Celebrating Our Patients

Immuno-oncology Update – An Exciting and Exploding Field

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Objectives

• Outline the main mechanisms of action of immuno-oncology agents
• Discuss the approved indications for each agent
• Identify side effects for immuno-oncology agents
• Describe potential future indications for approved agents and agents in the development pipeline

The Basics¹

• Immune system typically detects and destroys abnormal cells
• Cancer cells avoid detection by
  – Reducing expression of tumor antigens on surface
  – Expressing protein on surface to induce immune cell inactivation
  – Inducing microenvironment to release substances that suppress immune responses and promote tumor cell proliferation and survival

Immuno-oncology: What Is It?1,2
Increase strength of immune response against tumor


Advantages
- Not cytotoxic
- Durable responses
- Slows tumor growth

Disadvantages
- Immune-related adverse effect profile
- Unique treatment response
- Low response rates
American Society of Clinical Oncology Advance of the Year

- Several different strategies moved from bench to bedside
- Works against range of cancers
  - Even more advanced tumors
- Potential to control tumor growth longer and with fewer adverse effects

Cancer Moonshot

- 2016 State of the Union Address: national “moonshot” initiative to eliminate cancer as we know it
- Accelerate research efforts and break down barriers to progress by enhancing data access and facilitating collaborations
- Research areas
  - Prevention and Cancer Vaccine Development
  - Early Cancer Detection
  - Cancer Immunotherapy and Combination Therapy
  - Genomic Analysis of Tumor and Surrounding Cells

References:
Evolution of Treatment

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<td>OX40 PATHWAY</td>
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<tr>
<td>CAR=chimeric antigen receptor</td>
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<td>CSF-1R=colony-stimulating factor 1 receptor</td>
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<tr>
<td>CTLA-4=cytotoxic T-lymphocyte antigen-4</td>
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<td>IDO=indoleamine 2,3-dioxygenase</td>
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<td>PD-1=programmed death-1</td>
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<td>PD-L1=programmed death-ligand 1</td>
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Immuno-oncology

Treatment Options

- Immune Checkpoint Modulators
- Immune Cell Therapy
- Cancer Treatment Vaccines
- Therapeutic Antibodies

Immune System Modulators
Cancer Treatment Vaccines: How They Could Work

• Prime immune system to attack cancer cells
  – Treat existing cancers by strengthening body's natural defenses against cancer
• Examples
  – Dendritic-cell vaccine
  – Tumor-cell vaccine
  – Peptide/protein-based vaccine
  – Recombinant vector vaccine

Cancer Treatment Vaccines

• Approved Agent
  – Sipuleucel-T (Provenge®): prostate cancer
    • Immune cells removed from patient’s blood and sent to a lab
    • Exposed to chemicals to create dendritic cells and exposed to protein called prostatic acid phosphatase (PAP)
    • Dendritic cells given back to patient to produce immune response against prostate cancer cells
  • Adverse Effects: infusion-related reactions, fever, chills, back pain, fatigue, nausea
  • Ongoing Research: combination therapy, timing of vaccine, use of booster vaccine

**Immune Checkpoint Modulators**

- **Block immune checkpoint proteins**
  - Proteins limit strength and duration of immune responses
- **Release “breaks” on immune system**, increasing its ability to destroy cancer cells
- **Examples:**
  - Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor
  - Programmed cell death-1 (PD-1) inhibitor
  - PD-1 receptor ligand (PD-L1) inhibitor

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**Mediators of T-Cell Activation**

APC: antigen-presenting cells
CTL: cytotoxic T lymphocyte

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CTLA-4 Inhibitor\(^1-3\)

- **CTLA-4**
  - Protein on some T-cells that act as “off switch” to keep immune system in check

- **CTLA-4 Inhibitor**
  - Attaches to CTLA-4 and stops it from working
  - Boost body’s immune response against cancer cells

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**CTLA-4 Inhibitor (continued)**

- **Approved Agents**
  - Ipilimumab (Yervoy\(^\circ\)): melanoma

- **Ongoing Research**
  - Combination therapy
  - More tumor types: lung cancer, head and neck cancer, glioblastoma, prostate cancer, bladder cancer
PD-1 and PD-L1 Inhibitors\textsuperscript{1,2}

