Early-Phase Immunotherapy, Cellular Therapy, and Vaccine Trials in Sarcoma

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Learning Objectives

• Review mechanisms of immune evasion and highlight strategies for therapeutic targeting

• Present representative ongoing studies in immunotherapy and cellular therapy for sarcomas

• Discuss progress made towards better understanding of the immune microenvironment and potential biomarkers of immunogenicity in sarcomas

• Future directions and unanswered questions
Immunotherapy for Sarcoma – Past, Present and Future

1890s
William Coley

1980 - 2005
Cytokines +/- chemo
• IL-2 (high dose)
• IFN-α/β
• mifamurtide

Vaccines
• Autologous tumor cells
• Dendritic cells
• GVAX

2005 - 2012
Adoptive T cell therapy – NY-ESO-1+ synovial sarcoma

2010
Checkpoint inhibitor monotherapy 2013 - 2016

2017
- COMBINATIONS
Future – Biomarker driven precision immunotherapy

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Tumor Evasion Strategies To Suppress Antitumor Immunity

Chen & Mellman, Immunity, 2013

Promote immature, suppressive DCs and macrophages, exhausted T cell phenotypes (Treg)

Loss (or non-existence) of effective neoantigens

Produce suppressive cytokines that prevent migration and infiltration

Expression of checkpoint proteins
Targets for Clinical Immunotherapy

Generate neoantigens
- Vaccines
- Chemotherapy/radiation
- Oncolytic viruses
- Epigenetic agents

Boost antigen presentation
- DC vaccines
- Macrophage repolarization
- Bypass with adoptive T cell therapy

Alter microenvironment
- TKI (α-VEGF, TGF-β, IDO)
- IFN/IL administration
- Oncolytic viruses

Immunomodulators
- Checkpoint inhibitors
- Stimulatory agonists
- Anti-Treg therapy

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Immune environment in sarcomas

T cells
- Improved prognosis (ESFT, GIST, cutaneous angiosarcoma, LMS, SS, UPS)
- Worse/no effect on prognosis in other studies

TAMs
- Worse prognosis (GIST, ESFT, LMS, myxoid LPS, osteo)

Tregs
- Understudied – more prevalent in GIST vs. non-GIST sarcoma
- High CD3+CD8+ to Treg ratio favorable in GIST

Tan et al, Cancer Gen Ther, 2016
D’Angelo et al, Hum Pathol, 2014
Berghuis et al, J Pathol, 2011
Fujii et al, Int J Cancer, 2014
Immune environment in sarcomas

PD-L1 (about 20% expression in STS)
- Expression ranges from 12-65% of sarcomas
- 50/50 for whether PD-L1 expression is associated with worse prognosis
- 2 large retrospective studies showed coexpression of PD-L1 with CD8+ immune infiltrates in a subset of sarcomas

IDO1/Kynurenine
- expression associated with improved survival and response to therapy
- also co-expressed with CD8+ immune infiltrates and PD-L1 expression

Toulmonde et al, ASCO 2016
D'Angelo et al, Hum Pathol, 2014
Kim et al, BMC Cancer, 2016
Feng et al, Oncotarget, 2015
Van Erp et al, Eur Canc Congress 2017

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Immunosignatures in sarcoma

- Immune specific gene profiling (Nanostring), PD1/PD-L1 expression, T cell clonality
- UPS and LMS carry a robust immunosignature relative to LPS and SS
  - increased TCR oligoclonality
  - Increased expression of T-cell infiltration and antigen presentation genes
  - Increased PD-1/PD-L1 expression

Pollack et al, Cancer 2017, Ian Davis et al, SARC Meeting 2017

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Immune biomarkers in sarcomas

- Biomarker data from SARC028
  - 3/70 patients expressed PD-L1 (2 were responders, 1 unevaluable) – what about the other 4 responders?

- Genetic expression data
  - Identifies T cell clonality and upregulation of immune-related genes as well as PD-L1 expression in leiomyosarcoma
  - Yet no protein expression by IHC and no response to checkpoint inhibitors?

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Sarcomas likely... (with exception caveats)

- Lack innate robust immunogenicity
- Possess immunosuppressive immune infiltrates, but TAM and Treg ≥ dormant CD8+ T cells
- Exhibit immunogenic signatures
  - Gene expression or cytokines/immune cell/checkpoint coexpression? Both?
  - Prospective evaluation is needed- PD-L1 expression by IHC is not sufficient to predict activity
- Need combination approaches to set up checkpoint inhibitors for success in sarcoma

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Immunotherapy combinations
Boosting neoantigens - Vaccines

• Phase II FANG immunotherapy (Vigil) - autologous tumor cells transfected with rhGM-CSF (promotes DC recruitment/activation) and RNAi-shRNA<sub>furin</sub> (blocks TGF-β) – (NCT02511132)

• Phase II for NY-ESO-expressing sarcomas, randomized to CMB 305 (NY-ESO-1 lentivirus vaccine with TLR4 adjuvant) + atezolizumab vs atezolizumab alone (NCT02609984)
Immunotherapy combinations

Boosting neoantigens - Vaccines

- Dendritic cell vaccination therapy (APC cellular therapy) with autologous tumor lysates (source of neoantigens), +/- gemcitabine (counteract MDSCs) - NCT01803152

