Is there a role for allogeneic transplantation in Multiple Myeloma

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Allogeneic transplantation in MM

- MM used to be an incurable disease with standard chemotherapy
- With modern therapy which includes novel agents in induction and/or maintenance, and single/tandem autologous transplants, survival has markedly improved and survival beyond 10 years has become more common

- AlloSCT is the crudest and oldest immunotherapy for MM
  - Provides graft-versus-myeloma effect ("allo effect"): Donor lymphocyte infusion induce remission
  - Chronic GVHD is associated with lower relapse rate
  - Prospect of long term disease control

- Standard alloSCT is limited to younger patients, in good medical condition
  - Median age at diagnosis: 65-70y; only 7% < 55y
  - The role and timing of alloSCT during disease course is controversial
  - The availability of novel anti-MM agents have made alloSCT less appealing to the clinicians
Allogeneic Transplantation can cure some patients with MM.
Allogeneic Transplantation can cure some patients with MM

AlloSCT may induce cure in MM - long term follow up

German Study (DSMM)
n=18
TMI (9Gy)
Busulfan (9-12 mg/kg)
Cyclophosphamide (120 mg/kg)
ATG Fresenius
M. Myeloma (stage II/III)
1998-2001

Long term follow up
TRM: 17%
12y PFS: 35%
12y OS: 50%
For those with CR:
12y PFS/OS: 60%

Kroger N. et al. BBMT 16:861-864, 2010
AlloSCT is inducing cure in MM especially in patients achieving negative MRD: Clinical outcome by molecular remission status (GIMEMA Study)

Median Follow Up: 11.9 years

Probability of OS (A) and EFS (B) by molecular remission (MR) status. The curves refer to the series of 19 multiple myeloma patients receiving tandem auto-allo transplantation and evaluable in terms of minimal residual disease by polymerase chain reaction

Courtesy from B. Bruno
Allo SCT for Multiple Myeloma in Europe

EBMT registry: 7333 patients
Current upfront allograft 11.3% vs 36.6% relapsed after a first autograft (5 year PFS and OS of 26% and 33%)

Michallet ASH 2014

Sobh M et al Leukemia advance online publication 20 May 2016
## Allo SCT for Multiple Myeloma in US

<table>
<thead>
<tr>
<th>Annual Numbers 150-200 pts</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>After Prior auto</td>
<td>72%</td>
</tr>
<tr>
<td>Tandem Auto -&gt; Allo</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Early Relapse</strong></td>
<td><strong>15%</strong></td>
</tr>
<tr>
<td><strong>Later Relapse</strong></td>
<td><strong>52%</strong></td>
</tr>
<tr>
<td>Day 100 mortality</td>
<td>10%</td>
</tr>
</tbody>
</table>
Role of CR in Multiple Myeloma

- Achievement of CR is associated with prolonged overall survival and should be the objective for younger patients
- Depth of remission (CR < flow cytometry < molecular CR) is of great importance with respect to long-term freedom from disease
- New technologies for assessing MRD (NGS; MFC; PET-CT)
- Post-transplant strategies to obtain molecular remission includes consolidations and maintenance therapy
## Achieving MRD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASO-qPCR</th>
<th>MFC</th>
<th>VDJ Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applicability</td>
<td>60%-70%</td>
<td>Nearly 100%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Need for Baseline Sample</td>
<td>Yes, requires production of patient-specific probes</td>
<td>Not required, abnormal plasma cells can be identified in any sample by their distinct immunophenotypic pattern vs. normal plasma cells</td>
<td>Baseline samples required for identification of the dominant clonotype; alternatively, a stored sample from time-point with detectable disease can be used to define “baseline” status</td>
</tr>
<tr>
<td>Sample Requirements</td>
<td>&lt; 1 million cells sufficient</td>
<td>Recent, sensitive methodology requires over 5 million cells to be analyzed</td>
<td>&lt; 1 million cells sufficient</td>
</tr>
<tr>
<td>Sample Processing</td>
<td>Can be delayed</td>
<td>Needs assessment within 24-48 hours, requires a fresh sample</td>
<td>Can be delayed; can use both fresh and stored samples</td>
</tr>
<tr>
<td>Sample Quality Control</td>
<td>Not possible. Additional studies required</td>
<td>Immediate with global bone marrow cell analysis</td>
<td>Not possible. Additional studies required.</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>≥ 1 in 100,000</td>
<td>≥ 1 in 100,000</td>
<td>≥ 1 in 100,000</td>
</tr>
<tr>
<td></td>
<td>In frequent clones may not be evaluable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turnaround and Complexity</td>
<td>Labor intensive, requires development of patient-specific primers/probes, may take several days</td>
<td>Can be done in few hours, automated software available</td>
<td>Typically days for turnaround, requires intense bioinformatics support. Use of local laboratories may speed up turnaround</td>
</tr>
<tr>
<td>Clonal Consideration</td>
<td>Detects only single clone or some of the related clones</td>
<td>Considers all clones with similar phenotype but evolving clone with change in phenotype may not be evaluable</td>
<td>Can take into account all minor clones with infrequent occurrence</td>
</tr>
</tbody>
</table>