- **PD-1: checkpoint protein on T-cells**
  - Normally acts as “off switch” to help keep T-cells from attacking other cells in body
  - Does this when it attaches to PD-L1 protein on some normal and cancer cells
  - When PD-1 binds to PD-L1, this tells T-cells to leave other cells alone
  - Some cancer cells have large amounts of PD-L1, which helps them evade immune attack

- **Boost immune response against cancer cells**


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PD-1 and PD-L1 Inhibitor Mechanism\textsuperscript{1}

PD-1 and PD-L1 Inhibitors (continued)\textsuperscript{1,2}

- **Approved Agents**
  - Nivolumab (Opdivo\textsuperscript{®})
  - Pembrolizumab (Keytruda\textsuperscript{®})
  - Atezolizumab (Tecentriq\textsuperscript{®})

- **Ongoing Research**
  - Combination therapy
  - Additional tumor types: nearly all solid tumors, leukemias, lymphomas


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**Approved Indications for PD-1 and PD-L1 Inhibitors**

- **Nivolumab**
  - Hodgkin lymphoma
  - Melanoma
  - Non–small-cell lung cancer
  - Renal-cell carcinoma

- **Pembrolizumab**
  - Head and neck cancer
  - Melanoma
  - Non–small-cell lung cancer

- **Atezolizumab**
  - Urothelial carcinoma
BM1 small square graphics boxes are not opening in PP
Barbara Marino, 9/21/2016
Immune-Related Adverse Effects (irAEs)¹

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Enterocolitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitits
- Motor and sensory neuropathies
- Arthritis

Less common: hematologic, cardiovascular, ocular, renal


irAEs Time Line¹

irAEs Management\(^1\)

- Provide counseling for prompt identification of moderate or severe irAEs
- Rapid initiation of immunosuppression leads to favorable outcomes
  - Withhold treatment and do not resume until toxicity returns to grade ≤1
  - irAEs management options initiate corticosteroids
    - 0.5 to 2 mg/kg/day of prednisone equivalent
      - Infliximab
      - Mycophenolate mofetil (MMF)
      - Cyclophosphamide
- Supportive care and symptom management


irAEs Monitoring\(^1\)

- Reduction in tumor growth
- Liver function tests
- Serum creatinine
- Thyroid function tests
- S/S pneumonitis
- S/S colitis

Immune Cell Therapy¹

- **Adoptive Cell Transfer (ACT)**
  - Tumor-infiltrating lymphocytes (TILs)
    - Collect lymphocytes that have infiltrated a patient’s tumor
    - Grow cells that show greatest recognition of tumor cells
    - Activate with cytokines and reinfuse into the patient
    - Increase amount of cells with ability to target tumor


Immune Cell Therapy (continued)¹

- **Chimeric antigen receptor (CAR) T-cell therapy**
  - Collect patient’s T-cells
  - Genetically modify to express protein called chimeric antigen receptor (CAR) on T-cells
  - Multiply in lab and reinfuse into the patient
  - CAR T-cells attach to specific proteins on surface of cancer cells
  - Once bound, CAR T-cell becomes activated and attacks cancer cells

CAR T-Cell Therapy Mechanism\(^1\)

- MHC: major histocompatibility complex
- TCR: T-cell receptor
- scFv: single-chain variable fragment
- CAR: chimeric antigen receptors


CAR T-Cell Therapy Toxicity\(^1\)

- Ranges from mild to severe, life-threatening adverse effects
  - Therapy administered inpatient for monitoring and management of toxicities
- Adverse effects
  - Cytokine release syndrome (CRS)
  - Encephalopathy
  - B-cell aplasia
- Treatment options
  - Tocilizumab
  - Vasoactive pressors
  - Antiepileptics
  - Antipyretics

Therapeutic Antibodies¹

• **Unconjugated Monoclonal Antibodies (mAbs)**
  – Signaling mediated by cross-linking of surface antigen causing cells to commit suicide (apoptosis)
  – Block an activation signal needed for continued cell growth
  – Antibody-dependent cellular cytotoxicity (ADCC): recruit cytotoxic cells (monocytes and macrophages)
  – Complement mediated cytotoxicity (CMC): bind complement leading to direct cell toxicity

• **Approved Agents**
  – Too many to name!


