Immunotherapy in Genitourinary Cancers

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GU Oncology Fellow
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins Medicine
Outline

• Cancer Immunology
• Current Data of Immunotherapy in GU Cancers
• New Immunotherapy Concepts in GU cancers
• Future Research Directions
Immune System and Cancer

Tolerance

Innate Immunity
Recognition of tumor

Adaptive Immunity
T cell activation

Anti-tumor Response

Defective antigen presentation
Inhibition of CTL
Immunosuppressive TME
Cancer Immunotherapy

Break tolerance and reinvigorate antitumor immunity

1908

Albert Calmette (1863-1933)

Camille Guerin (1872-1961)

TIME
INTERFERON
The IF Drug
For Cancer

Science
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

Forbes
WILL THIS MAN
CURE CANCER?

2015
Immune System and Cancer

**Tolerance**

- **Innate Immunity**
  - Recognition of tumor
  - Defective antigen presentation

- **Adaptive Immunity**
  - T cell activation
  - Inhibition of CTL

- **Anti-tumor Response**
  - Immunosuppressive TME

**Combinational approach**
Vaccine combination

Innate Immunity
Recognition of threat

Adaptive Immunity
T cell activation

Anti-tumor Response

DC

Dendritic cell

Tumor
Sipuleucel-T
Autologous DC vaccine

- PBMCs collected by leukapheresis
  - Cultured in EX VIVO with PA2024 (fusion protein of PAP and GM-CSF)
- Re-infusion of vaccine product x 3
  - Prime and boost

HR 0.775; P .032
(25.8 vs. 21.7)

*No difference in PFS
1 PR
2.6% PSA response (↓ >50%)

Kantoff PW. N Engl J Med 2010
1 PSA response > 80%. No radiographic response
Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer

Sip-T induces long-lasting **cellular** and **humoral** immune responses

Sheikh, Cancer Immunol Immunother 2013
Hypothesis I

Enhanced sipuleucel-T-induced immune response may translate into better clinical outcome
Immune Modulation by Radiation

**RT-induced cell death = immunogenic cell death?**

- Release of TAAs
- Enhanced display of TAAs
- Enhanced expression of cell surface molecules
  - MHC class 1, ICAM-1
- Complex effects on TME

In-situ personalized “vaccine”

Sharabi et al Oncology 2015
In Vivo Evidence of Radiation + Vaccine

In Vivo Evidence of Radiation + Vaccine

WBRT:
Upregulation of MHC-I
CD4/CD8 T cell tumor infiltration
Radiation + Vaccine: Clinical trials

- Phase II Sipuleucel-T + EBRT (NCT01807065): closed
  - Feasibility
- Phase II Sipuleucel-T + SABR (NCT01818986): open
  - Time to progression
- Pilot Sipuleucel-T + EBRT (NCT01833208): open
  - Ag specific T cell activation
- Multicenter Sipuleucel-T + EBRT (NCT02232230): open
  - Ag specific T cell activation
Immune Modulation by Radiopharmaceuticals

$^{153}$Sm-EDTMP

Radiopharmaceutical + Vaccine

Phase II samarium-153 EDTMP (Sm-153) +/- PROSTVAC vaccine

<table>
<thead>
<tr>
<th></th>
<th>Sm-153</th>
<th>Sm-153 + PSA-TRICOM</th>
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<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
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<tr>
<td>At 4 mo</td>
<td>3/18 (16.7%)</td>
<td>8/21 (38.1%)</td>
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<tr>
<td>mPFS (mo)</td>
<td>1.7</td>
<td>3.7</td>
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<tr>
<td><strong>PSA decline</strong></td>
<td></td>
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<tr>
<td>≥ 30%</td>
<td>0</td>
<td>4/21 (19.0%)</td>
<td>0.073</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>0</td>
<td>2/21 (9.5%)</td>
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Sm-153 on D#8 and then Q12 weeks +/- PSA-TRICOM on D# 1, 15, 29, then Q4 weeks
Early closure of this trial due to poor accrual after 44 pts

Heery et al. GU ASCO 2013
Radium-223
Hypothesis II

Enhanced sipuleucel-T induced immune response may translate into better clinical outcome

Combined radium-223 may enhance sipuleucel-T induced immune response
Phase II Study of Sipuleucel-T with or without Radium-223

mCRPC with no or minimal Sx

1’ Objective:
To determine whether Rad-223 to sipuleucel-T enhances immunity.

