Introduction to Immunotherapy

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Virus associated cancer
Mutation associated neoantigens

Adapted from Padmanee Sharma, and James P. Allison Science 2015;348:56-61
Immunoprofiling as a predictor of patient’s response to cancer therapy—promises and challenges
Daniel Bethmann¹,², Zipei Feng²,³ and Bernard A Fox²,⁴

Table 1
Association of immune cell infiltrates with prognosis in cancer

<table>
<thead>
<tr>
<th>Histology</th>
<th>Markers tested*</th>
<th>Type of assessment</th>
<th>Effect on prognosis* and significance ###, #</th>
<th>First author</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>CD3, CD4, CD8, FoxP3, PD-1</td>
<td>Pathologist</td>
<td>High intratumoral number of CD3, CD4 and CD8 is favorable. High peritumoral number of PD-1+ lymphocytes is unfavorable [52]. ##</td>
<td>Kakavand</td>
<td>2015</td>
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<tr>
<td></td>
<td>CD8, CD20, CD45</td>
<td>Pathologist, Aperio Software</td>
<td>High intratumoral density of CD8, CD45 and CD20 is favorable [53]. ##</td>
<td>Erdag</td>
<td>2012</td>
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<tr>
<td></td>
<td>CD4, CD8, CD68, HLA-DR</td>
<td>Pathologist</td>
<td>High intratumoral density of CD4 and CD8 as well as the presence of HLA-DR cells is favorable [54]. #</td>
<td>Piras</td>
<td>2005</td>
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<td></td>
<td>CD3, CD4, CD8</td>
<td>Pathologist</td>
<td>High intratumoral number of CD4 and CD8 is favorable [55]. ##</td>
<td>Al-Batran</td>
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</tbody>
</table>

…87 references in 21 diseases correlating immune profiling with clinical outcome
T cell recognition of tumor cell
T cell function at tumor cell: to kill

Cell death via caspase cascade

Tumor cells

— Granzymes —

T-cell
T cell function at tumor cell: or not to kill

Cell death via caspase cascade

Antigen

FAS-L

FAS

MHC

TCR

ICAM

LFA-1

PDL1

PD1

IDO

TGF-β

IL-10

T-cell

Tumor cells

Treg

CTLA-4
Types of immunotherapy

- **T cell checkpoint modulation**
  - Activating receptors: CD28, OX40, GITR
  - Inhibitory receptors: CTLA-4, PD-1, 4-1BB, BTLA, TIM-3, VISTA, HVEM, LAG-3
  - Agonistic antibodies
  - T cell stimulation
  - Blocking antibodies

- **T cell adoptive transfer**
  - Targeting element: Single-chain variable fragments (scFvs)
  - Spacer
  - Transmembrane domain
  - Costimulatory domain (e.g. CD28 or 4-1BB)
  - CD3ζ: Essential signaling domain

- **Therapeutic cancer vaccines**
  - Viral and bacterial-based vaccines
  - VACCINE

- **Effector antibodies and antibody-drug conjugates**
  - Antibody: Specific to tumor-associated antigen
  - Cytotoxic agent: Designed to kill target cells when internalized and released/activated
  - Linker: Attaches cytotoxic agent to the antibody
Importance of PD1 / PDL1 blockade
PD1/PDL1 inhibition

Rapid, deep durable responses
Across a wide range of tumors
Seen in a subset of patients

NSCLC: Avelumab
Gulley JL et al. *Lancet Oncol* 2017

MSI hi CRC: Nivolumab
Overman MJ et al. *Lancet Oncol* 2017

Urothelial: Atezolizumab

NSCLC (squamous only): Nivolumab
Rizvi NA et al. *Lancet Oncol* 2015

Urothelial Ca: Avelumab
Apolo AB et al. *JCO* 2017

Urothelial: Durvalumab
Massard C et al. *JCO* 2016

HNSCC: Pembrolizumab

Urothelial Ca: Pembrolizumab
Requirements for Effective Immunotherapy
Multi-layered immunosuppression

- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor
Antigen spreading and the tumour immunity cycle

A. Tumour expresses different immunogenic targets
   - Neoepitope #1
   - MUC-1
   - PSA
   - Dying tumour cells

B. Dendritic cell phagocytoses tumour cell along with a transfer of tumour-specific antigens

C. Mature dendritic cell presents tumour-specific antigens to T cells

D. Newly activated tumour-specific T cells form in greater concentration and variation

E. Fully activated T cell destroys tumour cells
Antigen spreading and the tumour immunity cycle
Forest plots of relative risk of any all- and high-grade AEs associated with PD-1/PD-L1 inhibitors versus chemotherapy.

**Any all-grade AEs**

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p value</th>
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<tbody>
<tr>
<td></td>
<td>Robert 2014</td>
<td>0.982</td>
<td>0.878</td>
<td>1.099</td>
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**Any high-grade AEs**

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</table>

Tomohiro F. Nishijima et al. The Oncologist 2017;22:470-479
Kinetics of Immune Related Adverse Effects

Common Medications

• Corticosteroids
  – Prednisone
  – Dexamethasone
  – Methylprednisolone
  – Hydrocortisone
  – Cortisone

• Mycophenolate mofetil (CellCept)
  – Standard BID

• TNF inhibitors
  – Infliximab
  – Adalimumab
  – Others
Conclusions

• Immunotherapy can lead to rapid, deep and durable responses
• Immunotherapy may be curative in some cases
• Future efforts in combination therapy are seeking to expand the proportion of patients with clear clinical benefit
• These should focus not only on generating anti-tumor immune response but making sure effector cells are functional within TME
• Immune related AEs are typically transient and manageable but should be identified and treated promptly
• Overall, immunotherapy is better tolerated than chemotherapy