- Customized vaccines generated from neoantigen-prediction algorithms based on tumor sequencing data (ultimately + checkpoints) – clinical and preclinical
Immunotherapy combinations
Boosting neoantigens – Chemotherapy/Radiation

- SARC032 Randomized Phase II Neoadjuvant radiation with or without pembrolizumab (NCT03092323)
- Neoadjuvant Durvalumab + tremelimumab + radiation (NCT03116529)
- Doxorubicin + pembrolizumab (NCT02888665)
- Trabectedin + ipilimumab + nivolumab (NCT03138161)
- Gemcitabine-based regimens or pegylated liposomal doxorubicin combined with pembrolizumab for solid tumors (NCT02331251)
- Metronomic Cytoxan + pembrolizumab NCT02406781 (ASCO17)
Immunotherapy combinations

Boosting neoantigens – Oncolytic viruses

- Powerful approach that counteracts multiple mechanisms
- Underexplored in sarcomas
- Oncolytic vaccinia virus (JX-594) shown to be safe and induced immune responses in adult and pediatric patients with Ewing sarcoma and other cancers (Cripe et al., 2015)
- JX-594 with metronomic cyclophosphamide (inhibit Tregs) for advanced STS patients (NCT02630368)
- Talimogene laherparepvec plus radiation therapy (NCT02453191)
- Modified vaccinia virus expressing p53 protein, in combination with pembrolizumab (NCT02432963)
Adoptive Cellular Therapy

**Bypass neoantigen processing and recognition**

- Engineered autologous T cells
- Collect specific T-cell clones, expand in vitro, infuse
- NK cells

Chmielewski et al, Front Immunol 2013
Potential targets in sarcoma for ACT

- NY-ESO-1 engineered TCR (Adaptimmune) – Synovial, myxoid/round cell, other sarcomas coming soon
- HER2 CAR-T for HER2 expressing sarcomas (NCT00902044)
- GD2 CAR-T and engineered TCR (NCT01953900, NCT00743496).
- Dual target GD2/GD3 CAR-T for osteosarcoma (SFA grant – preclinical)
- C-KIT for GIST (preclinical)
- B7-H3 for osteosarcoma/Ewing sarcoma (Robbie Majzner, SARC CDA award)
### Combinations with Targeted Therapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Target</th>
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<tbody>
<tr>
<td>IDO inhibitor plus pembrolizumab (pending)</td>
<td>Treg</td>
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<tr>
<td>Axitinib plus pembrolizumab (NCT02636725)</td>
<td>VEGF</td>
</tr>
<tr>
<td>Sunitinib plus nivolumab (IMMUNOSARC, pending)</td>
<td>Multi-TKI</td>
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<tr>
<td>Imatinib plus ipilimumab (NCT01738139)</td>
<td>Multi-TKI</td>
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<tr>
<td>Liposomal IL-2 + pembrolizumab (pending)</td>
<td>Innate immunity</td>
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<tr>
<td>PLX3397 + pembrolizumab (NCT02452424)</td>
<td>Macrophage</td>
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<tr>
<td>PLX3397 + sirolimus (NCT02584647)</td>
<td>Macrophage</td>
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Checkpoint inhibitors

- Anti PD-1/PD-L1 monotherapy ongoing for selected populations (UPS, dedifferentiated LPS, ASPS, osteosarcoma)
- Ipilimumab/nivolumab expansion ongoing (Alliance)
- Ipilimumab/nivolumab in pediatric population (NCT02304458)
- Durvalumab plus tremelimumab (NCT02815995)
Novel targets

Take advantage of all-comers phase I trials of novel immunomodulators for sarcoma patients

Angiosarcoma on an all-comers Phase I

63 yo F with cutaneous angiosarcoma of the nose and cheeks, no locoregional or distant disease

Prior therapies:
- MAI x 5
- XRT to 70 Gy
- Gemcitabine x 2
- Rhinectomy
- High dose ifos x 4
- Pazopanib
- NOTCH inhibitor (Phase I)
- TMZ/Bevacizumab
- Doxorubicin monotherapy x 6 with dexrazoxane
- No propranolol

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Enrolled on Agenus Phase I trial of AGEN1884, novel CTLA4 inhibitor - Dose level 1 = 0.1 mg/kg every 3 weeks
Future Precision Medicine Approach for Metastatic STS

Pathology Review:
- IHC for MSI, NY-ESO-1, HER2
- WGS (fusions)
- Immunosignature

Chemotherapy + Checkpoint Inhibitor(s) + Customized Vaccine
OR TCR/CAR T cells
Future Precision Medicine Approach for Metastatic STS

Pathology Review
IHC for MSI, NY-ESO-1, HER2
WGS (fusions)
Immunosignature

Targeted therapy + Checkpoint Inhibitor(s)
Radiation
Checkpoint Inhibitor maintenance
Future Precision Medicine Approach for Metastatic STS

Pathology Review
IHC for MSI, NY-ESO-1, HER2
WGS (fusions)
Immunosignature

Chemotherapy + Checkpoint Inhibitor(s) + Radiation

Checkpoint Inhibitor maintenance
Conclusions

• Our biggest challenge now is to understand the drivers of response to immunotherapy – Approaching a customized multimodality treatment plan to counteract evasion mechanisms
• Combinations or serial therapies are likely to be the key to better outcomes
• Immunotherapy has a place in the sarcoma armamentarium
Thank you!

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