Therapeutic Antibodies (continued)¹

• **Antibody Drug Conjugates (ADCs)**
  – Created by chemically linking antibodies or fragments of antibodies to a toxic substance
    • Toxic substances: poison (bacterial toxin), small-molecule drug, radioactive compound
  – Antibody portion of ADC binds to target expressed on surface of cancer cells
  – Once bound, taken up by cell and toxic substance kills cell

• **Approved Agents**
  – Ado-trastuzumab emtansine (Kadcyla®): breast cancer
  – Brentuximab vedotin (Adcetris®): Hodgkin lymphoma, anaplastic large T-cell lymphoma
  – Ibrutinomab tiuxetan (Zevalin®): Non-Hodgkin’s lymphoma

ADCs


- Antibody
  - Specific for a tumor-associated antigen that has restricted expression on normal cells.
- Linker
  - Attaches the cytotoxic agent to the antibody. Newer linker systems are designed to be stable in circulation and release the cytotoxic agent inside targeted cells.
- Cytotoxic agent
  - Designed to kill target cells when internalized and released.

Bispecific T-Cell Engaging Antibody (BiTE)

- Made up of 2 different mAbs
  - Attach to 2 different proteins at the same time
    - CD19 and CD3
- Approved Agent
  - Blinatumomab (Blincyto®)
    - Acute lymphoblastic leukemia

Therapeutic Antibodies

- **Adverse Effects:** infusion-related reactions, chills, fever, immunosuppression, fatigue
  - ADCs: neuropathy, skin rash
  - BiTE Antibody: edema, neurotoxicity, headache, skin rash, febrile neutropenia, CRS

- **Ongoing Research:**
  - Nononcologic uses
  - Combination therapy
  - Maintenance therapy
  - Timing of therapy

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Immune System Modulators

- **Use proteins that normally help regulate or modulate immune system activity to enhance body’s immune response against cancer**

- **Given by themselves or as adjuvants**
  - Cytokines: chemicals made by some immune system cells
    - Control growth and activity of other immune system cells and blood cells

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Immune System Modulators (continued)\textsuperscript{1}

• **Approved Agents**
  – **Interferon alpha**: leukemia, melanoma
    • Helps body resist viral infections and cancers
    • Boosts ability of certain immune cells to attack cancer cells
    • Directly slows growth of cancer cells, and blood vessels
  – **Interleukin-2 (IL-2)**: melanoma, renal-cell carcinoma
    • Helps immune system cells grow and divide more quickly
  – **Talimogene laherparepvec (Imlygic\textsuperscript{®})**: melanoma
    • Oncolytic virus modified to make GM-CSF to boost immune response


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Immune System Modulators (continued)\textsuperscript{1}

• **Interferon alpha**
  – **Adverse Effects**: headache, fatigue, rigors, insomnia, alopecia, nausea, vomiting, neutropenia, increased liver function tests, weakness, myalgias, arthralgias, fever
  – **Ongoing Research**: combination therapy, primarily melanoma, renal cell, leukemia, hepatocellular carcinoma, and non-oncologic disease states

• **Interleukin-2 (IL-2)**
  – **Adverse Effects**: capillary leak syndrome (hypotension, edema, increased serum creatinine), fever, chills, confusion, malaise, weakness, skin rash, diarrhea
  – **Ongoing Research**: combination therapy, dosing strategy, leukemia, lymphoma, graft versus host disease, melanoma, renal-cell cancer, neuroblastoma

• **Talimogene laherparepvec (Imlygic\textsuperscript{®})**
  – **Adverse Effects**: fatigue, chills, nausea, vomiting, diarrhea, injection-site pain, flu-like symptoms
  – **Ongoing Research**: combination therapy, melanoma, breast cancer, sarcoma

Combination Therapy


Future...What’s Next?1

- **Cancer Treatment Vaccines**
  - Need better understanding of basic biology underlying how immune system cells and cancer cells interact
    - New imaging techniques to observe interaction of killer T-cells and cancer cells
  - Identify mechanisms of cancer cell evasion or suppression of anticancer immune response

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Future...What’s Next? (continued)1

