Cancer Immunotherapy
Review: Oncology Perspective
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Kaleidoscope of Oncology Care
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Speaker Disclosures
• Consultant and speaker for Dendreon
• Consultant for Bayer
• Consultant and speaker for Sanofi-Aventis
• Research support from Prometheus

Learning Objectives
• Review the evidence supporting the immune system’s role in cancer and the characteristics of an immune response
• Describe several mechanisms of immunotherapy
• Discuss treatment considerations for cancer immunotherapy
Talk Outline

- Immune System's Role in Cancer
- Immunotherapy Landscape
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

Cancer Pathogenesis: Formerly Characterized by 6 Hallmarks

Cancer Pathogenesis: Immune Evasion Now Recognized as a Hallmark
Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems\(^1\)\(^2\)
- Tumor / cancer risk in transplant patients compared to general population\(^1\)\(^2\)

Immune Cells Within Tumors Predicts Overall Survival

- T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers\(^1\)\(^2\)

Immunotherapy Proven Effective in Cancer

- Therapies that engage the immune system have been shown to improve patient survival in randomized, phase 3 cancer trials\(^1\)\(^2\)
- Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers\(^4\)
Dynamics Between Cancer and the Immune System

• In a dynamic process, the immune system can either
  – Block tumor growth, development, and survival
  – Allow tumor outgrowth

Dynamic Process Described by 3 Phases

• The 3 E’s
  – Elimination
  – Equilibrium
  – Escape

Elimination: Immune System Eradicates Cancer Cells

• A natural process involved with early disease
Equilibrium: Immune System Controls Cancer Cells

- Occurs with later stage tumors
- Represents a balanced “dynamic” between the immune system and cancer

Immune cells
Abnormal cells / tissue outgrowth controlled


Escape: Cancer Cells Evade Immune System

- Tumor cell variants grow, resulting in progressive disease

Immune cells
Abnormal cells / tissue
Abnormal cells / tissue continue to replicate


Key Components Involved in the Immune Response

- Antigens
  - Molecules produced by microbes or foreign agents that bind to T cells and antibodies
- Antigen presenting cells (APCs)
  - Identify and uptake foreign antigens
  - Present them to T cells
- T cells
  - Activated by APCs
  - Recognize and destroy cells containing foreign antigen
- B cells
  - Produce antibodies specific to foreign antigens

Abbas AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.
Initiation of Immune Response: Key Components

Adapted from Abbas AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.

Features of an Effective Immune Response¹,²

- Specificity
- Trafficking
- Adaptability
- Target elimination
- Durability (immune memory)

Immune Response: Specificity

- Ability of immune cells to identify and target a specific antigen¹

In type 1 diabetes, T cells recognize and destroy only β cells²

Pancreatic islets of Langerhans (normal) Pancreatic islets of Langerhans (type 1 diabetes)

α cells (black) β cells (brown)

α cells (black)

T cell infiltration

Reprinted with permission from Irene Visintin, MD.

¹ Abbas AK, Lichtman AH. Basic Immunology. 3rd ed. 2011.
² Drake CG. Nat Rev Immunol. 2010;10(8);580-593.
**Immune Response: Trafficking**

- Ability of activated immune system cells to migrate to particular antigens throughout the body\(^1\,\,^3\)
- In this example, activated T cells were mobilized to areas containing antigen\(^1\)

**Immune Response: Adaptability**

- Allows for a broader immune response\(^1\) (eg, immune response to additional antigens\(^2\))

**Immune Response: Target Elimination**

- Ability of immune cells to destroy their target (eg, cancer cells)\(^1\,\,^2\)
  - Usually via induction of apoptosis\(^2\)

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**Immune Response: Durability (Immune Memory)**

- Ability of immune system to recognize an antigen to which it has previously been exposed and provide long-lasting protection against it.

Shown is the durable virus-specific T-cell response after smallpox vaccination.

