Which is the best immune approach to replace ASCT?
CAR T or BiTEs?
BiTEs!!

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Agenda

Will immunotherapy replace ASCT or consolidate ASCT?

Why maintain ASCT?
- World-wide access
- Cost-benefit ratio
- Low TRM
- In SR MM long term disease control – Cure fraction
- Increase the cure rate by combination therapy!

BiTEs vs CAR T
- Availability
- Drug variability/precise dosing
- One shot therapy vs treatment until PD
- Efficacy/Safety
- Resistance mechanisms

Martinez-Lopez J et al., Blood 2011

Introduction
The poor man’s CAR T cells
Treatment forever!
Less effective!
Only for elderly/frail patients!

The race is on!!
CAR T cell product highly variable
T cell subset Composition
Transduction Efficacy
Viability

What do you get?
- CAR T cell product highly variable
- T cell subset Composition
- Transduction Efficacy
- Viability

What do you want?
- Precise dosing
  - s.c./i.v. application
  - Application qW, q2W, q3W etc.
- Which target?
  - BCMA/GPRC5D/FcHR5/CD38?

New Strategies: Allo-CAR T cells
- But: Immunogenicity/extensive genetic engineering → Persistence?

It can take up to 8 weeks from leukapheresis to CART infusion
Do we need to give BiTes until PD? **No!**

Retreatment with BiTEs possible/effective!

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Initial treatment</th>
<th>Intervening alloHSCT</th>
<th>Retreatment</th>
<th>RFS (months)</th>
<th>Overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>15–30 μg/m²</td>
<td>12.4</td>
<td>PD</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5–15 μg/m²</td>
<td>3.4</td>
<td>No response</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

**ORR 36% after 2nd application (comparable to the 44% reported for initial treatment!**

3 out of 4 responding patients still alive up to 20 mo. post retreatment!

Max. response in all our patients after 1-3 mo. (4-12 applications of BCMA-BiTEs)

Response-adapted therapy and retreatment
→ Reduce duration of therapy / T cell exhaustion/toxicity esp. infectious complications

Topp MS et al., Leukemia 2017
CAR T Cell Therapy in MM: One shot treatment? No

But: BCMA-CAR T limited persistence

CAR T Cell persistence over time

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>24</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>No. (%) with detectable vector</td>
<td>23 (96)</td>
<td>19 (86)</td>
<td>13 (57)</td>
</tr>
</tbody>
</table>

All 33 patients were included in the analysis. Data from samples with <50 ng total DNA input were excluded.

Raje N et al., NEJM 2019

CAR T Cell Therapy for MM

- Combination Therapy (continuous therapy)
  - IMiD/CelMODs
  - Immune Checkpoint Blockers
  - Anti-CD38 Ab ± IMiDs
  - TKI, e.g. Ibrutinib

Long-term persistence of CAR Ts, long term disease control/cure?
BCMA-directed CAR T Cell Therapeutics vs BCMA-directed Bispecifics

### Efficacy/Toxicity

<table>
<thead>
<tr>
<th></th>
<th>CAR T</th>
<th>Bispecifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>80 - 100 %</td>
<td>&gt;60 - 83 %</td>
</tr>
<tr>
<td>CR</td>
<td>40 - 85 %</td>
<td>13 - 50 %</td>
</tr>
<tr>
<td>PFS</td>
<td>&gt; 1 - 1.5 yrs</td>
<td>&gt; 6 mo.</td>
</tr>
<tr>
<td>CRS Gr. 3</td>
<td>3 - 6 %</td>
<td>0 - 3 %</td>
</tr>
<tr>
<td>ICANS Gr. 3</td>
<td>3 - 10 %</td>
<td>0 - 1 %</td>
</tr>
</tbody>
</table>

Following CAR T Cell Therapy grade 3 cytopenia can last for of 2-3 months !!

→ Hematotoxicity clearly less frequent/less severe/shorter after BiTEs vs CART cells

Munshi N et al. NEJM 2012; Madduri D et al. ASH 2020 #177; Garfall AL et al. ASH 2020 #180; Lesokhin AM et al. ASH 2020 #3206; Madduri D et al. ASH 2020 #291; Rodriguez et al. ASH 2020 #293; Chari A et al. ASH 2020 #290; Cohen AD et al. ASH 2020 #292; Harrison S et al. ASH 2020 #181; Costello C et al. ASH 2020 #134; Kumar et al. ASH 2020 #133; Piasecki et al. ASH 2020 #2350; Colonna et al. ASH 2020 #2358.

