Post ASH 2016: Transplantation

Willems Evelyne, CHU Liège
13-01-17
PLAN

– BETTER SELECT PATIENT: Graft and aging

– DECREASE GVHD
  • Impact of IEC and microbiome
  • Impact of immunosuppressive regimen
    – Use of ATG
    – MMF + CSA vs MMF + Sirolimus + CSA
  • Stem cell source and haplo

– New GRFS
Abstract 681: Allogeneic Hematopoietic Cell Transplantation in Elderly Patients Aged 65 and Older: A Retrospective Analysis By the Complications and Quality of Life Working Party of the EBMT

Basak et al.
Number of alloHSCTs/year in patients aged > 65 in EBMT transplant centers

- A total of 6046 alloHCT, including 214 second or subsequent procedures, from 270 EBMT centers in 32 countries were identified.

AlloHCT activity in elderly patients in EBMT transplant centers:
- 37 out of 6413 in 2000 ( <1% )
- 1057 out of 15765 in 2014 ( 6.7% ; p<0.001)
Non-relapse mortality (NMR) after alloHCT

<table>
<thead>
<tr>
<th></th>
<th>NRM (n=6046)</th>
<th>65-69 y (n=4914)</th>
<th>&gt;70 y (n=1132)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>27% (95%CI 26-28)</td>
<td>26% (25-28)</td>
<td>29% (27-36)</td>
<td>0.001</td>
</tr>
<tr>
<td>3 years</td>
<td>35% (95%CI 33-36)</td>
<td>34% (33-36)</td>
<td>39% (36-42)</td>
<td></td>
</tr>
</tbody>
</table>
## Overall Survival after alloHCT

<table>
<thead>
<tr>
<th>OS</th>
<th>All (n=6046)</th>
<th>65-69y (n=4914)</th>
<th>&gt;70y (n=1132)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>57% (95% CI 55-58)</td>
<td>57% (56-59)</td>
<td>53% (50-57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 years</td>
<td>39% (95% CI 37-40)</td>
<td>39% (38-41)</td>
<td>35% (31-38)</td>
<td></td>
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</tbody>
</table>
Outcomes in patients >75 years old at alloHCT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 year</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non relapse mortality</td>
<td>26% (95%CI 16-38)</td>
<td>34% (95%CI 21-47)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>57% (95%CI 45.5-70)</td>
<td>38.5 (95%CI 27-56)</td>
</tr>
<tr>
<td>Relapse incidence</td>
<td>25% (95%CI 15-36)</td>
<td>32% (95%CI 18-46)</td>
</tr>
</tbody>
</table>
Educational: biologic versus physiologic age in the transplant candidate

Andrew S. Artz
Survival from allogenic recipients > 70 years in US
Multiple comorbidity influences non relapse mortality and survival (HCT-CI)

Allograft

![Graph A]

Sorror et al, BBMT 2015

Autograft

![Graph D]
## Pronostic influence on survival of GA in patients 50+ after allograft

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total population (n=203)</th>
<th>50-59 years (n=124)</th>
<th>60-73 years (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>p</td>
</tr>
<tr>
<td>GA variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IADL impairment</td>
<td>2.38</td>
<td>1.59-3.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slow walk speed</td>
<td>1.80</td>
<td>1.14-2.83</td>
<td>0.01</td>
</tr>
<tr>
<td>Reduced mental health</td>
<td>1.67</td>
<td>1.13-2.48</td>
<td>0.01</td>
</tr>
<tr>
<td>Low albumin</td>
<td>1.52</td>
<td>0.94-2.46</td>
<td>0.09</td>
</tr>
<tr>
<td>High CRP</td>
<td>2.51</td>
<td>1.54-4.09</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Muffly et al. 2014
High comorbidity and functional limitation influence overall survival

Muffly et al, Haematologica 2014
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Educational: Role of the intestinal mucosa in acute gastrointestinal GVHD

Robert R. Jenq
Change in Intestinal bacteria during GVHD

• Obligate anaerobes, in particular *clostridium* species, are important mediators for intestinal homeostasis and prevent inflammation by upregulating intestinal T Reg (Atarashi et al, 2013)

• GVHD leads to change in the microbiota composition
  – Expansion of G- enterobacteriales and G+ lactobacillus
  – Loss of obligate anaerobes

• GVHD induce changes in the metabolites produced by these bacteria (*Butyrate*)
Potential targets of butyrate that ameliorate GVHD

- **T cells**
  - Induce FOXP3 expression (Arpaia et al. 2013, Furusawa et al. 2013)
  - Induce colonic homing of regT cells (Smith et al. 2013)

