Cancer Vaccines as Effective Immunotherapy

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Multiple Myeloma

- Approximately 20,000 new cases and nearly 11,000 deaths per year

- Presentation with anemia, pathologic fractures, infection, hypercalcemia and renal dysfunction

- Spinal cord compression, Renal failure, hyperviscosity


Case Presentation

• 49 year old physician presents with back pain and fatigue
• Labs demonstrate anemia IgG level of 6000 with kappa light chain of 600
• MRI demonstrates lytic lesions with pathologic vertebral compression fracture

• What is my prognosis?
Multiple Myeloma: Progress but No Cure

- Advent of biological therapy such as lenalidomide and bortezomib results in higher levels of cytoreduction
- Autologous stem cell transplantation prolongs PFS
- Maintenance therapy with lenalidomide prolongs duration of response potentially due to immune modulation
- Current therapeutic options are not curative
Efficacy of Cellular Immunotherapy for Myeloma: Graft versus Disease Effect

Cutaneous Acute GVHD
Can Cancer Vaccines Selectively Target Myeloma Cells?
Myeloma Associated Immune Suppression

Development an Effective Cancer Vaccine

Vaccine Design: Effective antigen presentation

Reversing the immunosuppressive milieu

Breaking tolerance

DC/TUMOR FUSION VACCINE

Diagram illustrating the interaction between DC and Tumor cells, showing the expression of various markers such as CD83, CD54, CD86, CD80, HLA Class II, MUC1, CD38, CD136, and CD138.
Animal Model: Fusion Vaccine Induces Disease Regression in Metastatic Disease

Vaccination with DC/MM Fusions: Phase 1 Trial

- 17 patients have completed vaccination
- Mean age 57 years old
- Mean BM Plasma Cell Involvement: 35%
- Median number of prior treatment regimens: 4
- 14 patients with prior autologous transplant
- Vaccine Dose:
  - 3 patients: $1 \times 10^6$
  - 4 patients: $2 \times 10^6$
  - 9 patients: $4 \times 10^6$

Blood. 2011 Jan 13;117(2):393-402
Adherent PBMCs cultured for 5-7 days with GM-CSF & IL-4; TNF-α added for 48-72 hours.

Myeloma cells isolated.

DCs assessed for DC & tumor specific markers.

DC & myeloma fused with 50% PEG at DC: tumor, 3:1 to 10:1.

Fusion cells quantified by measuring dual expression of unique DC & tumor markers.

Myeloma cells assessed for tumor & DC specific markers.

DCs assessed for DC & tumor specific markers.

Leukapharesis.

Bone marrow.

GM-CSF 100ug at vaccine site for 4 days.

Doses prepared & frozen microbiology testing sent.

Fusion cells quantified by measuring dual expression of unique DC & tumor markers.

GM-CSF 100ug

CD38

CD138

CD86

MUC

CD38

CD138

DC40

CD86

CD80

CD83
Vaccine Characterization

Myeloma Cells CD-38

Dendritic Cells CD86

DC/MM Fusions
CD38/CD86

Blood. 2011 Jan 13;117(2):393-402
Adverse Events

• Treatment associated events transient grade I-II
  – Injection site reactions 37
  – Edema 6
  – Muscle Aches 5
  – Fatigue 2
  – Fever 1
  – Chills/sweats 2
  – Diarrhea 1
  – Pruritis 1
  – Rash 2
  – Anorexia 1

• Episode of DVT/PE with antecedent history of DVT
Vaccine site reaction: Skin Biopsy

CD8 Staining

Blood. 2011 Jan 13;117(2):393-402
Cellular Immune Response

Blood. 2011 Jan 13;117(2):393-402
SEREX analysis of Humoral Response

Pre-vaccine serum from MM010 (RGS19 negative)

1 month post-vaccine serum from MM010 (RGS19 positive)
Vaccination with DC/Myeloma Fusions: Summary

• 66% with disease stabilization for at least 2 months post-vaccination, 3 patients ongoing at 7, 14, and 30 m

• A majority of patients with evidence of immunologic response

• Humoral response detected against novel antigens

• ? Of immunologic escape in some patients
Development an Effective Cancer Vaccine

Reversing the immunosuppressive milieu

Vaccine Design
Effective antigen presentation

Vaccination in Conjunction with Stem Cell Transplant

• Autologous transplant for myeloma offers a unique opportunity to explore the role of cancer vaccines
  – Patients achieve minimal disease state but reliably relapse
  – Transplant mediated cytoreduction minimizes immunosuppression

• Enhanced response to vaccination post-transplant in animal models
  – Depletion of regulatory T cells during the period of post-transplant lymphopoietic reconstitution
  – Expansion of tumor reactive clones
Phase II trial evaluating DC/Myeloma Fusion cell vaccination in conjunction with autologous transplant