1’ Endpoint:
PA2024-specific T-cell proliferation at 6 weeks after 1st sip.
Phase II Study of Sipuleucel-T with or without Radium-223

2’ Clinical Endpoints

- Safety (CTCAE v4.0)
- PSA progression (PCWG2)
- Radiographic progression (RECIST/PCWG2)
- Pain progression (Use of opioid analgesics)
- Occurrence of first SRE
- First chemotherapy use
Phase II Study of Sipuleucel-T with or without Radium-223

2’ Immune Endpoints

- PA2024-and PAP-specific T-cell proliferation
  - 3H-thymidine assay

- PA2024-and PAP-specific T-cell activation
  - IFNγ ELISPOT

- PA2024-and PAP-specific Ab (IgM/IgG) response
  - ELISA

- Sipuleucel-T induced antigen (epitope) spread
  - IgG responses to off-target Ags (Protein microarray)

- Product immune parameters
Humoral Immune Response against Nontargeted Tumor Antigens after Treatment with Sipuleucel-T and Its Association with Improved Clinical Outcome

Prototype IgG profiling

Compare serum IgG levels pre- vs. post-Tx

PSA

LGALS3

Antigen | HR | P
---|---|---
PSA | 0.63 | 0.003**
LGALS3 | 0.60 | 0.035*
ERAS | 0.79 | 0.075*
LGALS8 | 0.83 | 0.369
KRAS | 0.83 | 0.218
KLK2 | 0.75 | 0.051*
Sipuleucel-T induced Antigen Spread
CD8 T cell responses to secondary antigens

- PBMCs obtained from STAND (n=10) and STRIDE (n=4) trial
- CD8 T cell proliferation to secondary antigens
  - KRAS, LGALS3, PSA
  - At baseline, week 6, and month 6

Antonarakis and Drake et al. GU ASCO 2016
Immune Checkpoint

Innate Immunity
Recognition of threat

Adaptive Immunity
T cell activation

Anti-tumor Response
# Atezolizumab vs. Pembrolobizumab vs. Avelumab

## Post-platinum mUC

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Petrylak et al. ASCO 2015, Plimack al. ASCO 2015, Apolo et al. GU ASCO 2016
Dual Immune Checkpoint Inhibition: Anti-PD-1/PD-L1 + Anti-CTLA-4

Bruggemann et al. ASCO 2015
## Dual Immune Checkpoint Inhibition

**PD-1/PD-L1 +/- CTLA-4**

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Dual Immune Checkpoint Inhibition

**Primary Endpoint:**
- Tumor infiltrating CD8+ T-cell at cystectomy after MEDI4736/tremelimumab

**Secondary Endpoints:**
- Safety and antitumor efficacy of MEDI4736/tremelimumab

**Exploratory Endpoints:**
- Characterization of tumor tissue and peripheral lymphocytes
- Analysis of soluble immune markers (cytokines/chemokines)
- Analysis of tumor and blood genetic and epigenetic profiles
- Assessment of T-cell repertoire
Tumor Infiltrating Lymphocyte (TIL): prognostic marker?

Intratumor vs. margin/stroma? TIL vs. subtype? density vs % vs. ratio?

• The presence of TILs associated with improved survival in MIBC (n=154)
• ↑ CD8+ TILs (≥ 8/0.0625 mm\(^2\)) correlated with better survival in MIBC (N=69)

8/0.0625 mm\(^2\) ≈ 4/100 tumor cells

Lipponen et al. Eur J Cancer. 1992,
Sharma et al. PNSA 2007
Tumor Infiltrating Lymphocyte (TIL): prognostic marker?

Intratumoral CD8+ T cells (400x)

High CD8 density: ≥60 CD8+/HPF: 11/56 (19.6%): intratumoral (n=56)
Tumor Infiltrating Lymphocyte (TIL): prognostic marker?

Paradoxical correlation of CD8+ T-cell infiltration with poor prognosis


>50 CD8/0.25 mm²
Tumor Infiltrating Lymphocyte (TIL): prognostic marker?

Colon cancer lung mets

RCC lung mets

Primary RCC tumor

RCC Lung mets

Remark et al. Clin Cancer Res 2013
Immune Predictive Biomarker Pharmacodynamics

Unresectable/metastatic
Urothelial Ca (n=10)
Renal cell Ca (n=10)

TIL: CD8 density vs. CD8 delta vs. CD8/Treg ratio vs. Other
Immune gene expression signature (velocity?)
PD-L1 expression
TCR clonality
Mutational burden
MMR gene (microsatellite instability)
Prognostic vs predictive?
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Hammers et al. ASCO 2014
Immune System and Cancer

Innate Immunity
Recognition of threat

Adaptive Immunity
T cell activation

Anti-tumor Response

Loss/down-regulation of MHC I
Loss/masking of TAAs
Failed antigen presentation: MHC (HLA) I downregulation

