International Myeloma Workshop 2017: Immunotherapy

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UCLH
T cell activation occurs after interaction between T cell receptor (TCR) and antigen in the context of MHC (signal 1) plus CD28 costimulation (signal 2).
Immunotherapy in Myeloma

1. Monoclonal Antibodies that target the myeloma
2. Monoclonal Antibodies that take the brakes off the immune system
3. Engineering Immune Cells to attack myeloma
Monoclonal Antibodies that target the myeloma
Daratumumab

Licensed for:
• Patients with relapsed myeloma that have had a prior proteasome inhibitor and IMiD and whose disease worsened on last therapy
• in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for those that have received at least one prior therapy

NICE:
• Provisional “No” for monotherapy
• Final verdict expected July
Daratumumab

Treatment Schedule

Cycle 1-2: Weekly
Cycle 3-6: Every 2 weeks
Cycle 7 onwards: Every 4 weeks until disease progression
Each cycle is 28 days

1st Cycle Infusion Times

Intrusion time (hours)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st dose</td>
<td>9.7h</td>
</tr>
<tr>
<td>2nd dose</td>
<td>4.1h</td>
</tr>
<tr>
<td>3rd dose</td>
<td>3.6h</td>
</tr>
<tr>
<td>4th dose</td>
<td>3.5h</td>
</tr>
</tbody>
</table>

(9.4-17) (2.8-7.8) (2.8-6) (3.2-6)
Immune Checkpoint Inhibitors: “taking of the brakes”

T cell

Tumor cell or APC
Pembrolizumab + Revlimid + Dexamethasone

- 49 years, Male
- Diagnosed in 2010
  - MM IgGk
- Initial treatment
  - Bort + PLD: MR
  - ASCT: refractory
  - Len/Dex: refractory
MUK-14: Phase I/II trial of Pembrolizumab with Cyclophosphamide and Revlimid for Relapsed Myeloma

- For those that have had 2 or more prior lines
- Steroid sparing
- Designed to be an immune stimulating combination
- Scheduled to open by August 2017:
  - UCLH
  - Guys
  - Birmingham
  - Southampton
Cellular Immunotherapy: Engineering Immune Cells to attack myeloma
Myeloma CD19 CAR T cells

Garfall et al., NEJM 2015
Anti-BCMA CAR-T cell therapy

Dose Levels (x10^6/kg)

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N</th>
<th>Best Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>3</td>
<td>SDx2, PRx1</td>
<td>mild fever</td>
</tr>
<tr>
<td>1.0</td>
<td>3</td>
<td>SDx3</td>
<td>mild fever</td>
</tr>
<tr>
<td>3.0</td>
<td>4</td>
<td>SDx3, VGPRx1</td>
<td>Moderate CRSx1</td>
</tr>
<tr>
<td>9.0</td>
<td>2</td>
<td>sCRx1, PRx1</td>
<td>Severe CRSx2</td>
</tr>
</tbody>
</table>

Cytokine Release

CART Persistence

Kochenderfer et al., ASH 2015
Phase 1 Trial of CAR T cells for relapsed myeloma

1. A cancer patient’s immune system (T-cells) fails to recognise malignant cells
2. Autolus engineers the T-cells to express Chimeric Antigen Receptors (CARs)
3. Engineered CAR T-cells recognise and destroy malignant cells

Now open at UCLH
Summary

- Immunotherapy is a new way of targeting cancers
- May make a real change to how myeloma is treated in the future
- We are still learning how best to use them and the side effects
- May not be suitable for everyone
- Clinical trials are open/ will be soon opening at UCLH