Basic Concepts in Bladder Cancer Immunotherapy

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BCG Intravesical Immunotherapy

• BCG immunotherapy standard of care NMIBC
• Mechanism is still under investigation, is recognized as immunotherapy
• BCG is internalized by both urothelial cancer cells and immune cells
  – Causes secretion of cytokines and chemokines, and presentation of BCG and/or cancer cell antigens to activate T cells
• Safety: < 5% serious complications
  – Common SE: fever, hematuria, granulomatous prostatitis

Intravesical BCG Immunotherapy

- **BCG**
- **Bladder cancer cells**
- **CD8⁺ T cell**
- **HLA class I**
- **DC Processing and antigen presentation**
- **CD4⁺ T cell**
- **HLA class II**
- **apoptosis**
- **BCG or cancer antigen phagocytosis**
- **Macrophage**
- **NK cell**
- **Th-1 response**
  - IL-2, IL-12, IFN-γ, TNF-β
- **Cytokine production**
  - inflammation
  - side effects
- **Cell-mediated immune response**
Overview of Cancer Immunology and Immunotherapy
Hallmarks of Cancer

The immune system has a major role in cancer pathogenesis

- Avoiding immune destruction
- Evading growth suppressors
- Activating invasion and metastasis
- Enabling replicative immortality
- Inducing angiogenesis
- Resisting cell death
- Resisting growth suppressors
- Sustaining proliferative signaling
- Deregulating cellular energetics

Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems\textsuperscript{1-3}

![Bar chart showing the fold-increase in tumor/cancer risk for different types of cancer in transplant patients compared to the general population.]

- Non-melanoma skin cancer: 20-fold and beyond
- Non-Hodgkin’s lymphoma: 15-fold
- Kidney cancer: 8-fold
- Melanoma: 5-fold
- Hepatobiliary cancer: 3-fold
- Bladder cancer, Testicular cancer, Breast cancer, Prostate cancer, Colon cancer: 2-fold

\textsuperscript{3} Abbas AK, Lichtman AH. \textit{Basic Immunology}. 3rd ed. 2011.
Basics: Immune system and cancer interactions

• Immune system and cancer interact in a dynamic process known as “Immunoediting” or “the 3 E’s”
  – **Elimination**: initial tumor development, low tumor volume immune system can eradicate cancer cells
  – **Equilibrium**: immune system controls cancer growth
  – **Escape**: continued growth; genetic instability tumor heterogeneity takes place and overwhelms the immune system

Immune Evasion of Cancer

Progressive metastatic cancer represents a failure of immune surveillance

Anticancer Immunity is Mediated Through a Multi-step Process

1. Antigens released by cancer cells
2. Antigens presented to T cells
3. T cell priming and activation
4. T cell trafficking to tumors
5. T cell infiltration into tumors
6. T cell recognition of cancer cells
7. Killing of cancer cells

Immune Checkpoints Lead to Promotion or Inhibition of Immune Response


Activating:
CD28; CD137; OX40; GITR; IL-2

Inhibitory:
CTLA-4; PD-L1/PD-1; PD-L1/B7.1
Principles of Cancer Immunotherapy

• Immune response to cancer both stimulatory and inhibitory factors
• Inhibitory immune checkpoints include CTLA-4, PD-1, PDL-1
  – Limit immune response to protect self
  – Often upregulated in tumors and in immune cells invading tumors
  – Results in inhibition of the T cell immune response
  – Allows tumors to more easily “hide” from the immune system
• Checkpoint inhibitors
  – Antibodies block the immune checkpoint to enhance T-cell and other immune cell functions
  – Allow the immune response to expand
  – Examples of FDA-approved inhibitors include:
    • CTLA-4: Ipilimumab
    • PD-1: Nivolumab, Pembrolizumab
    • PD-L1: Atezolizumab

Clinical Cancer Immunotherapy

- Passive Immunotherapy:
  - Monoclonal antibodies directed against growth factors such as bevacizumab (VGEF), cetuximab (EGFR)
  - Chronically administered, no sustainable anti-tumor response
- Active Immunotherapy: induce host response to tumor by T-cell cascade -> CTL
  - Need T-cell for solid tumor kill (cytotoxic T lymphocyte or CTL)
  - T cell cannot respond to naked or circulating antigens
  - Require antigens to be “presented” to T cells on APC (antigen presenting cells)
  - Dendritic cells, Langerhans cells, monocytes, macrophages are APC
  - APC internalize antigens, couple to HLA molecules to “present” on the surface to activate T-cell
  - Immune response depends on stimulatory signals and inhibitory “checkpoints” to avoid excessive production of immune cells such as T cells that could be detrimental to normal tissue
Selected Immunotherapies in Oncology

