The Emerging Role of Immunotherapy in Cancer Care 2015

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I have no conflicts to disclose with respect to this presentation.
Learning Objectives:

1. Discuss the emerging role of immunotherapy in cancer care
2. Describe two new targeted therapies for cancer approved in the last 24 months
3. Define the terms prognostic marker and predictive marker
Improved survival remains a challenge in some advanced cancers

- 5-year survival remains poor for many patients with advanced metastatic solid tumors
- In the United States, it is estimated that:
  - A total of 589,430 deaths due to cancer will occur in 2015

There is an ongoing need for new treatments and therapeutic modalities for patients with advanced cancers

Hallmarks of cancer

As normal cells progressively evolve to a neoplastic state, they can acquire a succession of hallmark capabilities:

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Activating invasion and metastasis
4. Resisting cell death
5. Inducing angiogenesis
6. Enabling replicative immortality
7. Deregulating cellular energetics
8. Avoiding immune destruction

For Immuno-Oncology therapies (I-O therapies) to work, they generally incorporate an understanding of the mechanisms of tumor escape.

I-O therapies seek to modulate the immune system to promote antitumor activity, and counteract this hallmark.

*Emerging hallmarks

References:
1. Hanahan D, Weinberg RA. Cell. 2011; 144(5) 646-674
Immuno oncology is an evolving cancer treatment modality through I-O research, therapies are being investigated in an attempt to utilize the body’s own immune system to fight cancer.

Components of the immune system

**Antigen-presenting cells**
- take up antigens from infected or malignant cells and processes them into shorter peptide segments.
- present antigen to T cells to mobilize an immune response.

**Tumor-associated antigens**
- are abnormal cell substances/proteins (tumor antigens) which can be recognized and responded to by the immune system.

**T cells**
- have T-cell receptors, which can recognize tumor-associated antigens.
- play a major role in killing infected or malignant cells when activated.
- help perpetuate ongoing immune responses.

Components of the Immune System

**B cells**
- display B-cell receptors, which can bind free floating antigens in the blood or lymph
- once activated, B cells differentiate to become plasma cells which can secrete large quantities of antibodies against a specific antigen

**Antibodies**
- are secreted by activated B cells, called plasma cells
- tag antigen-containing cells for attack by other parts of the immune system, or neutralize their targets directly by blocking important mechanisms

**NK cells**
- can recognize infected or malignant cells innately without contact with an antigen-presenting cell or antibody (this allows NK cells to launch rapid responses against stressed cells)
- can also attack based on recognition of antibodies on a cell surface

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Immune system pathways

• Under normal conditions, there are a number of immune activation and inhibition pathways that modulate the immune response and protect healthy tissues from collateral damage during an immune response.\textsuperscript{1,7}

• Tumor evasion of the immune system may be associated with an imbalance in immune activation and inhibition.\textsuperscript{1-5}

Tumors may down-regulate co-stimulatory pathways.\textsuperscript{2-3}

Co-stimulatory receptors include:

• CD28
• CD40
• OX40
• CD137

Tumors may up-regulate immune checkpoints (inhibitory signaling pathways).\textsuperscript{2,3,5,6}

Checkpoint pathway molecules include:

• LAG-3
• CTLA-4
• B7-H3
• PD-1

Immuno-Oncology: Immune System Activating Pathways

- **Activating pathways** enable cytotoxic activity by binding to receptors or ligands on APCs; they can also be expressed or preferentially upregulated by tumor cells\(^1\)-\(^4\)
- Several activating receptors are thought to be involved in regulating **NK Cell** activity, including CD137 and SLAMF7\(^1,2\)
- **T-cell** activity may be regulated by pathways, including CD40, CD137, CD28, and OX40\(^3,4\)

APC, antigen-presenting cell; NK, natural killer.
**Immuno-Oncology:**
**Immune System Inhibitory Pathways**