Abbreviations: ASO-qPCR, allele-specific oligonucleotide polymerase chain reaction; MFC, multiparameter flow cytometry.
TTP and OS of series according to minimal MRD levels. (A) TTP and (B) OS for MRD levels ≤10\(^{-5}\) vs >10\(^{-5}\), as determined by deep sequencing.

Relapse is in correlation with MRD

P<0.001

Patients (%)

Months of follow-up

N at risk
MRD pos 65 57 43 30 4
MRD neg 172 166 151 86 17

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Attal M et al Blood 2015 126:391
AlloSCT provides the deepest MRD in MM

Tumor cells

Clinical CR

Long-term remission

Molecular CR

Cure

10^{-1}

10^{-2}

10^{-3}

10^{-4}

10^{-5}

10^{-6}

10^{-7}

10^{-8}

Conv. treatment
HD-therapy
Auto-allo therapy

1
2
3
4
5 years

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Myeloablative SCT in MM

- Multiple trials in the 80s and early 90s
- Multiple regimens (Cy/TBI, TBI/Mel, Bu/Cy) with no major differences in outcome
- CR rates ~50%, about 50% of CR molecular, suggesting a possible cure
- TRM 30-50% leading to almost complete abandonment of this approach
- 20-25% remain progression-free at 10 years
RIC alloSCT in MM

TRM

- Standard n=196
- RIC n=321
- p=0.001

Relapse

- P<0.0001

Crawley for EBMT Blood 2007
RIC alloSCT in MM: OS

Survival Probability

Time (Months)

RIC n=321

Standard n=196

P=0.3

Crawley for EBMT Blood 2007

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DLI post RIC alloSCT for MM

- 54 patients
- 52% responded, 17% CR
- median PFS 19 months
- High incidence of GVHD, low TRM

DLI for relapse

- Studies for relapsed patients: ORR: 40-67% and CR: 19-30%
- Acute GvHD: 52-56% and cGvHD: 26-44%
- Strong correlation between response and occurrence of GvHD

Tandem Auto / Allo SCT for MM

- **Standard-Allograft**
  - High-dose chemotherapy
  - Allogeneic Immunotherapy

  - Autologous SCT
  - Allogeneic SCT after reduced intensity conditioning

  - Adoptive Immunotherapy (DLI)