- **Number Enrolled**: 45  
  - 80% Male, 20% Female

- **Number Received Vaccine**: 35

- **Median Age at Enrollment**: 58

- **Median Bone Marrow Involvement at Enrollment**: 55% plasma cells

- **Median Time from Transplant to Post-Transplant Vaccine**: 48 days

### Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Number of episodes</th>
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<tbody>
<tr>
<td>Vaccine site reaction (erythema, itching)</td>
<td>1</td>
<td>38</td>
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<tr>
<td></td>
<td>2</td>
<td>6</td>
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<tr>
<td>Myalgia</td>
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<td>Leukopenia</td>
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<td>Headache</td>
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<td>Elevated TSH</td>
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<td>Decreased appetite</td>
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<td>Rash</td>
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<tr>
<td>ANA positivity</td>
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<tr>
<td>Periorbital edema</td>
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In Vitro Measures of T Cell Function

A

PHA stimulation

B

Tetanus Toxoid stimulation

Pre-mob post-transplant vaccination time points months post-vaccination

Pre-mob post-transplant vaccination time points months post-vaccination

Stimulation index

Stimulation index
Mean percentage of tumor reactive lymphocytes

**C**

**CD4⁺/IFNγ⁺ T cells**

- Pre-mobilization (n=23)
- Post-transplant (n=23)
- Peak (n=23)

**D**

**CD8⁺/IFNγ⁺ T cells**

- Pre-mobilization (n=23)
- Post-transplant (n=23)
- Peak (n=23)
Regulatory T cells decline following transplantation.
Clinical Response

COHORT 1

<table>
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<tr>
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<th>100 Day Post-Transplant</th>
<th>Post 100 Day (Best Response)</th>
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<tbody>
<tr>
<td>CR/nCR</td>
<td>29%</td>
<td>33%</td>
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<tr>
<td>VGPR</td>
<td>54%</td>
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<td>PR</td>
<td>13%</td>
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COHORTS 1 & 2

<table>
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<tr>
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<th>100 Day Post-Transplant</th>
<th>Post 100 Day (Best Response)</th>
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<tbody>
<tr>
<td>CR/nCR</td>
<td>31%</td>
<td>40%</td>
</tr>
<tr>
<td>VGPR</td>
<td>31%</td>
<td>29%</td>
</tr>
<tr>
<td>PR</td>
<td>11%</td>
<td>49%</td>
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Bone Marrow Findings: Patient 18

Assessment of clonality

Kappa restriction

Lamda restriction
Lenalidomide Maintenance Following Autologous Transplantation

Lenalidomide Decreases the Expansion of Tregs following stimulation with DC/MM Fusions

Lenalidomide Enhances CTL response to DC/MM Fusions
CTN Study 1401

- Randomized trial of vaccination + lenalidomide maintenance vs. maintenance alone
- Assessment of conversion from PR to CR
- Immune response
- First multicenter trial for immunotherapy
- 10 cancer centers participating
PUSH-PULL Approach to Optimizing Vaccine-induced T-cell Immunity

1. Optimize antigen (e.g. epitope enhancement)
2. PUSH (& steer)
   - Cytokines (e.g. IL-15, IL-12)
   - Costimulatory molecules
   - Toll-like receptor ligands (e.g. CpG, Poly I:C, MALP-2)
3. Block negative regulation (PULL)

Negative Regulators (e.g. Treg, reg NKT, CTLA-4, PD-1, IL-13, TGF-β)

Improve: Quantity, Quality (avidity, longevity, function)

Optimized Immune Response
Biomatrix for Vaccine Delivery

Schematic illustration of the proposed 3D lymphoid-like cell construct.

Legend:
- IL-7, IL-15, and CCL19

In vivo transplanted IL-7, IL-15, and CCL19 laden scaffold loaded with fusion DC/MM cells allows infiltration of T cells.
BALB/c mice inoculated with HOPC tumor cells

Control Group

- Inoculated with 0.5x10^6 HOPC tumor cells
- 4/4 mice developed hC138 plasma cell involvement in the marrow

Vaccination Group

- Day 0: Implanted scaffold embedded with vaccine + IL7, IL15
- Day 7: Inoculated with 0.5x10^6 HOPC tumor cells
- Week 7: 6/8 mice disease free
Marrow involvement in a control mouse compared to disease free mouse with scaffold implantation

Control

Vaccine + IL-7 +IL-15 in scaffold

CD138

CD45

17%

0.1%
Development an Effective Cancer Vaccine

Reversing the immunosuppressive milieu

Vaccine Design: Effective antigen presentation

Breaking tolerance

Tumor cells express PDL-1 resulting in promoting tolerance in potentially reactive T cells.

Tumor PDL-1 may interfere with CTL mediated lysis by tumor reactive clones.
Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgios D. Kollias, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Szol, M.D.

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Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

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