 2019; Neelapu, 2018)
Immune-Related Adverse Events (irAEs)
Immunotherapy works differently than other therapies.

15%-90% of patients will experience some grade of irAE while receiving immunotherapy.
Onset/Predictability of irAEs

Can depend on the organ system affected and the type of immunotherapy.

More immediate irAEs include hypersensitivity reactions, CRS, and TLS.

Onset may be delayed (months or even years after therapy).

Patients may have a prolonged duration for these adverse events compared to the pattern typically seen with chemotherapy.
irAE Assessment and Management

Early Identification → Grading of Toxicity → Multidisciplinary Assessment → Collaborative Management

(Connolly, Bambhania, & Naidoo, 2019)
Guidelines for irAE Management

ASCO/NCCN Guideline

SITC Guidelines

ESMO
Management Recommendations

Pneumonitis

**Grade 1 Mild**
- Consider holding ICI.
- Imaging
- Pulse oximetry

**Grade 2 Moderate**
- Hold ICI.
- Pulm consult
- Infectious/malignant workup
- Consider empiric antibiotics.
- Prednisone 1-2 mg/kg/day
- Close monitoring

**Grade 3-4 Severe**
- Discontinue ICI permanently.
- Admission
- Infectious/malignant workup
- Empiric antibiotics
- Methylprednisolone 1-2 mg/kg/day
- Consider TNF, IVIG, or mycophenolate mofetil for refractory.

(Brahmer, 2018; Naidoo, 2017)
Refractory/Severe irAEs

- Colitis
- Guillain-Barre syndrome
- Myocarditis
- Encephalitis
- Hepatitis
- Myasthenia gravis
- Transverse myelitis

These irAEs can become life-threatening or fatal and often require IV corticosteroids and admission.
Late/chronic irAEs

Endocrinopathies:
- adrenal hypophysitis
- adrenal insufficiency
- thyroid dysfunction
- hyperglycemia

Rheumatic:
inflammatory arthritis

These irAEs typically occur within **3-6 months**. However, they may occur at any time, even after therapy is discontinued.
Special Considerations

- Comorbidities/autoimmune disorders
- Baseline corticosteroids
- Opportunistic infections
- Combination therapy

(Abdel-Wahab, 2018; Johnson, 2016)
Nursing Considerations and Patient Education

- Telehealth/ triage management
- Stay up to date
- Educate patients early and often
- Side effects of corticosteroids
- Treatment response time

Most irAEs can be managed effectively if assessed and treated early!

(Abdel-Wahab, 2018; Johnson, 2016)
Care Coordination

• Patient engagement, encourage communication
• Educate emergency clinicians, PCP/FNPs, and hospitalists on assessment and treatment of irAEs.
• Oncology urgent/acute care
• ER algorithm

(Handley, 2018)
Immunotherapy Tools

- Wallet card
- Patient diaries
- Baseline symptom assessment forms
- Survivorship care plans
- Drug package insert
- National guidelines
- Care step pathways
irAE Management: Key Takeaways

- **Remain vigilant.**
- **Educate** yourself and peers to recognize irAEs.
- **Early recognition** and prompt intervention
- **Hospitalization** may be necessary for severe or refractory irAE.
- **Patient/caregiver education** is a vital component.
Reporting Adverse Events
Role of the Oncology Nurse

Inform
Empower
Educate

www.ons.org
Did You Know?

1. Which patients are typically included in phase I-III clinical trials that support FDA approval?
2. What informs the adverse event incidence rates posted in package inserts?
3. How often are package inserts updated?

Resources for Drug-Related Information

- Drugs@FDA
  - www.accessdata.fda.gov/scripts/cder/daf/
- NIH’s DailyMed
Where to Report Immunotherapy Adverse Events

How do we make this decision?

FDA

Case reports

Medical record

(Bristol-Myers Squibb, 2018; Wiley, Galiato, Dickman, & Winklejohn, 2018)
Safe Handling Considerations
What is a hazardous drug?

- Carcinogenicity
- Teratogenicity
- Genotoxicity
- Reproductive toxicity
- Organ toxicity at low doses

(Jorgenson & Rinehart, 2015; NIOSH, 2016)
What precautions are needed?

- Wear gloves.
- Assess the environment
- Prepare drug using BSC.
- Respiratory protection
- Hand washing
- Robust surface cleaning
- Handle with care.

(de Lemos et al., 2018; Jorgenson & Rinehart, 2015; Langford, n.d.)
Immuno-Oncology for the Oncology Nurse

*Funding for development of this activity was provided by an independent educational grant from Bristol-Myers Squibb.