Immunotherapy Update

Perspectives from a melanoma oncologist

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Disclosures

- I have nothing to disclose.
Outline

- Immunology 101
- Cancer Immunotherapy
  - Definition
  - Non-specific vs Specific
  - Mechanisms of Action
- Clinical Importance
  - Applications in Asian Health
- Future Directions

Immunology 101

- Self vs Non-self
- Mechanisms of central vs peripheral tolerance

“I am convinced that the development of aberrant cells occurs very frequently… but that these foci luckily remain completely latent in most humans because of protective mechanisms in the host. If these mechanisms were not existent, cancer would probably develop with incredible frequency.”

Paul Ehrlich (1854-1915)
The “Cancer-Immunity Cycle”

Cancer cells have developed ways to evade the host immune system by taking advantage of mechanisms of peripheral tolerance.

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Cancer Immunotherapy

- Clarifying “Immunotherapy” vs “Chemotherapy”
- Immunotherapy = treatment that uses the immune system to fight cancer by:
  - Providing immune system components to “boost” immune function (non-specific)
  - Stimulating/training immune system to work harder and/or smarter to attack cancer cells (specific)

Types of Immunotherapy (FDA approved)

<table>
<thead>
<tr>
<th>Non-specific</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>Immune checkpoint inhibitors</td>
</tr>
<tr>
<td>• Interferon</td>
<td>• CTLA-4</td>
</tr>
<tr>
<td>• IL-2</td>
<td>• PD-1/PD-L1</td>
</tr>
<tr>
<td>Oncolytic viruses</td>
<td>T-VEC</td>
</tr>
<tr>
<td>Manipulation of T cells</td>
<td>CAR T cells</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Sipuleucel-T</td>
</tr>
</tbody>
</table>
**Immune Checkpoint Inhibition**

- ipilimumab (Yervoy)
- pembrolizumab (Keytruda)
- nivolumab (Opdivo)
- avelumab (Bavencio)
- atezolizumab (Tecentriq)
- durvalumab (Imfinzi)


**CTLA-4 vs PD-1**

- **CTLA-4**
  - Stops potentially autoreactive T cells at initial stage of naïve T cell activation (lymph node)
  - CTLA-4 blockade → activation + proliferation of more T cell clones, reduces Treg-mediated immunosuppression

- **PD-1**
  - Regulates previously activated T cells at later stages of immune response (peripheral tissues)
  - PD-1 blockade → restores activity of antitumor T cells that have become quiescent


**CD8 T cell infiltration with pembrolizumab**


**Melanoma response to ipilimumab + nivolumab**

Dec 2016 Sept 2017
OS Estimates from CheckMate-037

RFS Estimates for Adjuvant Immunotherapy

Oncolytic Viruses

Tamilargene laherparepvec or T-VEC (Imlygic)
- First-in-class intratumoral oncolytic viral therapy
- Modified HSV-1 virus
T Cell Manipulation

- Manipulating patient-specific T cells ex vivo to make them more reactive to specific antigens
- Chimeric antigen receptor (CAR) T cells

CAR T Cell Therapy

- Tisagenlecleucel (Kymriah) approved Aug 2017 for patients up to 25 yo with B cell precursor ALL that is refractory or in second or later relapse
- First in class gene therapy; one-time treatment
- 4-1BB costimulatory domain to enhance cellular expansion, persistence

Vaccines

- Long history of attempts to harness adaptive immune system’s ability to recognize cancer antigen to effect antitumor response
- Choice of antigen
  - Simple peptides (easy to administer but narrow spectrum)
  - Whole cell preparations (broader range but costly, time-consuming)
- Single-peptide vaccine results have been largely disappointing in melanoma

Sipuleucel-T (Provenge)

- Sole currently approved vaccine-based therapy
- OS benefit in castrate-resistant prostate adenocarcinoma
- Autologous dendritic-cell preparation targeting prostatic acid phosphatase (PAP)
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Why do we care?