- Tumors may enhance **inhibitory pathways** to block NK cell and T-cell activation\(^1\)\(^-\)\(^3\)
- Several inhibitory receptors are thought to be involved in regulating **NK cell** activity, including inhibitory KIRs\(^2\),\(^3\)
- **T-cell** activity may be negatively regulated by pathways including LAG-3, CTLA-4, B7-H3, and PD-1\(^2\)

*Defined receptors are not yet known and precise mechanism of T-cell inhibition by B7-H3 is currently unknown.*

KIR, killer-cell immunoglobulin-like receptor; NK, natural killer.
Immune Surveillance: Identification and Elimination of Cancer Cells by the Immune System


APC, antigen-presenting cell; NK, natural killer.
B Cell–Mediated Cytotoxicity

B cells

Immune cells that bind free-floating antigens in the blood or lymph through B-cell receptors

Activated B cells

Once activated, B cells differentiate to become plasma cells, which can secrete large quantities of antibodies against a specific antigen

Mature B cell

Natural Killer cells

Cytotoxic lymphocytes that attack infected or malignant cells based on recognition of antibodies on a cell surface

NK cells

Tumor cells

Tumor-associated antigens

Apoptotic tumor cell

NK, natural killer.

T Cell–Mediated Cytotoxicity

**Antigen-presenting cells**\(^1,2\)

Take up antigens from infected or malignant cells and process them into shorter peptide segments

APCs present antigens to naïve T cells, which can recognize tumor-associated antigens

Together with a second, positive co-stimulation signal, T cells become activated...

...and play a major role in killing infected or malignant cells when activated

APC, antigen-presenting cell.
Immune Evasion in the Tumor Microenvironment

- The tumor microenvironment, a network of cells and structures that surround a tumor, creates conditions that may foster tumor growth and immune evasion\(^1,2\).
- Immune cell activity is regulated by multiple activation and inhibition pathways that modulate the duration and level of the immune response\(^2\).
- Tumors may target these pathways to alter the immune system’s response to cancer cells, resulting in tumor evasion of the immune system\(^3\).

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Immunotherapies Encompass a Wide Variety of Classes

Immunotherapy\(^1,^2\)

**Passive**
*(Designed to act on the tumor)*
- Antitumor mAbs
  - Tumor-directed mAbs
- Adoptive
  - Cell therapies

**Active**
*(Designed to act on the immune system itself)*
- Cytokines
  - Interleukins
  - Interferons
- Therapeutic cancer vaccines
- I-O therapies
  - Cell-based
    - Single antigen/peptide-based
  - Immune effector cell modulators
    - Checkpoint inhibitors
    - Co-stimulatory agonists

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I-O, immuno-oncology; mAb, monoclonal antibody.
**Interleukin 2**

- Has pleiotropic effects on both cytotoxic T cell function as well as Treg cell maintenance

  - High dose – promotes CD8+ effector T cell and natural killer (NK) cytolytic activity and promotes differentiation of CD4+ cells into T helper subclasses

  - Lower Dose – preferentially expands Treg populations and inhibits the formation of Th17 cells implicated in autoimmunity
Interleukin 2 (cont.):

- High dose achieved durable responses in a small percentage of patients with metastatic renal cell carcinoma and melanoma
- First example of an immunotherapy that could eliminate cancer cells
Interferon alpha 2B:

- Promotes TH-1-mediated effector cell responses such as IL-12 secretion
- Used in the past as an adjuvant treatment for high risk melanoma - ? impact on long term survival
Lenalidomide and Pomalidomide:

- Mediate an antitumor effect largely via the cereblon-mediated destruction of Ikaros-family proteins which in turn inhibit IL-2 secretion

- Prolong survival in multiple myeloma
Known molecules involved in inhibition

**LAG-3** (aka CD223) is an immune “checkpoint” molecule.¹
- It can **inhibit T-cell activity** and serve as a modulator of T-cell activation.¹,²