  **2 - 3 Months**
# Auto-allo tandem approach

<table>
<thead>
<tr>
<th></th>
<th>Maloney</th>
<th>Kröger</th>
<th>Carella</th>
<th>Bruno</th>
<th>Seok</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GvHD II – IV</strong></td>
<td>38.5 %</td>
<td>32 %</td>
<td>44 %</td>
<td>36 %</td>
<td>33 %</td>
</tr>
<tr>
<td><strong>Acute GvHD III – IV</strong></td>
<td>8 %</td>
<td>6 %</td>
<td>18 %</td>
<td>11 %</td>
<td>8 %</td>
</tr>
<tr>
<td><strong>Chronic GvHD</strong></td>
<td>64 %</td>
<td>28 %</td>
<td>37 %</td>
<td>31 %</td>
<td>50 %</td>
</tr>
<tr>
<td><strong>Chronic extensive GvHD</strong></td>
<td>46 %</td>
<td>8 %</td>
<td>18 %</td>
<td>n. d.</td>
<td>9 %</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>52 %</td>
<td>55 %</td>
<td>62 %</td>
<td>58 %</td>
<td>83 %</td>
</tr>
<tr>
<td><strong>Partial remission</strong></td>
<td>29 %</td>
<td>27 %</td>
<td>6 %</td>
<td>25 %</td>
<td>n. d.</td>
</tr>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>18</td>
<td>16</td>
<td>30</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td><strong>Estimated overall survival</strong></td>
<td>78 % (at 2 years)</td>
<td>70 % (at 3 years)</td>
<td>62 % (at 3 years)</td>
<td>n. d.</td>
<td>100 % (at 2 years)</td>
</tr>
<tr>
<td><strong>Estimated progression-free survival</strong></td>
<td>55 % (at 2 years)</td>
<td>54 % (at 3 years)</td>
<td>56 % (at 3 years)</td>
<td>n. d.</td>
<td>100 % (at 2 years)</td>
</tr>
<tr>
<td><strong>Treatment-related mortality at day 100 at 1 year</strong></td>
<td>0 %</td>
<td>6 %</td>
<td>0 %</td>
<td>2 %</td>
<td>0 %</td>
</tr>
<tr>
<td><strong>Complete donor chimerism</strong></td>
<td>100 %</td>
<td>100 %</td>
<td>87 %</td>
<td>n. d.</td>
<td>100 %</td>
</tr>
</tbody>
</table>
### Newly diagnosed MM patients: Double auto versus auto- RIC allo

<table>
<thead>
<tr>
<th>Institution</th>
<th>Patients</th>
<th>%CR</th>
<th>EFS (m)</th>
<th>OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM¹</td>
<td>166 vs 46</td>
<td>37 vs 52</td>
<td>25 vs 31</td>
<td>57 vs 41</td>
</tr>
<tr>
<td>GIMEMA²</td>
<td>82 vs 80</td>
<td>26 vs 55</td>
<td>33 vs 37</td>
<td>64 vs NR</td>
</tr>
<tr>
<td>PETHEMA³</td>
<td>85 vs 25</td>
<td>11 vs 40</td>
<td>20 vs 26</td>
<td>58 vs 60</td>
</tr>
<tr>
<td>Hovon⁴</td>
<td>138 vs 122</td>
<td>42 vs 45</td>
<td>28 vs 22%* 6y</td>
<td>55 vs 55% 6y</td>
</tr>
<tr>
<td>EBMT⁵</td>
<td>250 vs 110</td>
<td>41 vs 52</td>
<td>15 vs 36% 6y</td>
<td>50 vs 65% 6y</td>
</tr>
<tr>
<td>BMT CTN⁶</td>
<td>436 vs 189</td>
<td>58 vs 45</td>
<td>43 vs 46% 3y</td>
<td>77 vs 80% 3y</td>
</tr>
</tbody>
</table>

4. Lokhorst Blood 2012 (PFS better for those who did proceed to allo)
5. Bjorkstrand B, JCO 2011
Auto-Allo vs. Tandem Auto in MM (n=241)

**EBMT Study: Intention-to-treat comparison: auto+allo** (N=109) **vs. tandem auto** (N=249)

* Long term or OS was significantly better in the auto/allo group as the auto/allo group had significant reduction of risk in time (p=0.006) with longer hazard of death after 3y (p=0.004)

**PFS since 1st transplant**
- Reduction of risk in time: p=0.0012 (Cox)
- At 60 mns: 35% (CI: 27% - 45%)
- Auto+Allo
- At 60 mns: 18% (CI: 13% - 24%)
- Auto only

