Improving the Overall Understanding of Immunotherapy in Multiple Myeloma

Webinar 2, August 19, 2015
Myeloma Vaccines: A New Use of a Time-Tested Treatment

The Four Pillars of Cancer Therapy

- Surgery
- Radiation therapy
- Chemotherapy
- Immunotherapy
  - Monoclonal antibodies
  - Vaccines
  - Adoptive cell transfer
  - Checkpoint inhibitors
Speakers

Moderator:

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  Multiple Myeloma Research Foundation
  Norwalk, Connecticut

Faculty:

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  Harvard Cancer Center
  Boston, Massachusetts

• Hearn Jay Cho, MD, PhD
  Mount Sinai Hospital
  New York, New York

Immune System Basics
How the Immune System Works

- Defends you against various “germs” or foreign invaders that cause infection, illness, or disease
  - Bacteria
  - Viruses
  - Fungi
  - Parasites

Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Antigen</td>
<td>A microbe or cancer protein that can be targeted by T and B cells</td>
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<tr>
<td>Peptide</td>
<td>A short piece of protein</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>A mixture of synthetic components that help stimulate antigen-specific immunity</td>
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<tr>
<td>Priming</td>
<td>Activation of antigen-specific T cell immunity</td>
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<tr>
<td>Co-stimulation</td>
<td>Positive “second signal” for T cells to become fully activated</td>
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How Does the Body Fight Against Foreign Invaders?

Immunity

Innate (natural)

- Defender components are always ready to defend you
- Your first line of defense against invaders that get into your body

Adaptive (acquired or specific)

- The invader awakens your immune cells to mount their defense
- Can have a long-lasting effect against future invaders

Your Defense Team Line Up

NK Cells, Macrophages, Dendritic Cells, T Cells, B Cells

NK, natural killer.
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**Defense Team Coordination:**
*Boosting the Adaptive Immune Response*

![Diagram](image1)

- **To lymph node:**
  - Dendritic cell
  - Antigen presentation and co-stimulation
  - CD8+ "killer" T cell

- **To periphery:**
  - T cell priming
  - T cell expansion
  - CD4+ T helper cell
  - **To periphery:**
    - Virus antigen-specific immunity

- **Virus-infected cell**:
  - Virus proteins

- **Normal cell**:
  - "Self" peptide

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**Myeloma Vaccines: A New Use of a Time-Tested Treatment**
Immunotherapy

Directing the immune system to fight cancer
How Do Myeloma Cells Hide From the Immune System?

• Antigen presentation in a way that favors tolerance
• Inactivation of T cells
• Increased presence of inhibitory cells in the tumor microenvironment
• Upregulation of inhibitory pathways on myeloma cells

Cancer Vaccine Therapy

What is it?

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

Are cancer vaccines the same as other vaccines?

• Cancer vaccines are considered therapeutic NOT preventive

How does it work against myeloma?

• It stimulates myeloma-specific T and B cell immunity
## Types of Cancer Vaccines

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Vaccine Components</th>
<th>How They Are Made</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-based</td>
<td>Antigen presenting cells (APCs)</td>
<td>Immune cells isolated from myeloma patient, stimulated in lab, injected back into patient</td>
</tr>
<tr>
<td></td>
<td>• Dendritic cells pulsed with myeloma protein</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• APCs are made to express myeloma proteins via (noninfectious) viral carrier</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Myeloma cells fused to immune cells</td>
<td></td>
</tr>
<tr>
<td>Allogeneic stem cell-based</td>
<td>Primed anti-myeloma stem cells from a vaccinated donor</td>
<td>Allogeneic donor vaccinated with myeloma patient’s idiotype protein, donor stem cells harvested, donor stem cells transplanted into myeloma patient</td>
</tr>
<tr>
<td>Non-cell-based</td>
<td>Protein/peptide-based</td>
<td>Proteins isolated from myeloma cells in lab, injected into myeloma patient</td>
</tr>
<tr>
<td>Mutation-based</td>
<td>Mutated (synthetic peptides based on genomic sequencing from individual patient tumor cells)</td>
<td>Proteins made in a lab, injected into myeloma patient</td>
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</tbody>
</table>

### Cell-Based Vaccines

- **Viral transduction with tumor DNA**
- **Loading of exogenous peptide**
- **Loading of tumor lysates**
- **Loading of exogenous protein**
- **Pulsing with RNA or DNA**
- **Apoptotic bodies**
- **Tumor cell fusion**
Cell-Based Vaccines: Dendritic Cell/Myeloma Cell Fusion

- Patient-derived tumor cells fused to dendritic cells
- In a phase 2 trial, patients underwent vaccination following ASCT
- Vaccination resulted in the expansion of MM-specific T cells and conversion of partial response to complete response

ASCT, autologous stem cell transplant.