But: Few patients treated with BiTEs in highest dose level: In some trials MTD not reached!
Short follow up for bispecifics!
Treatment of elderly patients?

<table>
<thead>
<tr>
<th>Inclusion:</th>
<th>Ide-cel (all treated) N=128</th>
<th>Cita-cel N=97</th>
<th>Bispecific mAbs (pooled data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, medium</td>
<td>61 yrs (up to 78)</td>
<td>60 yrs (up to 75)</td>
<td>64 yrs (up to 88)</td>
</tr>
</tbody>
</table>

Ide-cel resulted in an ORR of **73 %**
- Patients > 65 yrs (n=45): **84 %**
- Patients ≥ 70 yrs (n=20): **90 %**
- Tolerability, PFS and DoR are comparable with the ITT population

Bispecific TCE successful and safe in frail patients!

Munshi NC et al., J Clin Oncol 2020; Berdeja JG et al., J Clin Oncol 2020; Mailankody S et al., J Clin Oncol 2020; Costa LJ et al., EHA 2020; Usmani SF et al., J Clin Oncol 2020

Mosunetuzumab CD20xCD3-BiTE

Olszewski A et al., ASH 2020, Abstract #401
Antigen escape in BCMA CAR T Cell Therapy for MM

Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma

Matteo C. Da Vià, Oliver Dietrich®, Marietta Truger®, Panagiota Arampatzis®, Johannes Duell®, Anke Heidemeyer®, Xiang Zhou, Sophia Danhof®, Sabrina Kraus, Manik Chatterjee®, Manja Meggendorfer®, Sven Twardziok®, Maria-Elisabeth Goebeler®, Max S. Topp®, Michael Hudecek®, Sabrina Prommersberger®, Kristen Hege®, Shari Kaiser®, Viktoria Fuhr®, Niels Weinhold®, Andreas Rosenwald®, Florian Erhard®, Claudia Haferlach®, Hermann Einsele®, K. Martin Kortüm®, Antoine-Emmanuel Saliba© and Leo Rasche®

Homozygous BCMA loss in response to T-cell Engagiers (TCE)

Truger MS et al. Blood Adv 2021

719 Cite-Seq Profiling of T Cells in Multiple Myeloma Patients Undergoing BCMA Targeting CAR–T or Bites Immunotherapy

Program: Oral and Poster Abstracts
Type: Oral
Session: 651. Myeloma: Biology and Pathophysiology, excluding Therapy II
Hematology Disease Topics & Pathways:
multiple myeloma, Biological, Diseases, CAR-Ts, Therapies, Biological Processes, Technology and Procedures, Plasma Cell Disorders, immunotherapy, Lymphoid Malignancies, Clinically relevant, immune mechanism, integrative –omics, NGS, RNA sequencing

Monday, December 7, 2020: 1:30 PM
Noemie Echbaly, PhD®, Ranjan Maity, PhD®, Elie Barakati®, Sylvia McCulloch, MD, MSc®, Peter Duggan, MD, FRCPC®, Victor Jimenez-Zepeda, MD, Nizar Bahls, MD© and Paola Neri, MD©

ARTICLE

Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma

Mehmet Kemal Samur®, Mariateresa Fulchirr® ©, Anil Aikat Samur©®, Abdur Hamid Bazazbach® ©, Yu-Tsu Tai® ©, Ranc Prabhula® ©, Alejandro Alonso®, Adam S. Sperling®, Timothy Campbell®, Fabio Petrocca®, Kristen Hege®, Shari Kaiser®, Hervé Avet Loiseau®, Kenneth C. Anderson®© © & Nikola C. Munshi® ©

BCMA targeting chimeric antigen receptor (CAR) T cell therapy has shown deep and durable responses in multiple myeloma. However, relapse following therapy is frequently observed.
How to deal with BCMA loss?

Produce CAR T cells targeting surface antigens beyond BCMA on MM

→ But: Time-consuming production / successful production after CAR T cell failure?