**OS since 1st transplant**
- Improved in time: p=0.0048 (Cox)
- At 60 mns: 65% (CI: 56% - 74%)
- Auto+Allo
- At 60 mns: 58% (CI: 52% - 65%)
- Auto only

Björkstrand for EBMT et al., JCO 2011/Gahrton Böood 2013
**US Study BMT CTN 0102**
Second Transplant Auto vs. Allo Reduced Intensity

**Newly diagnosed MM after response to induction**

- **Auto-Auto**
  - $N=436$
  - 16% dropout rate
  - 3 year PFS 46% vs. 43%
  - 3 year OS 80% vs. 77%

- **Auto-Allo**
  - $N=189$
  - 16% dropout rate

- **Second Auto Transplant**
  - $N=366$

- **Second Allo Transplant**
  - $N=156$

**High Risk vs. Low Risk stratification**
- Beta 2 Microglobulin $>4$
- Karyotypic del 13

**Thal-Dex Maintenance**
- 84% discontinued at Day 365

Krishnan A et al Lancet Oncology 2011 Dec;12(13):1195
BMT CTN 0102 auto-allo vs. Tandem auto

Is this evidence relevant today?

- Tandem Auto vs. Auto- Allo Studies started in the pre novel agent induction and maintenance era
- Higher TRM and ever improving post auto transplant outcomes

CALGB 100104 study of single Auto – Len maintenance

A

B

PFS median - Len 58 mo

OS median - Len 113 mo
Discussion

• The Tandem auto vs. Tandem auto-allo data may be of less relevant today
  – Not risk adapted by modern standards
  - Post auto PFS and OS have improved dramatically

Relevant questions are:

1. High risk subset – is allo better? Risk defined by ....? When should allo be done?
2. Is an allogeneic immune system better for some pts? Can we use an allo immune system better as a platform for immune modulation?
Can upfront Allotransplant "cure" high risk?

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>HIGH RISK DEFINITION</th>
<th>High risk Allo vs. Auto</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT NMAM</td>
<td>92</td>
<td>Deletion 13 q</td>
<td>PFS - 8 years 21% vs. 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - 8 years 47% vs. 31%</td>
</tr>
<tr>
<td>Knop</td>
<td>199</td>
<td>DEL 13q + DEL 17p</td>
<td>Median PFS NR vs. 6 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS NR vs. 23 mo</td>
</tr>
</tbody>
</table>

Hi Risk MM < 65 years
N - 199

Tandem AUTO

Auto #1 → Flu MEL + ATG ALLO with Sib or URD (incl 9/10)

2-year PFS 59% vs. 47% with Auto.

1:1

2 Yr PFS

Knop S et al; ASH abstract 2014 Dec #43
### Auto-allo vs. auto-auto in MM (n=199)
**German Multicenter Study (incl MUD)**

<table>
<thead>
<tr>
<th>Parameter / Group</th>
<th>auto-allo</th>
<th>auto-auto</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS / del 13</td>
<td>34,5 Mo</td>
<td>21,8 Mo</td>
<td>0,005</td>
</tr>
<tr>
<td>Medianes PFS / t(4;14)</td>
<td>19,1 Mo</td>
<td>19,3 Mo</td>
<td>0,251</td>
</tr>
<tr>
<td>Median PFS / del 17p</td>
<td>Not reached</td>
<td>6 Mo</td>
<td>0,0002</td>
</tr>
<tr>
<td>Median OS / del 17p</td>
<td>Not reached</td>
<td>23,4 Mo</td>
<td>0,011</td>
</tr>
</tbody>
</table>

- Medians Follow-up = 49 Months
- No difference in OS (at 2 y)
- 2- year NRM for auto-allo = 11,9%

Knop ASH 2014
DSMM Tandem auto vs. auto-allo in high risk MM: DFS

Subgroup of FISH del(13q)+del(17p) pts.; n=25

- del17 allo: median PFS 37.5 mos (95% CI: 14.8-14.8)
- del17 Mel: median PFS 6.1 mos (95% CI: 2.1-21.4)

Log-Rank Test (del17p pts) for auto/allo versus tandem-Mel: p=.0002
BMT CTN 0102 Progression-free Survival - High Risk: no advantage for allo