Cell-Based Vaccines: Additional Studies

- Additional phase 2 studies investigating:
  - ASCT followed by Revlimid maintenance ± vaccination with fusion vaccine
  - ASCT followed by the combination of the fusion vaccine with a checkpoint inhibitor—pidilizumab

<table>
<thead>
<tr>
<th>Newly Diagnosed Myeloma Patients</th>
<th>Tumor Cell Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Therapy</td>
<td>Maintenance Revlimid + vaccine + GM-CSF</td>
</tr>
<tr>
<td>Autologous Stem Cell Transplant</td>
<td>Maintenance Revlimid + GM-CSF</td>
</tr>
<tr>
<td>Dendritic Cell Collection</td>
<td>Maintenance Revlimid alone</td>
</tr>
</tbody>
</table>

n=66  n=33  n=33
Immune Checkpoint Inhibitors

Myeloma cell

Cytotoxic T cell

Inhibitory receptors
PD-1/PD-L1

Anti-PD1/PD-L1

T cell activation

Engineered T Cell Therapy

Peripheral Blood

TCR transgene

Myeloma-specific TCR eg MAGE-A3 TCR

OR

Chimeric Antigen Receptor (CAR) Transgene

Tumor-specific CAR eg anti-CD19

In vitro T cell expansion

Adoptive T cell therapy

T cells kill myeloma cells
Non-Cell-Based Vaccines: Recombinant Proteins

- Myeloma cells
- Myeloma protein gene (e.g., MAGE-A3)
- Recombinant myeloma protein
- Protein + adjuvant = vaccine
- Multiple vaccinations stimulate T and B cells
- MAGE-A3-specific T cells
- T cells kill myeloma cells

Mutation-Based Vaccines

- Myeloma cells
- Genomic sequencing
- Identify mutations
- Synthesize mutant peptides
- Mutation-specific T cells
- Peptides + adjuvant = vaccine
- Multiple vaccinations stimulate T and B cells
- T cells kill myeloma cells
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### Therapeutic Vaccines in Development

<table>
<thead>
<tr>
<th>MM Vaccine</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cell fusion vaccine + CT-011 (monoclonal antibody)</td>
<td>Post-transplant</td>
<td>Phase 2</td>
<td>Beth Israel Deaconess Medical Center/Dana-Farber</td>
</tr>
<tr>
<td>Hiltonol (MAGE-A3 vaccine Poly-ICLC)</td>
<td>Post-transplant</td>
<td>Phase 2</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>Oncolytic measles virus (MV-NIS)</td>
<td>R/R</td>
<td>Phase 1</td>
<td>Mayo Clinic (Rochester, MN)</td>
</tr>
<tr>
<td>PVX-410</td>
<td>SMM</td>
<td>Phase 1/2</td>
<td>Emory / Illinois Cancer Specialists / Beth Israel Deaconess Medical Center / Massachusetts General Hospital / MD Anderson Cancer Center</td>
</tr>
</tbody>
</table>

Majority of studies post-transplant, with the goal of eliminating any remaining cancer cells

### Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets

**Novel Therapy**

- Revlimid
- Thalidomide
- Velcade
- Doxil
- Kyprolis
- Pomalyst
- Farydkin
- Elotuzumab
- Isatuximab
- CAR-T
- Atezolizumab
- Nivolumab
- Isatuximab
- Vaccines

**Novel Therapies and Immunotherapy**

- IMiD
- HDAC inhibitor
- Monoclonal antibody
- Chemotherapy
- Adoptive T cell therapy
- Checkpoint inhibitors

- Kyprolis
- Velcade
- Doxil
- Pomalyst
- Farydkin
- Elotuzumab
- Isatuximab
- CAR-T
- Atezolizumab
- Nivolumab
- Isatuximab
- Vaccines

IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export. *Not yet FDA-approved for MM; only available in clinical trials. †Treatments studied in MMRC trials.
Immunotherapy for Myeloma: Where Are We Heading?

- Rational combinations of vaccines with checkpoint inhibitors, engineered T cells, targeting antibodies, immunomodulatory drugs, and other strategies

Questions & Answers
Question
Can vaccines be used in the treatment of smoldering multiple myeloma?

Question
What are the expected side effects of vaccine therapy?
Question

Are vaccines available to patients now? Have any shown promise in other cancer indications?

Question

Would you expect the effectiveness of immunotherapy to be better in patients with high-risk features of myeloma?
Question

Will patients who had an allogeneic transplant be able to train their new immune cells to resist myeloma through the use of vaccines?

Question

How long does it take to produce vaccines?
We wish to thank the faculty for their contributions and Bristol-Myers Squibb for providing an educational grant in support of this activity.

Additional Information

Speak to an MMRF Nurse Specialist
Call Monday – Friday, 9:00AM – 7:00PM EST
866-603-MMCT (6628)

Need information about clinical trials?
Go to: myelomatrials.org

Join the MMRF CoMMunity Gateway to Share and Connect with other Members of the Myeloma Community
Go to: mmrfcommunitygateway.org