Bladder

RCC

Innate Immunity

Cytotoxicity *in the absence of MHC/Ag complex*
NK Cells

- Rc-based recognition of “abnormal cell”
  - **Missing-self**: loss of MHC I
  - Non-self: pathogen-encoded molecules
  - Stressed-self: stress-induced ligands

- Tumor immune surveillance
  - Direct tumor cell cytotoxicity
    - Perforin and granzymes-dependent necrosis
    - Death Rc-mediated apoptosis (TRAIL, FasL)
  - Bridge to adaptive immune response
    - Release of cytokines and chemokines
    - Recruitment of other accessory/effectector immune cells
Role of NK Cells in Antitumor Response

NK cell depletion

T-cell depletion

NK cell deficient beige mice

Bladder

NK-WT mice

RCC

Bladder BCG therapy

RCC IL-21 therapy

NK Cell Activity

Balance of activating and inhibitory Rc stimulation

Vivier. Science. 2011
Killer cell Ig-like Receptors (KIRs):
KIR2DL: Inhibitory Rc

• MHC I-specific receptors: inhibitory vs activating
  • KIR2DL (1/2/3) interacts with HLA-C allotypes
  • KIR3DL interacts with HLA-A and B allotypes

• KIR/HLA interaction determines the responsiveness

• NK cells preferentially kill cells with low MHC I

Vey et al. ASCO 2015 Annual Meeting

 NK inhibition by KIR

Activation through KIR blockade

Lirirumab
Combination of Adaptive and Innate Immunity

Innate Immunity
Recognition of threat

Adaptive Immunity
T cell activation

Anti-tumor Response
Combination of **Adaptive** and **Innate** Immunity

**Anti-PD-1** and **KIR** mAB

**Figure 1-1:** Anti-PD-1 and Anti-KIR in MC38 Murine Colon Carcinoma Model

- **Control**
- **Anti-PD-1 mAB**
- **Anti-KIR mAB**
- **Anti-PD-1 mAB**
- **Anti-KIR mAB**
Phase II Nivolumab + Lirilumab

Primary Endpoint:
• Tumor infiltrating CD8+ T-cell at cystectomy after

Secondary Endpoints:
• Safety and antitumor efficacy (the rate of < pT2N0)
• Immunologic Biomarkers and clinical association:
  Peripheral/tissue lymphocyte subsets, cytokine, PD-L1, KIR2DL1/2/3 expression
4-1BB (CD137): Co-stimulatory Rc: Urelumab

Vinay et al. J Immunol 2004
Wilcox et al. J Immunol 2002
Primary Endpoint:
• Tumor infiltrating CD8+ T-cell at cystectomy after

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• Safety and antitumor efficacy (the rate of < pT2N0)
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  Peripheral/tissue lymphocyte subsets, cytokine, PD-L1, KIR2DL1/2/3 expression
Selective Ongoing Combination Immunotherapy Trials

- Dual checkpoint inhibition
  - Anti-PD-1/PD-L1 + Anti-CTLA-4
  - INCB24360, Indoximod (IDO1)
  - BMS-986016 (LAG3)
  - MGA271 (B7-H3)
- Checkpoint + costim Rc
  - Varilumab (CD27)
  - Urelumab, PF-05082566 (4-1BB)
  - MEDI6469 (OX40)
  - MK-4166 (GITR)
- Checkpoint + Radiation
  - EBRT, SBRT
- Checkpoint + chemoRx
- Checkpoint + NK-cell
  - ALT-803 (IL-15), Lirilumab (Anti-KIR)
- Checkpoint + Epigenetic agents
  - Demethylating agents: 5-azacitidine
  - HDACi: Entinostat, Vorinostat
- Checkpoint + Vaccine
  - GVAX, Sipuleucel-T, ProstVac, pTVG-HP
- Checkpoint + Cytokines
  - IL-2, IFN
- Vaccine + Cytokine
  - modified gp100 peptide + IL-2
  - ProstVac + GM-CSF
- Checkpoint + TKIs
  - VEGF
  - BTK (Ibrutunib, ACT-196)
## Selective Ongoing Combination Immunotherapy Trials in GU Cancers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial Design</th>
<th>Phase</th>
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<td>Pembrolizumab + ACT-196</td>
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Mix & Match? Shotgun?

- Biologic rationale
- Clinically unmet need
- Biomarker
- Novel trial design
Randomize to activated arms (some arms may activate earlier than others)
Conclusions/Future Directions

• The promising data of cancer vaccine and checkpoint inhibitors have opened new frontiers in IT for cancer
• Limitations exist with current IT such as low response rate and lack of reliable biomarkers
• Combinational approach is expected to overcome current limitations and maximize the benefit of IT
• New IT trials with sold biologic rationale and novel trial designs in clinically unmet need population are warranted