<table>
<thead>
<tr>
<th>Volunteers with CD4+ T-Cell Memory After One Smallpox Vaccination</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Percentage</td>
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**Program Agenda**

- Immune System’s Role in Cancer
- Immunotherapy Landscape
- Clinical Considerations of Immunotherapy
- State of Immunotherapy

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**Immunotherapy**

**Definition**

- Treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases

**Examples in cancer**

- Monoclonal antibodies
- Cytokines
- Checkpoint inhibitors
- Therapeutic vaccines

The Renaissance of Immunotherapy

Types of Immunotherapy

- Cytokines
- Monoclonal antibodies
- Checkpoint inhibitors
- Therapeutic cancer vaccines

Cytokines

- Proteins that are naturally secreted by immune system cells
- Mechanism of action: stimulates T-cell proliferation
- Examples: interleukins, interferons
- Efficacy: high dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma
Cytokines

- Interferon-α (IFN-α): “the control”
  - Median PFS: 4.7 mo
  - Median OS: 13 mo
- High dose Interleukin (IL-2)
  - Response rate: 15-20%
  - 5-7% durable CRs
  - NCI 1986-2006

Medial Overall Survival
CR: Not reached
PR: 39.1 mo
No response: 15.1 mo

Toxicity


Monoclonal Antibodies (mABs)

- Mechanism of action
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death
- Efficacy
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

Checkpint Inhibitors

- Mechanism of action
  - Block immune checkpoints that regulate T cell activation/funcion
- Examples
  - CTLA-4 and PD1
- Efficacy
  - Extends overall survival in certain metastatic diseases
  - A significant effect on PFS not consistently observed

Adapted with permission from Sharma P, Allison JP, et al.
Anti CTLA therapy. Ipilimumab in melanoma


Melanoma

- pembrolizumab (Keytruda, MK-3475)
  - First PD-1 FDA approved (September 2014) 2mg/kg q2W
  - Advanced melanoma (post Ipilimumab and BRAFi if BRAF mutant)
  - Relatively well tolerated (fatigue, pruritus and rash, 2 patients with hepatitis, hypophysitis)
- Nivolumab

nivolumab in untreated melanoma w/o BRAF mutation

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>ORR</th>
<th>DCR</th>
</tr>
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<tbody>
<tr>
<td>Arm A</td>
<td>5.0 mos</td>
<td>24%</td>
<td>57%</td>
</tr>
<tr>
<td>Arm B</td>
<td>4.6 mos</td>
<td>26%</td>
<td>61%</td>
</tr>
</tbody>
</table>

*ORR: Objective Response Rate; DCR: Disease Control Rate*
### Bladder Cancer: MPDL3280

<table>
<thead>
<tr>
<th>PD-L1 tumor infiltrating immune cells</th>
<th>ORR % (95% CI)</th>
<th>Dx+ vs Dx- ORR % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n=10)</td>
<td>50% (22-78)</td>
<td>43% (26-63)</td>
</tr>
<tr>
<td>IHC 2 (n = 26)</td>
<td>40% (21-64)</td>
<td></td>
</tr>
<tr>
<td>IHC 1 (n=23)</td>
<td>13% (4-32)</td>
<td>11% (4-26)</td>
</tr>
<tr>
<td>IHC 0 (n=12)</td>
<td>8% (0.4-35)</td>
<td></td>
</tr>
</tbody>
</table>

- 2 CRs (IHC 2, IHC 3)
- 16 of 17 responding pts had ongoing responses at time of data cutoff
- ORR = 52% (95% CI, 32-70) for Dx+ with ≥ 12 weeks of f/u

Breakthrough therapy designation by FDA
phase II started phase III planned

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### Kidney Phase I Nivo + Ipi

![Graph](image)

Powles et al
ASCO 2014

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### Nivolumab: Hodgkins

![Graph](image)

Hammers et al
ASCO 2014

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[3/16/2015]
Cellular Therapy

- **Heme.** Chimeric antigen receptor (CAR) Modified T-Cells
  - Targeting CD 19 (CLL, NHL, ALL and others)
  - Leukopheresis, expose T cells to lentivirus …
- Nearly 50% RR in heavily treated patients
- Toxicity relatively well tolerated
  - Reversible hepatotoxicity, renal toxicity
  - Reversible tumor lysis syndrome
  - B cell aplasia (toxicity or efficacy?)
    - Supported with IVIG
  - No excessive or frequent infections
  - Cytokine release syndrome

David Porter

Therapeutic Cancer Vaccines

- **Mechanism of action**
  - Activation of T cells to seek out and destroy target cancer cells

- **Efficacy**
  - Extended overall survival in certain metastatic diseases without an effect on PFS

Preventive vs Therapeutic Vaccines

“Cancer treatment vaccines are designed to treat cancers that have already developed. They are intended to delay or stop cancer cell growth; to cause tumor shrinkage; to prevent cancer from coming back; or to eliminate cancer cells that have not been killed by other forms of treatment.”