**CTLA-4** is an immune “checkpoint” receptor that plays a key role in modulating T-cell function.¹,³
- Interaction of CTLA-4 on T cells with its ligand CD80 (aka B7-1) and CD86 on APCs leads to **T-cell inhibition**.¹,³
CTLA 4 inhibitors:

- Considered a physiologic brake on CD4+ and CD8+ T cell activation

- Ipilimumab – first checkpoint inhibitor to be FDA approved, based on its ability to prolong survival in metastatic melanoma
  - Also has a survival impact on high risk Stage 3 melanoma
Known molecules involved in inhibition

**B7-H3** (a member of the B7 family) is thought to be an immune “checkpoint” pathway.\(^1\)
- It may inhibit the T-cell response beyond CD80/CD86 T-cell response.\(^2\)
- Precise mechanism is under investigation.

**PD-1** is an immune “checkpoint” receptor that inhibits the T-cell response and plays a key role in modulating T-cell function.\(^1\)

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PD-1:

- Expressed on the surface of multiple tissue types and many tumor cell types
- Its interaction with PD ligand (1 or 2):
  - Directly inhibits apoptosis of the tumor cell
  - Promotes T effector cell exhaustion
  - Serves as a brake on unrestrained cytotoxic T effector cell function
Immune Evasion in the Tumor Microenvironment

- The tumor microenvironment, a network of cells and structures that surround a tumor, creates conditions that may foster tumor growth and immune evasion\(^1,2\)
- Immune cell activity is regulated by multiple activation and inhibition pathways that modulate the duration and level of the immune response\(^2\)
- Tumors may target these pathways to alter the immune system’s response to cancer cells, resulting in tumor evasion of the immune system\(^3\)

**Diagram:**

- **Tumor cells**
- **Tumor-associated antigens**
- **APC (antigen-presenting cell)**
- **Active T cell**
- **Inactive T cell**

**References:**
Nivolumab (Opdivo):

1. Improved survival and less toxic as compared to docetaxel in chemotherapy pretreated patients with squamous nonsmall cell lung cancer (Checkmate-057 - 582 patients – ASCO 2015 LBA 109)

2. Improved survival (9.2 versus 6 months; p= 0.00025) and less toxic as compared to docetaxel in chemotherapy pretreated patients with nonsquamous nonsmall cell lung cancer (Checkmate-017 264 patients)
Nivolumab (Opdivo):

3. Improved progression free survival (PFS) as first line monotherapy or in conjunction with ipilimumab therapy in metastatic melanoma, as compared to ipilimumab alone (Checkmate-067 – 945 patients)
Pembrolizumab (Keytruda):

1. Approved by the FDA in 2014 for the treatment of patients with metastatic melanoma following treatment with BRAF inhibitors and/or ipilimumab (Keynote 001 – Lancet 2014;384:1109-1117)

2. Ongoing trials in nonsmall cell lung cancer
MPDL3280A (Genentech/Roche):
1. A human mAB that targets PD-L1
2. It prevents binding of PD-L1 to its receptor (PD-1 and B7-1), thereby restoring T cell activity and proliferation
3. Effective and relatively safe in several early phase lung cancer trials
Tumor types in which these agents may be effective:

1. Metastatic melanoma
2. Nonsmall cell lung cancer
3. Renal cell carcinoma
4. Hodgkin’s Disease
5. Hepatocellular carcinoma
6. Triple negative breast cancer
7. Ovarian cancer
8. Certain colorectal cancers
# Potential Patterns of Response to I-O Therapy

Therapies that affect the immune system may not induce a measurable impact on tumor growth immediately after administration. Potential effects may be seen weeks to months after initial administration. The potential patterns of response to I-O therapies that modulate T-cell activity are:\(^{1,2}\):

<table>
<thead>
<tr>
<th>Immediate response(^3)</th>
<th>![Image of immediate response]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of tumor shrinkage but a slowing of tumor progression(^3)</td>
<td>![Image of lack of tumor shrinkage]</td>
</tr>
<tr>
<td>Early but clinically insignificant progression(^3)</td>
<td>![Image of early progression]</td>
</tr>
<tr>
<td>Tumor regression after early radiographical progression that may be caused by T cells infiltrating the tumor site or appearance of new lesions upon imaging(^3,4)</td>
<td>![Image of tumor regression]</td>
</tr>
</tbody>
</table>

There is also the potential that patients may not respond to therapy.