Auto/Auto (n=48)
Auto/Allo (n=37)

<table>
<thead>
<tr>
<th></th>
<th>Auto/Auto</th>
<th>Auto/Allo</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value</td>
<td>0.4896</td>
<td></td>
</tr>
<tr>
<td>@ 6 years</td>
<td>14 (5-26)</td>
<td>27 (14-42)</td>
</tr>
<tr>
<td>PFS</td>
<td>47 (33-61)</td>
<td>51(37-65)</td>
</tr>
<tr>
<td>OS</td>
<td>78 (64-88)</td>
<td>54 (38-70)</td>
</tr>
<tr>
<td>Relapse</td>
<td>8 (2-18)</td>
<td>19 (8-33)</td>
</tr>
<tr>
<td>NRM</td>
<td>8 (2-18)</td>
<td>19 (8-33)</td>
</tr>
</tbody>
</table>

Unpublished data

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Novel therapies to prevent relapse and augment immune response post alloSCT in MM

Patients with non-complete remission after allogeneic SCT (n = 32) (evaluable for response: according EBMT criteria: n = 32, FACS: n = 27, molecular methods: n = 30)

- Escalating DLI (n = 30), median: 2 DLIs
- Thalidomide (n = 1) Bortezomib (n = 1) (due to cGvH)
  - PD n = 2
  - non CR n = 24

CR
- EBMT: n = 8 (27%)
- FACS: n = 7
- Molec.: n = 7

CR
- EBMT: n = 11
- FACS: n = 10
- Molec.: n = 8

Overall: CR (EBMT): n=19 (59%); FACS: n=17 (63%); molecular: n= 15 (50%)

Post-relapse Survival: Is relapse after Allo different?

AUTO/AUTO vs. AUTO/ALLO (≤12 months after relapse)
HR = 0.72 (0.47-1.09)
p-value = 0.1172

AUTO/AUTO vs. AUTO/ALLO (>12 months)
HR = 1.55 (1.14-2.11)
p-value = 0.0052

Htut et al 2016 ASH abstract 833; Gahrton et al Blood 2013
Patient selection:
Early Relapse after Auto

Overall survival for early relapse versus others

Kaplan-Meier plot for dead by strata

- No relapse by 2 years: 5-year OS 80%
- Relapse by 2 years: 5-year OS 32%
• AlloSCT for relapsed MM should be performed early
  – More sensitive to Graft vs. MM effects
  – Less clonally evolved?
  – More sensitive to treatments at subsequent relapse
  – More likely to be in CR at transplant
Multiply Relapsed Patients do not benefit from traditional allo

Relapse/Progression (95% CI):
- @ 1 yr: allo 72% (64-79), auto 53% (44-61)
- @ 3 yrs: allo 80% (73-86), auto 84% (76-90)
- @ 5 yrs: allo 83% (77-89), auto 91% (85-96)

Freytes et al Bone Marrow Transplant. 2014 Mar;49(3):416
### Haplo HCT for very advanced MM with PTCy

The Medical College of Wisconsin experience

N = 41 – haplo Reduced Intensity with post transplant Cy

<table>
<thead>
<tr>
<th>Median Age</th>
<th>55 (36-73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT CI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (39)</td>
</tr>
<tr>
<td>1-2</td>
<td>8 (20)</td>
</tr>
<tr>
<td>3+</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Prior auto</td>
<td>35 (85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time from diagnosis to transplant</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>3 (7)</td>
</tr>
<tr>
<td>6- 12 months</td>
<td>3 (7)</td>
</tr>
<tr>
<td>12- 24 months</td>
<td>6 (15)</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>29 (71)</td>
</tr>
</tbody>
</table>

Courtesy of Parameswaran H.
## Transplantation outcome

<table>
<thead>
<tr>
<th>TRM</th>
<th>100 day</th>
<th>2-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (2-18)%</td>
<td>8 (2-18)%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse</th>
<th>100 day</th>
<th>1-yr</th>
<th>2-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 (13-40)%</td>
<td>72 (57-85)%</td>
<td>89 (78-97)%</td>
<td></td>
</tr>
</tbody>
</table>
Survival after Haplo Post CY grafts

