Clinical Advances in Immunotherapy in Myeloma

Webinar 2, July 26, 2017
Vaccines for Myeloma
(and Other Advances in Immunotherapy)

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Multiple Myeloma Research Foundation

**Moderator:**
- **Mary DeRome**
  Multiple Myeloma Research Foundation
  Norwalk, Connecticut

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**Speakers**

**Kenneth C. Anderson, MD**
Dana-Farber Cancer Institute
Boston, Massachusetts

**David Avigan, MD**
Beth Israel Deaconess Medical Center
Boston, Massachusetts

**Noopur Raje, MD**
Massachusetts General Hospital
Boston, Massachusetts
Topics for Discussion

• What is immunotherapy?
• Myeloma vaccines
  – What are they?
  – Vaccination strategies
    • Cell-based
    • Non–cell-based

Immunotherapy

Directing the immune system to fight cancer
Why May Myeloma Cells Hide From the Immune System?

- They look too much like normal cells and so are not identified as foreign
- Antigen presentation on myeloma cells in a way that favors tolerance
- Myeloma may inactivate normal T cells
- Myeloma may increase presence of immune-inhibiting cells in the tumor microenvironment
- Myeloma cells have increased activity of immune-inhibiting pathways

Cancer Immunotherapies Already Available

- mAbs are used in a variety of solid and hematological tumors; examples include Rituxan, Herceptin, Campath
- Vaccines are being used in prostate cancer; one example is Provenge
- Checkpoint inhibitors are being used in melanoma (for example, Yervoy)
Main Targets for Immunotherapy

- Monoclonal antibodies
  - Directly targeting myeloma cell markers
  - Overcoming immune suppression
- CAR-T cells
  - Boosting myeloma-fighting T cells
  - Activating myeloma-specific immunity
- Vaccines
  - IMiDs, checkpoint inhibitors

Cancer Vaccine Therapy

**What is it?**
- **Cell Based**
  1. Extract WBCs from MM patient
  2. Modify and expand cells in lab
  3. Infuse MM-targeted cells back to MM patient

**Protein Based**
- It is an injection of a combination of myeloma proteins and immune cell-stimulating agents similar to infectious disease vaccines

**How does it work against myeloma?**
- It stimulates myeloma-specific T- and B-cell immunity

Are cancer vaccines the same as other vaccines?

Cancer vaccines are typically considered therapeutic *NOT* preventive*

Infectious Vaccines
- Administered to healthy individuals
- Existing immune system intact

Cancer Vaccines
- Administered in the presence of existing cancer
- Existing immune system dysfunction

*Vaccination of smoldering MM can be thought of as preventative, as it is attempting to delay or avoid progression to active MM

When are vaccines used during myeloma treatment?

Vaccines typically applied after ASCT with the goal of eliminating any remaining cancer cells
The Promise of Effective Cancer Vaccine Strategy

- An immune response that selectively targets malignant cells
- A broad anti-tumor immune response has the potential to target the different tumor clones, including malignant stem cell populations
- Immune response provides the potential for memory and long-term surveillance

Overcoming the Tumor Microenvironment

Cancer Vaccine Strategies

Designing a Cancer Vaccine: Choosing the Right Target to Load Dendritic Cells

- Selecting the right targets
  - Shared: NY-ESO, MUC1, XBP1, SOX2, WT1, PRAME, Survivin
  - Patient Specific
    - Idiotype
    - Neoantigens
DC/Tumor Fusion Vaccine

1. **Adherent PBMCs** cultured for 5-7 days with GM-CSF & IL-4; TNF-α added for 48-72 hours.
2. Myeloma cells isolated.
3. **DCs** assessed for DC & tumor specific markers.
4. DC & myeloma fused with 50% PEG at DC: tumor, 3:1 to 10:1.
5. Fusion cells quantified by measuring dual expression of unique DC & tumor markers.
6. Doses prepared & frozen microbiology testing sent.
7. Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-α added for 48-72 hours.
8. **GM-CSF 100ug at vaccine site for 4 days**.
9. **Leukapheresis**
10. Dose prepared & frozen microbiology testing sent.
11. **Bone marrow aspiration**
12. **Myeloma cells** isolated.
13. Myeloma cells assessed for tumor & DC specific markers.
14. DCs assessed for DC & tumor specific markers.
15. CD38, CD86, CD138, MUC
16. CD80, CD83, CD40
17. CD3, CD4, CD8
18. HLA Class I, II
19. CD68
20. CD14
21. CD54
22. CD40L
23. CD86
24. CD83
25. CD80
26. CD138
27. CD171
28. MUC1
29. CD44
30. CD38
31. DR
32. CD40
33. CD80
34. CD83