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I-O, immuno-oncology.

Non-Conventional Response and I-O Therapy

Apparent progression upon radiographic imaging after initial I-O therapy can actually be a sign of non-conventional response to I-O therapy. This response may occur when T cells infiltrate the tumor site and cause tumors to flare or appearance of new lesions upon imaging.\(^1,2\)

Differentiating Disease Progression From Non-Conventional Response With I-O Therapy

- T-cell infiltration can cause tumors to flare or new lesions may appear upon imaging\(^1\)
- Considerations that may indicate disease progression vs. non-conventional response include\(^1,2\):

<table>
<thead>
<tr>
<th></th>
<th>Disease Progression</th>
<th>Non-Conventional Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>Deterioration of performance</td>
<td>Remains stable or improves</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Worsen</td>
<td>May or may not improve</td>
</tr>
<tr>
<td>Symptoms of tumor</td>
<td>Present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td>enlargement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor burden Baseline</td>
<td>Increase</td>
<td>Increase followed by response</td>
</tr>
<tr>
<td>New lesions</td>
<td>Appear and increase in size</td>
<td>Appear then remain stable and/or subsequently respond</td>
</tr>
<tr>
<td>Biopsy may reveal</td>
<td>Evidence of tumor growth</td>
<td>Evidence of T-cell infiltration</td>
</tr>
</tbody>
</table>

I-O, immuno-oncology.
Immune-mediated adverse reactions related to T-cell modulation may affect certain organ systems

Clinical Implications of Immune-Mediated ARs

Since I-O can increase immune system activity, the potential exists for toxicity against healthy tissues in addition to cancer cells\(^1\)

- ARs can be serious and potentially fatal\(^2,3\)
  - An AR is any unfavorable medical occurrence temporally associated with the use of a medical treatment\(^2\)
  - Serious ARs are defined as any AR that requires hospitalization, is life-threatening, results in death, or otherwise causes persistent or significant incapacity\(^3\)

- Remain vigilant throughout and after treatment\(^4\)
  - Educate and encourage patients to monitor for and report symptoms of immune-mediated ARs

Not all immune-mediated ARs will require permanent cessation of therapy. Providing optimal care for your patients includes following management algorithms for certain immune-mediated ARs.\(^4\)

AR, adverse reaction; I-O, immuno-oncology.
Prognostic Marker:

1) Used to classify an individual patient’s risk of, or time to, cancer death and/or other disease events independent of the effects of treatment.

2) Can also be used to determine the need for further treatment
   - Patients at very low risk of disease events can safely avoid treatment if risks of adverse events outweigh the estimated benefits.
   - Alternatively, high-risk patients may benefit from a more aggressive treatment regimen

3) In some cases, a prognostic marker also predicts treatment response because it is also a therapeutic target (i.e., it is also a predictive marker).
   - For example, estrogen receptor expression provides prognostic information in women with early breast cancer and RCTs have provided evidence that it predicts response to hormonal therapy
Prognostic Marker:

- Usually an indicator of growth, invasion and metastatic potential

Examples:
- Weight loss
- Poor performance status
- Sites of metastases (bone, CNS, etc.)
- Hormone receptor positivity in breast cancer
- Weight loss
- HER 2 over expression in breast cancer
Predictive Marker:

1) Used to classify response to specific treatment options; predictive markers are used to guide the selection of treatment and identify targets for the development of new molecular-targeted therapies.

2) Used to select the most appropriate treatment by identifying patients most likely to respond and avoiding treatment for patients unlikely to respond or those at unacceptably high risk of adverse events.