- Haplo OS: 48% at 2 years
- Haplo PFS
- TRM: 8% at 2 years
Future of Haplo Grafts for MM

• Haplo with post transplant CY –
  – lowest TRM and aGVHD risk compared with other forms of allo HCT
• Relapse Prevention post allo is key:
  – Cells +/- Antibodies \(\rightarrow\) Daratumumab, Elotuzumab post NK DLI
  – Planned IMID/ELO maintenance
  – PD-1 Blockade
  – Haplo earlier in the disease course incl. upfront for high risk
  – KIR directed donor selection
  – More MM specific conditioning – Flu Mel +/- TBI
Probability of Benefit, Alternatives vs. Risk who to select

Factors to consider:
Probability of being in the tail of the survival curve
Risk sensitivity of the patient

Benefit of Allo

Breakeven

Standard Risk Pts (MAJORITY)
Zone of Low Benefit
RISK OF TRM (fixed)

Predicted Highest Risk pts
TRM Risk needs to be lower to be attractive
At relapse from ALLO – immune manipulation

Early Relapse after AUTO – proven risk
More risk from MM; Willing to take on more TRM risk

Demonstrably Highest Risk pts - High risk / high gain
Multi Relapsed Patients “Last Ditch Transplant”
Clinical Trials for post HCT Immune Manipulation

Increasing Risk from MM

Graph Courtesy Taleb NN

COMy Congress 2017
Adoptive cell therapy: Engineering anti-MM responses using affinity-enhanced TCR-engineered T cells

1. Isolation of T cells from blood

2. Gene modification of T cells to express CARs or TCRs with viral/non viral vectors

3. Ex vivo T cell expansion

4. Lymphodepletion (preconditioning therapies) and reinfusion of gene modified T cells

5. Close monitoring of tolerability, tumor kinetics and immune surveillance: rationale to combine with other therapies (e.g.: IMIDs or checkpoint inhibitors)

CD19-CAR T cells in MM University of Pennsylvania Philadelphia, Pa

- RRMM

- **Rationale:** Minor component of the MM clone that is drug-resistant and has disease proagating properties has a B-cell origin

- CD19-CAR after Mel140.

- CD19 was negative in 99.95% PC.

Stadtmauer E, et al. NEJM 2015

DOR > 12 m
<table>
<thead>
<tr>
<th>ID</th>
<th>Age/Sex</th>
<th>TTP1 (days)</th>
<th>Follow-up (days)</th>
<th>Prior #Tx</th>
<th>Mel. Dose (mg/m²)</th>
<th>High-risk Features</th>
<th>Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>58 M</td>
<td>341</td>
<td>N/A</td>
<td>7</td>
<td>200</td>
<td>Complex karyotype, BRAFV600E</td>
<td>Progression d42</td>
</tr>
<tr>
<td>3</td>
<td>65 F</td>
<td>210</td>
<td>N/A</td>
<td>3</td>
<td>140</td>
<td>Plasma cell leukemia</td>
<td>Progression d182</td>
</tr>
<tr>
<td>5</td>
<td>64 F</td>
<td>127</td>
<td>222</td>
<td>7</td>
<td>140</td>
<td>t(4;14), +1q, &lt;PR to induction</td>
<td>VGPR, progression-free</td>
</tr>
<tr>
<td>6</td>
<td>53 M</td>
<td>100</td>
<td>N/A</td>
<td>2</td>
<td>140</td>
<td>BRAF V600E mutation</td>
<td>Progression d76</td>
</tr>
<tr>
<td>7</td>
<td>62 F</td>
<td>342</td>
<td>70</td>
<td>6</td>
<td>140</td>
<td>N/A*</td>
<td>PR, progression-free</td>
</tr>
<tr>
<td>8</td>
<td>57 F</td>
<td>334</td>
<td>96</td>
<td>4</td>
<td>200</td>
<td>t(4;14), +1q,</td>
<td>PR, progression-free</td>
</tr>
<tr>
<td>9</td>
<td>62 M</td>
<td>266</td>
<td>N/A</td>
<td>4</td>
<td>140</td>
<td>+1q, t(4;14)</td>
<td>Progression d92</td>
</tr>
<tr>
<td>10</td>
<td>68 F</td>
<td>249</td>
<td>37</td>
<td>10</td>
<td>140</td>
<td>del(17p), +1q</td>
<td>Not yet evaluable, progression-free</td>
</tr>
<tr>
<td>12</td>
<td>59 M</td>
<td>325</td>
<td>35</td>
<td>6</td>
<td>200</td>
<td>N/A*</td>
<td>Not yet evaluable, progression-free</td>
</tr>
</tbody>
</table>