**Clinical Advances in Immunotherapy in Myeloma**

**Webinar 2: Vaccines for Myeloma (and Other Advances in Immunotherapy)**

**7/26/17**
Vaccination Induces T Cell and Antibody Responses Targeting Myeloma Cells

Vaccination-Induced Expansion of Myeloma-Reactive T Cells and Targeting of Minimal Residual Disease
Multicenter Trial of Single Autologous Hematopoietic Cell Transplant Followed by Revlimid Maintenance for Multiple Myeloma with or without Vaccination with Dendritic Cell (DC)/Myeloma Fusions (MY T VAX)

Cell-Based Myeloma Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. Patients</th>
<th>Route of Administration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiotype-pulsed dendritic cells²</td>
<td>12</td>
<td>IV</td>
<td>17% in CR</td>
</tr>
<tr>
<td>Idiotype-pulsed dendritic cells³</td>
<td>26</td>
<td>IV</td>
<td>65% alive at 30 mos</td>
</tr>
<tr>
<td>Idiotype-pulsed dendritic cells⁴</td>
<td>27</td>
<td>IV</td>
<td>Median OS 5.3 yrs (vs. 3.4 yrs for unvaccinated patients)</td>
</tr>
<tr>
<td>MAGE3-, survivin-, or BCMA-mRNA-loaded dendritic cells⁵</td>
<td>12</td>
<td>IV and ID</td>
<td>83% OS at 55 mos</td>
</tr>
<tr>
<td>Dendritic cell/tumor cell fusion⁶</td>
<td>18</td>
<td>SC</td>
<td>69% with SD</td>
</tr>
<tr>
<td>Dendritic cell/tumor cell fusion⁷</td>
<td>24</td>
<td>SC</td>
<td>47% CR/nCR 78% CR/VGPR</td>
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</table>

*Following ASCT
Myeloma GVAX Vaccine

- MM patients on a Revlimid-containing regimen (RVD, Rd, BiRD, or R)
- nCR
- Single-agent Revlimid + GVAX*
- 15 patients evaluated
- median PFS not yet reached

The generation of tumor-specific immunity in a low disease burden state can significantly delay relapse. A larger randomized phase 2 study will attempt to answer this question.

*GVAX is a GM-CSF–based vaccine consisting of 2 allogeneic cell lines: H929 and U266, coupled to a GM-CSF–secreting bystander cell line, K562/GM


Combination Immunotherapy and the Role of Checkpoint Inhibition

Diagram showing the interaction of T cells, tumor cells, and immune checkpoint inhibitors such as PD-1 and PD-L1.
Types of Cancer Vaccines: Non–Cell-Based

**Recombinant proteins**
- Myeloma cells
- Myeloma peptide genes (for example, WT)
- Myeloma peptides
- Peptides + adjuvant = vaccine
- Multiple vaccinations stimulate T and B cells

**Mutation-based**
- Myeloma cells
- Genomic sequencing
- Identify mutations
- Synthesize mutant peptides
- Peptides + adjuvant = vaccine
- Multiple vaccinations stimulate T and B cells

**Non–Cell-Based Vaccines: Recombinant Proteins**

**MAGE-A3 Peptide Vaccine¹**
- A high frequency of vaccine-specific T-cell responses were generated after transplant

**WT-1 Vaccine²**
- A small phase 1 study of 18 patients showed encouraging results in overall and progression-free survival
- A phase 2 study is planned

**PVX-410 Vaccine³**
- Studied in smoldering MM patients at high risk of progressing to active MM
- PVX-410 was well-tolerated
- An immune response to PVX-410 was seen with PVX-410 alone, which was enhanced by the addition of Revlimid

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PVX-410 Multi-Peptide Vaccine Study Schema: SMM Patients

**Cohort 1:** Vaccine Alone

- 1 V
- 2 V
- 3 V
- 4 V
- 5 V
- 6 V

- WK 0 Baseline
- WK 2
- WK 4 Post-2V
- WK 6 Post-4V
- WK 8
- WK 10
- WK 14
- WK 22

**Cohort 2:** Vaccine + Revlimid

- 1 V
- 2 V
- 3 V
- 4 V
- 5 V
- 6 V

- WK 0 Baseline
- WK 2
- WK 4 Post-2V
- WK 6 Post-4V
- WK 8
- WK 10
- WK 14
- WK 22