3) Classify patients according to their predicted response or resistance to a treatment

4) The use of predictive markers clearly has enormous clinical implications to optimize the selection of treatments to those patients most likely to respond and avoid the use of treatment in patients unlikely to respond, or those at high risk of treatment-related adverse events.

5) Non-responders may benefit from the earlier use of alternative therapies or can be identified as a population in need for the development of new treatments
Predictive Marker:

1. Such markers are usually within the target of the treatment or the surrounding stroma

   Or

2. Serve as modulators or epiphenomena related to expression and/or function of the target

Examples:
- Hormone receptor positivity in breast cancer
- HER 2 overexpression in breast cancer
- EGFR mutations and ALK gene rearrangements in lung cancer
- ?PD-1 ligand expression in lung cancer
CANCER THERAPY 2015

- Assay Development
- Analytical validation
  - Assess assay performance, reproducibility, sensitivity and specificity
- Clinical validation
  - Prospective-retrospective validations (investigators blinded to outcome data)
- Clinical utility
  - Use of convenience samples and data – subject to bias
  - Second prospective-retrospective study (investigators again blinded to outcome)
  - Randomized prospective trial
Predictors of response to immune-based therapy

**PD-1 inhibitors:**

1. PD-L1 expression – efficacy of nivolumab was more significant in pretreated patients with nonsquamous nonsmall cell lung cancer (Checkmate 057).

2. PD-L1 expression was not linked with efficacy outcome in squamous nonsmall cell lung cancer (Checkmate 017)

3. PD-L1 expression in tumors correlates with response to MPDL3280A (a PD-L1 inhibitor) in the POPLAR Study (ASCO 2015, abstract 8010)

4. MMRD (mismatch repair deficiency) – correlation with benefit in a phase 2 study of patients with metastatic colorectal cancer and other tumor types with MMRD (ASCO 2015, abstract LBA 100)
PD-1 inhibitors and PD-L1 inhibitors are emerging as novel immune modulating agents for the treatment of various refractory cancers.

The side effects associated with these agents are autoimmune in nature (pneumonitis, hepatitis, colitis, dermatitis, thyroiditis, etc).

No definitive predictive marker for PD-I inhibitors has emerged as of yet; the role of PD-L1 remains controversial.
IMMUNO ONCOLOGY IS AN EVOLVING CANCER TREATMENT MODALITY
1. Knowledge of the molecular phenotype of the cancer
2. Knowledge of the pharmacogenomics of the patient
3. Knowledge of the angiogenic profile/status of the cancer
4. Knowledge of the immunocompetence of the patient
5. Understanding of the comorbidities of the patient
The Conquest of Cancer

1. Knowledge of the molecular footprint of the tumor
   1. Susceptibility to one or a combination of targeted therapies
   2. Needs to be in real time and with the understanding of possible metastatic site heterogeneity
2. Knowledge of the pharmacogenomics of the patient
   1. Verification that the therapeutic molecule will achieve therapeutic concentrations and will be appropriately metabolized
   2. Knowledge of drug/drug interactions during administration of the therapeutic agent
3. Knowledge of the angiogenic profile/status of the tumors
   1. Determine that in fact the appropriate targeted agent, metabolized appropriately, can effectively arrive at its target at every site
4. Knowledge of the immunocompetence of the patient

Some tumors co-opt the patient’s immune system so as to be able to evade it.

A perfect vaccine may not work in every patient in light of a different level of immune competency, which in turn can be impacted by:

1. Age
2. Exposure to prior immunosuppressive/immune destroying agents
5. Understanding of the co-morbidities of the patient

The perfect treatment, in the perfect context (pharmacogenomics, etc, that arrives to target (appropriate angiogenic profile), but exacerbates two of the four co-morbidities that the patient has, thus not conferring a survival benefit.
1. Knowledge of the molecular phenotype of the cancer
2. Knowledge of the pharmacogenomics of the patient
3. Knowledge of the angiogenic profile/status of the cancer
4. Knowledge of the immunocompetence of the patient
5. Understanding of the comorbidities of the patient