Off-the-shelf Bispecific T cell engagers available against various surface antigens:

- BCMA
- GPRC5D
- FcHR5
- CD38

→ Can they be used sequentially?
Patient Case

<table>
<thead>
<tr>
<th>Year</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/2011</td>
<td>3x PAD</td>
</tr>
<tr>
<td>05/u. 08/2011</td>
<td>Tandem-Mel $\rightarrow$ CR</td>
</tr>
<tr>
<td>4/14</td>
<td>PD $\rightarrow$ RD 6 cycles</td>
</tr>
<tr>
<td>12/15 - 12/16</td>
<td>RD $\rightarrow$ 16 cycles Panobinostat/Bortezomib/Dexa $\rightarrow$ PD</td>
</tr>
<tr>
<td>05 – 11/17</td>
<td>6x Ixa/Thal/Dex $\rightarrow$ PD</td>
</tr>
<tr>
<td>11 – 12/12</td>
<td>1x Rd $\rightarrow$ PD</td>
</tr>
<tr>
<td>01/18</td>
<td>BCMA-Bite (AMG420) $\rightarrow$ sCR</td>
</tr>
<tr>
<td>09/19</td>
<td>PD $\rightarrow$ KRd 18x</td>
</tr>
<tr>
<td>07/20</td>
<td>PD $\rightarrow$ Dara/Vel/Dex $\rightarrow$ PD</td>
</tr>
<tr>
<td>12/20</td>
<td>Belantamab $\rightarrow$ PD (Documented irreversible BCMA-loss)</td>
</tr>
<tr>
<td>12/20</td>
<td>VTD-PACE 3x $\rightarrow$ PD</td>
</tr>
</tbody>
</table>

→ GPRC5D-targeting BiTE!

Yes:
After failure of BCMA BiTE targeting BiTEs targeting other MM-surface Ag with BiTEs like GPRC5D/FcHR5 have been successful

57 year ♂, LC-MM, ISS-IIIB, acute renal failure, hypercalcemia (short-term dialysis), multiple osteolyses

Data
Bispecific Antibodies/T Cell Engagers (TCE) vs CAR T cells

The race is finished!!

And the winner is: Bispecific T cell engager (BiTE)!
Bispecific Antibodies/T Cell Engagers (TCE)

= Best immune approach to replace or consolidate ASCT

- Better availability (off the shelf vs time consuming production)
- Precise dosing (vs drug variability)
- Broad range of specificities as off the shelf products (vs long production time/failure)
- Better tolerability (CRS/ICANS/hematotoxicity)
- Retreatment more successful with BiTEs
- Duration of treatment not necessarily longer (optimal response after 1-3 mo BiTE therapy vs CAR T cells > 2 mo therapy)
- Efficacy similar with further dose escalation of Bites or combination therapies?
Retreatment with CAR T cells (at least the same product) of limited value!

<table>
<thead>
<tr>
<th>Best overall response—no. (%)</th>
<th>Total Enrolled (N=140)</th>
<th>Total Retreated (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response</td>
<td>94 (67)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>25 (18)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>27 (19)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22 (16)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (6)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Not evaluable*</td>
<td>14 (10)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Median progression-free survival (95% CI)—mo</td>
<td>9.5 (6.9–12.5)</td>
<td>1.0 (1.0–2.1)</td>
</tr>
</tbody>
</table>
### BCMA-directed CAR T Cell Therapeutics vs BCMA-directed Bispecifics

<table>
<thead>
<tr>
<th></th>
<th>CART</th>
<th>BiTEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ide-Cel²</td>
<td>Cilta-Cel¹</td>
</tr>
<tr>
<td>Neutropenia Grade ≥ 3</td>
<td>89%</td>
<td>80%</td>
</tr>
<tr>
<td>Anemia Grade ≥ 3</td>
<td>60%</td>
<td>45%</td>
</tr>
<tr>
<td>Thrombocytopenia Grade ≥ 3</td>
<td>52%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Following CAR T Cell Therapy grade 3 cytopenia can last for of 2-3 months!!

→ Hematotoxicity clearly less frequent/less severe/shorter after BiTEs vs CART cells

1. Berdeja J et al., Lancet 2021
2. Munshi N et al., NEJM 2021
3. Harrison S et al., ASH 2020 Abstract#181
4. Krishnan A et al., ASCO 2021 Abstract#8007
5. Costa LJ et al., ASH 2019 Abstract#143