*No Len for 3 weeks

Revlimid Cycle 1
Revlimid Cycle 2
Revlimid Cycle 3

PVX-410 Multi-Peptide Vaccine Study: Immune Responses

**Gated: Total CD3⁺CD8⁺ T cells**

- **Vaccine Alone (Cohort 1)**
- **Vaccine (Cohort 1)**
- **Vaccine + Len (Cohort 2)**
**SUMMARY**

Induction of XBP1/CD138/CS1-Peptides-Specific CTL by Vaccine

**Vaccine Gradually Induces XBP1/CD138/CS1-Specific Cytotoxic T Lymphocytes (CTL) in SMM Patient**

Stimulator: XBP1us / XBP1sp / CD138 / CS1 Peptides

<table>
<thead>
<tr>
<th>Status, no. patients</th>
<th>PVX-410</th>
<th>PVX-410 + Revlimid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active treatment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Completed/off study</td>
<td>12</td>
<td>9/1</td>
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</table>

**Disease responses, no. patients (%)**

<table>
<thead>
<tr>
<th></th>
<th>PVX-410</th>
<th>PVX-410 + Revlimid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall best clinical response (≥MR)</td>
<td>0/12 (0%)</td>
<td>4/9* (44%)</td>
</tr>
<tr>
<td>Best response (≥PR)</td>
<td>0/12 (0%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7/12 (58%)</td>
<td>4/9 (44%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5/12 (42%)</td>
<td>1/9* (11%)</td>
</tr>
</tbody>
</table>

*1 patient who achieved an MR later progressed to active disease at 5 months post treatment

**PVX-410 Multi-Peptide Vaccine Study: Clinical Response Summary**
## Ongoing Clinical Trials of Myeloma Vaccines

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Phase</th>
<th>Site(s)</th>
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<tbody>
<tr>
<td>Survivin Vaccine</td>
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<td>H. Lee Moffitt Cancer Center</td>
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<tr>
<td>Vaccination with PD-L1 Peptide</td>
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<td>Non-US</td>
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<tr>
<td>Enhancing Anti-Myeloma Vaccine Response After Autologous Stem Cell Transplantation</td>
<td>2</td>
<td>Emory University</td>
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<tr>
<td>Dendritic Cell/Myeloma Fusion Vaccine</td>
<td>2</td>
<td>National Heart, Lung, and Blood Institute (NHLBI) (CTN 1401)</td>
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<tr>
<td>SVN53-67/M57-KLH Peptide Vaccine in Treating Patients With Newly Diagnosed Multiple Myeloma Receiving Lenalidomide Maintenance Therapy</td>
<td>1</td>
<td>Roswell Park Cancer Institute</td>
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<tr>
<td>CT7, MAGE-A3, and WTI mRNA-electroporated Autologous Langerhans-type Dendritic Cells as Consolidation</td>
<td>1</td>
<td>MSKCC</td>
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<tr>
<td>A Study of PVX-410, a Cancer Vaccine, and Durvalumab +/- Lenalidomide for Smoldering MM</td>
<td>1</td>
<td>Massachusetts General Hospital</td>
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<td>Vaccine Therapy With or Without Cyclophosphamide in Treating Patients With Recurrent or Refractory Multiple Myeloma</td>
<td>1/2</td>
<td>Mayo Clinic</td>
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### Questions & Answers
Closing

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<tr>
<td>Hot Topic</td>
<td>Minimal Residual Disease</td>
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<td>Continuous Therapy</td>
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<td></td>
<td>Precision Medicine</td>
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## MMRF Multiple Myeloma Summits Fall 2017

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<td>Saturday, September 16, 2017</td>
<td>Chicago, Illinois</td>
<td>Andrzej Jakubowiak, MD–Chair</td>
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<td>University of Chicago Medical Center</td>
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<td>Saturday, October 14, 2017</td>
<td>Charlotte, North Carolina</td>
<td>Saad Z. Usmani, MD–Chair</td>
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<td>Friday, November 3, 2017</td>
<td>New York City, New York</td>
<td>Ajai Chari, MD–Chair</td>
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<td>Mount Sinai Health System</td>
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<td>Tisch Cancer Institute</td>
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<td>Mount Sinai School of Medicine</td>
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<td>Levine Cancer Institute</td>
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<td>Saturday, November 18, 2017</td>
<td>Los Angeles, California</td>
<td>James Berenson, MD–Co-Chair</td>
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<td>Institute for Myeloma and Bone Cancer Research</td>
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<td>Amrita Y. Krishnan, MD–Co-Chair</td>
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<td>Judy and Bernard Briskin Center for Multiple Myeloma Research</td>
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<td>City of Hope Medical Center</td>
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