TTP1 = time-to-progression after prior ASCT (off-study). All subjects received melphalan at 200 mg/m² dose with ASCT #1. VGPR = very good partial response. PR = partial response. *Cytogenetic data not available.

Garfall et al, NEJM September 10 2015
First-in-human clinical trial of T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor: 4/12 Pts (2 PR, 1 VGPR; 1sCR)

Patient 10 obtained SCR of chemotherapy-resistant IgA myeloma after CAR-BCMA T-cell infusion

- Serum and urine IFE-negative
- Bone marrow flow cytometry-negative

BCMA: B-cell maturation Ag
a member of the TNF superfamily

• Patient 10 experienced cytokine release syndrome including fever, tachycardia, hypotension, elevated liver enzymes, and elevated creatinine kinase—all resolved in 2 weeks or less

Abbas, & Kochenderfer, ASH 2015 (LBA1)
CAR-BCMA T cells specifically recognized BCMA
Exhibited antimyeloma activity in humans.

Reliable Elimination of MM plasma cells
Even works in chemotherapy refractory
Need higher doses than CART19?
Deep Remissions induced
Toxicity incl. CRS
Relapses noted despite CR
Soluble BCMA – Not a factor
BCMA CART – early data

11 pts screened, and 6 treated in cohort 1.
Grade 4 PRES
Grade 3 CRS
# Ongoing clinical trials with CAR therapy in MM

<table>
<thead>
<tr>
<th>Target Antigen</th>
<th>Expression on cell subsets</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD138</td>
<td>All plasma cells/epithelium</td>
<td>Phase I with 2nd gen. T cell CAR (General Hospital of PLA, Beijing, NCT 01886976)</td>
<td>mucositis, down regulating CD138</td>
</tr>
<tr>
<td>CD38</td>
<td>All plasma cells/T-cells, prostate, myeloid</td>
<td>2nd gen. T cell CAR active in vitro and xenografts for B-cell NHL, in vitro in MM3,4 Amsterdam</td>
<td>Immune def /cytopenias</td>
</tr>
<tr>
<td>CS1/SLAMF7 (CRACC, CD319)</td>
<td>&gt;95% plasma cells/T-cells, NK, DC</td>
<td>2nd gen. CAR in NK92 or NKL human cell lines: In vitro killing of CS1+ MM lines and 1º MM cells Delayed growth of IM9 MM xenografts</td>
<td>Immune def</td>
</tr>
<tr>
<td>Kappa light chain</td>
<td>2/3rds plasma cells</td>
<td>Phase I of 2nd gen. T cell CAR in CLL, NHL, 3 SD MM Baylor</td>
<td>light chain intracellular in myeloma cells ?Impact of high circulating light chains</td>
</tr>
<tr>
<td>BCMA (B cell maturation antigen)</td>
<td>All plasma cells/B-cells</td>
<td>anti-BCMA-MMAF (GSK2857916) Induces apoptosis and ADCC against MM cells In vivo activity against MM xenografts4 NIH and Penn Phase I trials</td>
<td>Off target effects</td>
</tr>
</tbody>
</table>
Vaccines in Multiple Myeloma

- Vaccination combining different antigen formats and adjuvants has been investigated in MM (Rosenblatt et al., 2013),

- but active vaccine strategies are restricted by the insufficient numbers of induced T cells, their poor homing to tumor sites, and the immunosuppressive tumor microenvironment.