- Revolutionary approach to cancer therapy
- **Effective and durable** responses
- Tolerable toxicity profile BUT
  - Watch for late & long-term toxicities

Toxicities of Immune Checkpoint Inhibition

**OCULAR**
- Uveitis/scleritis

**CARDIAC**
- Myocarditis

**ENDOCRINE**
- Hypophysitis
- Thyrotoxicosis
- Adrenal insufficiency
- Diabetes

**GASTROINTESTINAL**
- Diarrhea/colitis
- Hepatitis
- Pancreatitis

**PULMONARY**
- Pneumonitis

**DERMATOLOGIC**
- Rash
- Pruritus
- Vitiligo
- SJS/TEN

**RHEUMATOLOGIC**
- Arthralgia/myalgia

**NEUROLOGIC**
- Motor/sensory neuropathy

Ipilimumab-induced Hypophysitis

"The striking finding is diffuse enlargement of the pituitary which measures 1.3 cm in height, 1.3 cm AP and approximately 1.1 cm maximum transverse. The gland appears heterogeneous without discrete focal mass and bulges superiorly into the suprasellar cistern without definite compromise of the optic chiasm. No evidence of parasellar mass."
### Immune-related Adverse Events (irAEs)

*Table S. Treatment-related Adverse Events, Severity Preparations.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Mild/moderate (Grade 1)</th>
<th>Severe (Grade 2)</th>
<th>Life-threatening (Grade 3)</th>
<th>Life-threatening (Grade 4)</th>
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</tbody>
</table>

**Managing iRAEs: General Principles**

- **Patient education**
- **Evaluate patients prior to infusions (basic labs, H&P)**
- **General principles:**
  - Steroids
    - Burst/quick taper
    - 1-2 mg/kg, taper over 1 month
  - **Immunosuppression**
    - infliximab
    - mycophenolate mofetil
    - cyclophosphamide
  - **Referral to appropriate specialists**

### Common Terminology Criteria for Adverse Events (CTCAE)

- **Toxicity Grade**
  - Grade 1: Toxicity <10% body surface area (BSA)
  - Grade 2: Toxicity 10-30% BSA
  - Grade 3: Toxicity >30% BSA
  - Grade 4: Life-threatening consequences, urgent intervention

- **Skin**
  - Rash
  - Pruritus
- **Diarrhea**
  - Increase of <4 stools over baseline
  - Increase of 4-8 stools over baseline
  - Increase of ≥9 stools, hospitalization indicated, incontinence
- **Hepatotoxicity**
  - AST or ALT >5 x ULN or T. bilirubin >1.5 x ULN
  - AST or ALT >20 x ULN or T. bilirubin >10 x ULN

- **Endocrine, pneumonitis**
  - Asymptomatic
  - Symptomatic
  - Severe symptoms, hospitalization indicated

**References:**
Do Asians Get Melanoma?

• YES!
  • Clinically and genetically heterogeneous disease
  • Predominance of acral lentiginous melanoma (ALM)

Melanoma in the Asian Population

• 42-65% incidence of ALM in studies from Taiwan, China, South Korea, Singapore, Japan
  • Contrast with 2-3% ALM incidence in Caucasian population
  • Presentation at later stage
  • Different risk factors: long-term physical stress, trauma

Different Outcomes in Melanoma Subtypes with Anti-PD-1 Therapy

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FDA Approvals for PD-1/L1 Antibodies

- Melanoma
- Non-small cell lung cancer
- Head and neck squamous cell carcinoma
- Urothelial carcinoma
- Renal cell carcinoma
- Hodgkin lymphoma
- Merkel cell carcinoma
- Microsatellite instability high (MSI-H) colorectal cancer
- Any MSI-H or dMMR (deficient mismatch repair) pediatric/adult solid tumor

Somatic mutation frequency across human cancer types

Identification of Other Checkpoints

- Immune checkpoint inhibitors in other cancers
- Novel combinations
- Targeting other cells in tumor microenvironment
- Biomarker research

Ongoing Investigation
Thank you!
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