- **Cancer Treatment Vaccines**
  - Areas of research
    - Identification of novel cancer-associated antigens or neoantigens that may be more effective in stimulating immune response
      - Early phase clinical trials testing neoantigen-based personalized vaccine for patients with glioblastoma and melanoma
    - Development of methods to enhance ability of cancer-associated antigens to stimulate immune system
    - Determine how to combine multiple antigens within a single cancer treatment vaccine to maximize immune response

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Future...What’s Next? (continued)¹

• **Cancer Treatment Vaccines**
  – Agents in development
    • Dendritic cell vaccines: renal-cell carcinoma, glioblastoma, prostate cancer
    • Autologous tumor cell vaccines: colorectal cancer, follicular lymphoma
    • Anti-idiotypic vaccines: lymphomas and some solid tumors
    • Allogeneic vaccines: lung cancer
    • DNA-based vaccines: metastatic breast cancer


Future...What’s Next? (continued)¹

• **Immune Checkpoint Modulators**
  – Need better understanding why checkpoint inhibitors are effective in some patients and not others
  – Areas of research
    • Identifying ways to expand use in other cancers
    • Combination therapy
      – PD-1 and CTLA-4 inhibition, combination with chemotherapy

Future...What’s Next? (continued)¹,²

• Immune Checkpoint Modulators
  – Agents in development:
    • Anti-GITR (glucocorticoid-induced tumor necrosis factor [TNF] receptor) antibody: enhance immune system response by enabling T-cells to be more effective in attacking cancer cells
    • IDO (indoleamine-2,3 dioxygenase) inhibitor: prevents tumor invasion of immune system by preventing tryptophan depletion and starvation of cytotoxic T-cells within tumor microenvironment
    • LAG-3 (lymphocyte activation gene 3) antibody: given with PD-1 inhibitor to work together to suppress antitumor T-cell immune response and restore T-cells to full function resulting in stronger antitumor immunity
    • 4-1BB also known as CD137 antibody: costimulatory agent for activated T-cells; stimulates first wave of antitumor reaction
    • OX40 (CD134) agonist: augments T-cell differentiation and cytolytic function leading to enhanced antitumor immunity against tumors
    • TIM3 (T-cell immunoglobulin mucin 3) antibody: block cell surface receptor on effector T-cells to produce tumor regression


Future...What’s Next? (continued)¹⁻³

• Immune Cell Therapy
  – CAR T-Cell Therapy
    • Need to improve management of side effects, identify appropriate patients, refine production process
  – TILs
    • Need to improve methods of obtaining TILs from patients

• Areas of Research
  – CAR T-Cell Therapy: development of better receptors and identification of better targets
  – TILs: application in melanoma and other solid tumors

Future...What’s Next? (continued)1-3

• Therapeutic Antibodies
  – Need to decrease immunogenicity and adverse effects, develop using parts of antibodies to increase efficacy, continue to create bispecific antibodies

• Areas of Research
  – Combination therapy
  – New targets
  – New and radiolabeled ADCs
  – Bispecific antibodies


Future...What’s Next? (continued)1-4

• Agents in development
  – ESK1 antibody: targets protein called WT1 inside cancer cells
  – IMMU132: ADC with SN38 as toxin attached to TROP2 inhibitor
  – Catumaxomab: trifunctional bispecific antibody - Anti-EpCAM x Anti-CD3
  – AFM13: tetravalent bispecific antibody - CD30 + CD16

Future...What’s Next? (continued)\textsuperscript{1,2}

- **Immune System Modulators**
  - Need to improve upon side effects of interferon and IL-2
  - Need better understanding of tumor biology and virology to maximize efficacy

- **Areas of Research**
  - Combination therapy
  - Utilizing different viruses
  - Altering host immune response to virus to prevent immune system from targeting virus

- **Agents in Development**
  - GL-ONC1: oncolytic vaccinia virus (Lister strain - used as vaccine against smallpox)
  - Ad5-yCD/mutTKSR39rep-hIL12: oncolytic adenovirus-mediated cytotoxic and IL-12 gene therapy
  - HSV1716: oncolytic herpes simplex virus


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**Learning Objectives**

- Outline the main mechanisms of action of immuno-oncology agents
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Questions

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