- The strategy of isolating tumor infiltrating lymphocytes (TILs), expanding them in vitro, and then transferring them back to the patient has also been investigated (Noonan et al., 2015).

Patient-derived PC chemically fused with autologous dendritic cells → broad spectrum of MM antigens are presented in the context of dendritic cell mediated costimulation

- n=18 patients. Median of prior lines: 4; Well tolerated.
- ORR: Stable disease. Several patients with SD lasting for 12 to 41 months.
PD-L1/PD-1 inhibitors in Multiple Myeloma

Expression of PD-L1 in CD138+ PCs, two studies:
- PD-L1 is commonly present (although at low levels)\(^1\) vs only 25% of patients\(^2\).

PD-L1 expression across all disease stages

Increase PD-1 among T cells of MRD/RR pts.

Pembrolizumab as consolidation in MRD+ patients post-ASCT.

Elotuzumab + Urelumab or Lirilumab in MRD+ patients post-ASCT

American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma.


Author information

Abstract

In contrast to the upfront setting in which the role of high-dose therapy with autologous hematopoietic cell transplantation (HCT) as consolidation of a first remission in patients with multiple myeloma (MM) is well established, the role of high-dose therapy with autologous or allogeneic HCT has not been extensively studied in MM patients relapsing after primary therapy. The International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation convened a meeting of MM experts to: (1) summarize current knowledge regarding the role of autologous or allogeneic HCT in MM patients progressing after primary therapy; (2) propose guidelines for the use of salvage HCT in MM; (3) identify knowledge gaps, (4) propose a research agenda, and (5) develop a collaborative initiative to move the research agenda forward. After reviewing the available data, the expert committee came to the following consensus statement for salvage autologous HCT: (1) In transplantation-eligible patients relapsing after primary therapy that did not receive autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months; (3) High-dose therapy and autologous HCT can be used as a bridging strategy to autologous HCT. (4) The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors; (5) Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short (less than 18 months) relapses after primary therapy; and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing it to "best non-HCT" therapy. The expert committee also underscored the importance of collecting enough hematopoietic stem cells to perform 2 transplantsations early in the course of the disease. Regarding allogeneic HCT, the expert committee agreed on the following consensus statements: (1) Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or high-risk features (i.e., cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be considered in the context of a clinical trial if possible; (3) The role of postallogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role salvage allogeneic HCT in patients with MM relapsing after primary therapy.
Allo-SCT is frequently used as a last option, when other approaches are no longer effective. Some patients may benefit from the treatment, but earlier use of this modality in the tandem ASCT/RICallo setting may be a better option although tolerability can be challenging. Studies of RIC allo modalities are in progress both for treatment of patients with relapsed disease and for the upfront treatment of high-risk patients. Such studies should be compared with the best options using new drug combinations, like bortezomib plus thalidomide and dex which showed encouraging results in a recent prospective European Blood and Marrow Transplantation (EBMT) trial of patients relapsing after ASCT. Such studies may help better define the role for allogeneic SCT in the treatment of RR MM.
AlloSCT in MM: Conclusions

- TRM after allografting for MM patients significantly reduced
- Allogeneic transplantation is a valid treatment option for high risk MM patients (high risk cytogenetics): early relapse (after optimized induction & AutoSCT)
- Allogeneic SCT is an effective treatment for multiple myeloma with a fraction of patients achieving long-term remission, molecular remission and potentially cure
- Achievement of MRD negativity induces long-term freedom from disease and cure
- The role of Allo should be revisited in the era of novel drugs: “integrated programs”
- T-replete Haplo and PTCy are emerging attractive approaches
- It is likely that freedom from progression and survival will further increase with the introduction of more effective anti MM drugs as part of the induction treatment and post transplant consolidation with DLI, NK, other cell therapy approaches or novel agents
- CAR, TCR engineering, tumor vaccination and immune checkpoint inhibition are emerging exciting strategies that can be used in conjunction with alloSCT for MM
Thanks

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