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Understanding the Immune System in Myeloma

Living Well with Myeloma Teleconference Series

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The Immune System is Like a Swiss Watch

Changing one thing affects all the others!
Parts of the Immune System

- B Cell
- Plasma Cell
- T Cell
- Dendritic Cells
- Natural Killer (NK) Cell
- Stromal Cell/Fibroblast
- Monocyte/Macrophage
**Normal vs. Myeloma**

**Normal**
- Pneumonia
- B Cells
- Plasma Cells
- Memory Cells

**Myeloma**
- Antigen Trigger
- Idiotypic B Cells
- Idiotypic Plasma Cells
- Persistence/Build up of Myeloma Cells

**Persistence/Build up of Myeloma Cells**
How Myeloma Evolves

Monoclonal gammopathy of unknown significance
- Progenitor clones competing for bone marrow niche
- Tumour initiating cell

Mutation x
- Minor diagnostic subclone

Myeloma
- Dominant diagnostic clone
  - Mutation x

Mutation xy
- Minor diagnostic subclone

Relapse or plasma cell leukaemia
- Mutation x
  - (A) clone with unique mutations = diagnostic clone
- Mutation xy
  - (B) dominant clone already detectable as minor subclone at diagnosis
- Mutation z
  - (C) clone with unique mutations = diagnostic clone

Therapy
How Myeloma Messes Up the Normal Immune System

- Reduced Ig
- IgG
- IgA
- IgM

Normal B Cells

Normal Plasma Cells

Stromal Cell

Macrophage

Myeloma
Bone Marrow Microenvironment: Wow! A Lot Going On!

Why Myeloma Grows

Abnormal B Cells

Idiotypic T Cells

Fed By

Myeloma Cells Persist and Grow

Fed By

Myeloma

Block 2

Block 1

NK Cells

Macrophage

Stromal Cell
Immune Impact of Myeloma
Many Effects

- Normal Ig reduced
- Suppressive $T_{\text{regs}}$ over reactive
- Lack of specific cytotoxic $T_8$ cells (TILs)
- Helper T cells blocked
- Natural killer (NK) cells reduced/blocked
How to Recover Immune Function?

Very complex, multiple factors…
…NOT easy

• Treat the myeloma
• Enhance/reconstitute immune cell numbers and/or functions
Types of Immune Therapy

• Direct antibody attack on myeloma
• Enhance “good” immune cell activity
  – NK cells
  – T cells
  – Dendritic cells e.g. with vaccines
  – Macrophages
• Infuse T, Dendritic, or NK cells
  – engineer/grow in laboratory
6 Ways Anti-CD38 Attacks Myeloma*

1. Apoptosis with crosslinking
2. Apoptosis without crosslinking
3. Inhibition of ectoenzyme function
4. ADCC
5. ADCP
6. MAC

*Daratumumab
SAR650984
MOR202
Anti CD38 MoAB: Daratumumab

Response with higher doses
Using Your Own Natural Killer (NK) Cells to Attack with Elotuzumab (Anti-SLAM F7)

NK Cell

SLAM F7

Elotuzumab Trigger

CD16

SLAM F7

Myeloma Cell

Elotuzumab Linkage
Examples

• IMiDs (e.g. Revlimid) enhance NK cell killing

• Proteasome inhibitors (e.g. Velcade) increase dendritic cell activated T-cell cytotoxicity
What IMiDs Do

IMiDs = Immune Modulatory Drugs

Enhanced NK Cell Killing

IMiDs

IFN γ

IL-2

Trigger

IL-6 Block

Myeloma Cell
Synergy from Combinations: Elotuzumab (SLAMF7 Antibody) + Len/Dex*

10 mg/kg Elotuzumab (n=36)

Dramatic benefit

≥ PR 92%
- VGPR 17
- CR/sCR 5

Elotuzumab + Len + LoDex

Median time to progression/death:
- 10 mg/kg (n=36): not yet reached
- 20 mg/kg (n=37): 18.6 mos (95% CI 12.9-29.7)

What about Velcade?

Another immunomodulatory pathway:

Vaccine can enhance HSP90, HSP60, and HSP90.

Enhanced T8⁺ mediated cytotoxicity.

International Myeloma Foundation
Value of Combinations

- Many drugs have immune effects

So combinations make sense!
Possible Role for Anti-PD 1

- **Normal individual**
  - Active NK cell
  - Active T cell
  - Target cell
  - Captured by immune response

- **Patient with MM**
  - NK cell
  - T cell
  - MM cell
  - Escapes immune response
  - Inhibition of NK cell function
  - Inhibition of T-cell activation
  - Inhibition of T-cell proliferation
  - PD-L1

Diagram illustrates the interaction between immune cells and myeloma cells, highlighting the role of anti-PD-1 treatment in normal individuals versus patients with MM.
Current Options for MoAb Therapy

Antibody Therapies
- Ulocuplumab
- Dacetuzumab
- Lorvotuzumab
- Lucatumumab
- Elotuzumab
- Daratumumab
- SAR650984
- MOR202

Antibody Therapies
- BI-505
- Revtansine
- Indatuximab
- Pidilzumab
- Rivolumab
- Pembrolizumab
- Milatuzumab
Impact of Successful Treatment

At Diagnosis

Excellent Response

Survival ≥ 10 Years

Reconstitution

- T4+T8; Th: IL-17
- NK Cells
- Normal B Cells
- Plasma Cells
- Macrophages
- Dendritic Cells

Unique Immune Signature
What Does All This Mean in 2015?

• The immune system matters!
• Immune attack is largely independent of underlying mutations/high risk features (e.g. 17p-; t(4;14) 1q+)

We must learn how to sequence and combine immune and other therapies!
Key Opportunities

• Immune modulation early
• Combinations to achieve best initial results
• Use immune approaches to achieve/enhance MRD status
MRD Sensitivity and Treatment Outcomes

- Serum Tools
- Immunophenotype
- RQ-PCR
- Next-Generation Flow
- Next-Generation Sequence
- Cure

Years

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Black Swan 3-Step Approach

1 Early Diagnosis
   • Add immune Rx to primary therapy

2 MRD Assessment of Response
   • Study MRD myeloma and immune cells

3 Clinical Trials
   • To eradicate MRD
Details of 3-Step Plan

**MRD Assessment**
- **If negative**
  - Immune Maintenance
  - Monitor
- **If positive**
  - Study Residual MRD
  - Develop specific Rx
- **Assess Relapse/Resistant Disease**
  - Immune Rx
  - Alternate Rx

**Immune Maintenance**

**Alternate Rx**
Bottom Line

Immune therapy matters

Can be key to better and longer remissions...

...and lead to cure