- NCI (2011)
Characteristics of Immunotherapy

<table>
<thead>
<tr>
<th>ACTIVE</th>
<th>PASSIVE</th>
</tr>
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<tbody>
<tr>
<td>Engages immune system</td>
<td>Enhances pre-existing immune response</td>
</tr>
<tr>
<td>Durable</td>
<td>Short-lived</td>
</tr>
<tr>
<td>Some examples: therapeutic cancer vaccines</td>
<td>Some examples: mAbs, cytokines</td>
</tr>
</tbody>
</table>

Characteristics of Therapeutic Vaccines

<table>
<thead>
<tr>
<th>Therapeutic Vaccines</th>
<th>Immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Immune system</td>
</tr>
<tr>
<td>Response Kinetics</td>
<td>Delayed</td>
</tr>
<tr>
<td>Potential for Memory Response</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor Evolution Potential</td>
<td>New immunologic targets</td>
</tr>
<tr>
<td>Patient Considerations</td>
<td>Requires uncompromised immune system (both systemically and at tumor site)</td>
</tr>
<tr>
<td></td>
<td>Tolerable safety profile</td>
</tr>
</tbody>
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Program Agenda

- Immune System’s Role in Cancer
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- State of Immunotherapy
Immunotherapy: Treatment Considerations

- Relative efficacy of immunotherapy may be greater with lower tumor burden\(^1,2\)
- Patient given immunotherapy earlier in disease course might have a better outcome\(^3\)

Tumor Growth Rate

Tumor Burden

Time

- Expected clinical outcome if no treatment is provided
- Death
- Patient given a vaccine earlier
- Patient given a vaccine later

Adapted with permission from Gulley JL, Drake CG.\(^3\)

Immunotherapy: Treatment Considerations

- Standard practice in oncology is the use of combination agents with different mechanisms of action\(^1-3\)
  - Chemotherapy and mAbs
  - Radiation and chemotherapy
  - Multiple chemotherapy regimens
- Immunotherapy offers potential for synergy with other therapies\(^1-6\)

Program Agenda

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Immunotherapy: An Established Treatment Strategy

- More than a dozen different immunotherapy agents have been approved\(^a\), with the majority over the last decade\(^1-5\).
- Immunotherapy agents currently approved target >10 different cancer types\(^1-5\).

<table>
<thead>
<tr>
<th>FDA-Approved Immunotherapies(^a)</th>
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<tbody>
<tr>
<td>Class</td>
</tr>
<tr>
<td>Checkpoint inhibitor</td>
</tr>
<tr>
<td>Therapeutic vaccine</td>
</tr>
</tbody>
</table>

\(^a\)Not inclusive of all immunotherapy classes.


Immunotherapy: Future Promise

- Rapid increase in immunotherapy clinical research
  - Doubling of abstracts at major conferences from 2009 to 2012
  - Approximately 800 clinical trials in various phases ongoing
    - eg, breast, colon, head and neck, kidney
- Trials utilize agents alone and in combination with conventional therapies\(^2\)

HER2 targeted therapy

- Breast cancer historically not considered immune responsive cancer
  - HER2\(^+\) and TNBC may be exceptions
  - Immune-related gene expression signatures
  - Prognostic value of TILs
- High levels of TILs are associated with benefit to trastuzumab and chemotherapy

Loi et al, 2013
Mahmoud et al, JCO 2011
Summary

- The immune system plays a critical role in controlling cancer.¹
- Key features of an effective immune response include:
  - Specificity
  - Adaptability
  - Durability (immune memory)
- Future clinical considerations:
  - May elicit better immune system response if used earlier in disease.²⁻⁴
  - Potential for durable clinical effects and synergy with subsequent therapies.⁵⁻⁸


Questions?