Clinical Advances in Immunotherapy in Myeloma

Webinar 3, August 9, 2017
Engineered Immune Cells

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Clinical Advances in Immunotherapy in Myeloma
Webinar 3: Engineered Immune Cells

Multiple Myeloma Research Foundation

Moderator:
• Mary DeRome
Multiple Myeloma Research Foundation
Norwalk, Connecticut

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Speakers

Ivan Borrello, MD
Johns Hopkins Hospital
Baltimore, Maryland

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Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Topics for Discussion

- Introduction to immunotherapy
- CAR T–cell therapy
  - CD19
  - BCMA
- NY-ESO-1 T–cell receptor
- Additional T-cell approaches
  - Universal CAR T–cell therapy
  - Antibody-coupled T-cell receptor (ACTR)
  - Marrow infiltrating lymphocytes

How the Immune System Works

- Defends you against various “germs” or foreign invaders that cause infection, illness, or disease
  - Bacteria
  - Viruses
  - Fungi
  - Parasites
How does the body fight 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 Lineup**

- **Natural killer cells**
- **Macrophages**
- **Dendritic cells**
- **T cells**
- **B cells**

NK, natural killer.
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The Normal Function of the T Cell

Normal cell
- Major histocompatibility complex (MHC)
- "Self" peptide
- CTL
- Inhibitory receptor ligand (for example, PD-L1, "immune checkpoint")

Infected cell
- Virus "non-self" antigen
- CTL
- Infected cell

T cell is prevented from killing the normal cell because it recognizes it as "self."
T cell is activated to kill the infected cell because it recognizes it as "foreign."

Immunotherapy
Directing the immune system to fight cancer
How may myeloma cells hide from the immune system?

- They look too much like normal cells and so are not identified as foreign.
- Antigen presents 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

- **1990s**
  - Monoclonal antibodies are used in a variety of solid and hematological tumors; examples include Rituxan, Herceptin, Campath
- **2000s**
  - Vaccines are being used in prostate cancer; one example is Provenge
  - Checkpoint inhibitors are being used in melanoma (for example, Yervoy)
Immune Cell Therapy

What is it?
- It is an infusion of autologous myeloma-directed T cells

In two main ways:
1. Patient's T cells are harvested and then engineered in a lab to be able to identify specific surface markers on myeloma cells
2. These engineered T cells are then stimulated in a lab to make them more active and to proliferate and grow

How are the T cells directed to MM cells?

How does it work against myeloma?
- Infused, myeloma-directed T cells directly kill myeloma cells and stimulate T-cell immunity

Types of Immune Cell Therapy

- Chimeric antigen receptor (CAR) T cells
- T-cell receptor (TCR) engineered T cells
- Marrow-infiltrating lymphocytes (MILs)
How T Cells Are Engineered

- **Natural T cell with T cell receptor (TCR)**
  - Needs a jump start to target and kill myeloma cells

- **Engineered T cell with chimeric antigen receptor (CAR)**
  - Homing beacon built in to target and kill myeloma cells

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**CAR T Cell Process**

1. **Leukapheresis**
   - CAR T technology involves harvesting a patient’s white blood cells and stimulating certain T cells to grow

2. **Insert-engineered vector**
   - The gene sequences for the CAR construct are transferred into the T cell. T cells are then grown to numbers sufficient for the desired patient dose

3. **Re-introduce new T cells**
   - These genetically engineered cells, which express the receptors that can recognize the exact proteins that are characteristic of specific cancers, are then infused back into the patient
CAR T–Cell Therapy in Multiple Myeloma

- CART T–cell therapy: CTL019
- Myeloma precursor cell surface target: CD19
- Preliminary results of phase 1 study
  - 10 patients treated
  - 6 patients with ongoing responses
  - 1 patient (so far) attained minimal residual disease (MRD)-negative stringent complete response for > 1 year

Patient outcome evaluated

Myeloma patients with disease progression within 1 yr of prior ASCT

Second ASCT

CTL019 infusion


Advanced in Immunotherapy: CAR T Cell Therapy

- Anti-BCMA CAR T cells (LCAR-B38M)
  - 22 of 22 relapsed/refractory myeloma patients had a partial to complete response

- Anti-BCMA CAR T cells (bb2121)
  - Out of 6 relapsed/refractory patients treated so far, promising efficacy including 2 stringent complete responses and ongoing clinical responses at 6 months

BCMA, B cell maturation antigen
NY-ESO-1 TCR Engineered T-Cells in Myeloma

• T-cells genetically modified to express affinity-enhanced T cell receptors (TCRs) which recognize NY-ESO-1, an immunogenic cancer testis antigen, in HLA-A201 complex
  – NY-ESO-1 expression correlates with high risk features; present in 60% of advanced myelomas