- **Vaccine based therapies:** T cell activation to seek out tumor cells
  - Eg, Sipuleucel-T, BCG
- **Cytokines:** naturally occurring, modulate immune response
  - Eg, IL-2, interferon-alpha
- **Monoclonal antibodies:** block specific growth factors, etc causing cell death cascade
  - Eg, bevacizumab targeting VGEF

NEWEST THERAPIES

- **Checkpoint inhibitors:** monoclonal antibodies block the immune checkpoint response; “take the brakes off” immune system
  - Eg, CTLA-4, PD-1, PD-L1 inhibitors
- **Chimeric Antigen Receptor (Car) T-cell Therapy**
  - Patient’s T cells are reengineered to recognize cancer (experimental)

Immune Checkpoint Inhibition

PD-1 T cell receptor  PDL-1 tumor ligand
PD-1/PD-L1 inhibitors result in higher response rates across a wide range of tumors than most other immunotherapies

• **Pembrolizumab**: PD-1 monoclonal antibody
• **Nivolumab**: PD-1 monoclonal antibody
• **Atezolizumab**: monoclonal antibody to programmed death ligand 1 (PD-L1)
• **Avelumab**: anti-PD-L1 monoclonal
• **Durvalumab**: anti-PD-L1 monoclonal

Markham A. Drugs. 2016 Aug;76(12):1227-32
PD-1/PD-L1 Activity

Suppression of T-cell response.....“Taking the brakes off”

Why is Bladder Cancer A Good Target for Immunotherapy?
Urothelial bladder cancer (UBC) as an target for immunotherapy

- Patients with UBC have a high rate of somatic mutations similar to tumors associated with tobacco use or environmental carcinogen exposure
- Host immune system can recognize tumor antigens. Antigens detected seen as foreign, stimulating an immune anti tumor response

Basis of Urothelial Cancer Immunotherapy

• High rates of somatic mutations
  – May enhance immune response
• Urothelial cancers may express compounds that suppress the immune system such as programmed death-ligand 1 (PD-L1)
• CD4+ and CD8+ T cells express inhibitory PD-1 to prevent overstimulation of the immune response
• PD-L1/and PD-1 are the immune checkpoints
• Check point inhibitors enhance anti-tumor effects by allowing a more robust immune response

Immune Cells Within Tumors Predict Overall Survival: MIBC Example

- Higher immune cell density (T cells) predictive of survival of patients with MIBC
- Suggests importance of immune response in MIBC

Checkpoint Inhibitors and Biomarkers

• FDA approved complementary diagnostic, the PD-L1 (SP142) assay with atezolizumab
  – detects PD-L1 expression on tumor-infiltrating immune cells
• Phase 1 study of atezolizumab: higher response rates were with higher tumor levels of PD-L1 expression in tumor-infiltrating lymphocytes, not tumor cells.
• While promising, many other PD-L1 antibodies exist limiting generalizability
• Genomic and other testing being utilized to determine best response to a given checkpoint inhibitor

mRNA expression levels of PD1/PDL1 and CTLA4 genes in a series of 155 bladder tumors.

Pignot, et al. J Clin Oncol 34, 2016 (suppl; abstr 4523)
PD-L1 Diagnostic Testing Clinical Experience at the Thomas Jefferson University Hospital

PD-L1 IHC Staining Using Ventana SP142

Urothelial Carcinoma Tumor Cells

Urothelial Carcinoma Tumor-infiltrating Immune Cells

Courtesy of Charalambos C. Solomides, MD, Director of Cytopathology
## Checkpoint inhibitors for systemic use in advanced UC (7/2017)

*(Mark R et al In press American J Hematology Onc)*

<table>
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<th>Generic/Dosing</th>
<th>Brand</th>
<th>Manufacturer</th>
<th>Target</th>
<th>Comp. Biomarker</th>
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<th>Date(s) of UC Approval</th>
<th>Approval in Other Malignancies</th>
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<td>Genentech</td>
<td>PD-L1</td>
<td>VENTANA PD-L1 (SP142)*</td>
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</table>

1. Locally advanced or metastatic UC with progression during or after treatment w/platinum chemo.
2. Locally advanced or metastatic UC progressing within 12 mo of neoadjuvant/ adjuvant platinum chemo.
3. Locally advanced or metastatic UC if platinum ineligible.
* Indicates FDA approved companion biomarker
$ FDA approved biomarker in other malignancies
Why did early BCG studies use 6 weeks of therapy?

- Because BCG was packaged in 6 packs.

Why does beer come in 6 packs?
The first six-pack was produced by Pabst Brewery in the 1940s. The company conducted several studies, which found that six cans were the ideal weight for the average housewife to carry home from the store.

source: beerfacts.net