• Study of 20 patients with rMM, HLA-A201 positive with tumor expressing NY-ESO-1 and/or LAGE-1
  – On day 2 post ASCT, 2.4 billion NY-ESO-1 engineered CD3-T-cells infused
  – 80% ORR, 70% CR
  – Median PFS 19.1mo, median OS 32.1 months
  – AEs: No clinically apparent cytokine release syndrome; Autologous GVHD in 3 patients

Additional Studies of CAR T–Cell Therapy in Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>CAR T–Cell Therapy</th>
<th>MM Surface Target</th>
<th>Patient Population</th>
<th>Results</th>
<th>Institution</th>
</tr>
</thead>
</table>
| 1     | CAR.k              | Kappa light chains| Relapsed           | • Infusion safe  
|       |                    |                   |                    | • Modest anti-myeloma activity  
|       |                    |                   |                    | (3 patients with stable disease) | Baylor College of Medicine |
| 2     | CART-138           | CD138             | Refractory         | • Safe, feasible, tolerable  
|       |                    |                   |                    | • 4 of 5 patients with stable disease | China |

**Universal CAR T–Cell (UCART) Therapy**

- **Genetic additions by gene editing**
  - T-Cell
  - CAR T-Cell

**Antibody-Coupled T-Cell Receptor (ACTR) Therapy**

- **Specific for one type of cancer**
- **Always “on” after infusion into the patient**

- **Universal: ACTR T cell can attack many different cancers**
- **Activity is controlled by antibody dosing**

- **ACTR**
  - Antibody: tumor targeting
  - CD16: Fc receptor
  - 4-1BB: co-stimulation
  - CD3ζ: TCR signaling
**Marrow-Infiltrating Lymphocytes (MILs)**

### Features of MILs
- Broad antigenic specificity
- Ability to traffic to the BM
- Persistence over time

1. Extract MILs from patient
2. Stimulate and expand MILs in lab
3. Infuse stimulated MILs back to patient

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**Marrow-Infiltrating Lymphocytes (MILs)**

- Phase 1 study to examine feasibility, safety, and efficacy
  - Results showed
    - A strong correlation between clinical outcome and tumor-specific activity
    - Achieving at least a 90% reduction in disease burden increased progression-free survival

Newly diagnosed or relapsed myeloma patients → MILs collection, expansion, and activation → Initial therapy → Autologous stem cell transplant → Activated MILs reinfusion → Myeloma-specific activity measures

## Immune Cell Therapy in Development

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<tr>
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<th>Trial</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Site(s)</th>
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<tr>
<td><strong>CAR T</strong></td>
<td>CART-19 for multiple myeloma</td>
<td>Relapsed/refractory</td>
<td>1</td>
<td>University of Pennsylvania</td>
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<tr>
<td></td>
<td>Safety study of CAR-modified T cells targeting NKG2D-ligands</td>
<td>Relapsed/refractory</td>
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<td>Dana-Farber Cancer Institute</td>
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<tr>
<td></td>
<td>Study of T cells targeting B-cell maturation antigen (BCMA) for previously treated multiple myeloma</td>
<td>Relapsed/refractory</td>
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<td>National Cancer Institute University of Pennsylvania</td>
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<tr>
<td><strong>MILs</strong></td>
<td>Tadalafil and lenalidomide maintenance with or without activated marrow infiltrating lymphocytes (MILs) in high-risk myeloma</td>
<td>Newly diagnosed; relapsed (without prior ASCT)</td>
<td>2</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
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<tr>
<td></td>
<td>Adoptive immunotherapy with activated marrow-infiltrating lymphocytes and cyclophosphamide graft-versus-host disease prophylaxis in patients with relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation</td>
<td>Relapsed/refractory</td>
<td>1</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
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<tr>
<td><strong>Affinity-enhanced T cells</strong></td>
<td>Engineered autologous T cells expressing an affinity-enhanced TCR specific for NY-ESO-1 and LAGE-1</td>
<td>Relapsed/refractory</td>
<td>1/2</td>
<td>City of Hope University of Maryland</td>
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<tr>
<td><strong>DLI</strong></td>
<td>CD3/CD28 activated Id-KLH primed autologous lymphocytes</td>
<td>Post-transplant</td>
<td>2</td>
<td>University of Pennsylvania</td>
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### Questions & Answers
Closing

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<td>Anrita Y. Krishnan, MD–Co-Chair</td>
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