- **Macrophage**
  - Reduced response to LPS (Chang et al. 2014)

- **Epithelial cells** (Mathewson 2016)
  - Improved IEC junctional integrity
  - Decreased apoptosis by alloreactive T cells
Gut microbiome–derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease

Butyrate induce Treg, and inhibit histone deacetylase ➔ Oral feeding with butyrate or introduction of butyrate producing clostridium ➔ improved survival in mice with acute GVHD

Mathewson et al, Nat immunology 2016
Effect of frequently administered antibiotics on GVHD mortality

- Retrospective analysis, n=857 alloHCT
- Neutropenic fever
- Treatment with imipenem or pip-tazo:
  - Increase grade II-IV aGVHD (p=0.0167 and p=0.0165)
  - Increase upper GI aGVHD (p=0.002 and p=0.045)
  - Increase lower GI aGVHD (p=0.019 and p=0.036)
  - Increase GVHD mortality (p=0.02 and p=0.007)
  - No change in OS

Shono at al, Sci Trans Med 2016
Evaluating the effect of antibiotics on murine GVHD

• 3 patients with steroid refractory and 1 with steroid-dependent GVHD
• Treated with FMT from a spouse of relative administered by NJ tube
• Appeared to be safe
• 3 CRs and 1 PR
Developing strategies to address intestinal mucosa injury in GVHD

Epithelial regeneration
- Growth factors
- Cellular therapies

Probiotics
- Fecal microbiota transplant
- Introducing rationally selected cultured bacteria

Postbiotics
- Identifying and introducing bacterial metabolites that mediate the anti-inflammatory effects

Prebiotics
- Encouraging eating
- Gastric nutritional supplementation
- Flora-targetted nutritional supplementation

Antibiotics
- Selecting antibiotics that spare bacteria with beneficial potential
- Alternatively, target potentially harmful bacteria
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Abstract 505: A Prospective Randomized Double Blind Phase 3 Clinical Trial of Anti- T Lymphocyte Globulin (ATLG) to Assess Impact on Chronic Graft-Versus-Host Disease (cGVHD) Free Survival in Patients Undergoing HLA Matched Unrelated Myeloablative Hematopoietic Cell Transplantation (HCT).

Soiffer et al.

• Trial design and Eligibility
  – Design:
    • Placebo controlled double blind randomized trial
    • ATG (n=128) versus placebo (n=132)
    • In addition to standard tacrolimus/MTX GVHD prophylaxis
  – ATG dose: 20 mg/kg iv on Days -3, -2, -1
  – Eligibility:
    • Patients 18-65 ys with ALL/AML in remission or MDS (<10% blasts) undergoing MA 8/8 matched UD allo-HCT
## Engraftment, Infusion reactions, Viral infections

<table>
<thead>
<tr>
<th></th>
<th>ATG (n=128)</th>
<th>Placebo (n=132)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>Graft failure</strong></td>
<td>3.4%</td>
<td>0.8%</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Engraftment</strong></td>
<td></td>
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<tr>
<td>ANC&gt;500</td>
<td>24 (5-45)</td>
<td>19 (8-41)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Plt &gt; 30000</td>
<td>28 (6-205)</td>
<td>19 (5-45)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Day30 ANC recovery</strong></td>
<td>85% (77-90)</td>
<td>95% (89-97)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Day 100 Plt recovery</strong></td>
<td>79% (71-86)</td>
<td>94% (88-97)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>CMV reactivation</strong></td>
<td>32%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td><strong>EBV PTLD</strong></td>
<td>1.6%</td>
<td>0%</td>
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</table>
Chronic GVHD

ATLG 16% vs placebo 38%,
p<0.00002

Mod-severe cGVHD

ATG 12% vs placebo 33%,
p<0.000007
Abstract 666: The Use of Anti-Thymocyte Globulin Is Associated with Increased Chance of Survival Free from Relapse and Graft-Versus-Host Disease after Allogeneic Peripheral Blood Stem Cell Transplantation for Adults with Philadelphia-Negative Acute Lymphoblastic Leukemia: An Analysis By the Acute Leukemia Working Party of the EBMT.

Giebel et al.

• Design:
  – 682 ALL patients in CR 1
  – between 1997-2014
  – PBSC
  – MA 81%
  – 339 sibling, 343 8/8 UD
  – ATG used in 22% of siblings, 78% of UD
Multivariate analysis - Use of ATG associated with:

- Reduced risk of grade II-IV aGVHD ($\text{HR}=0.64$, $p=0.007$)
- Reduced risk of grade III-IV aGVHD ($\text{HR}=0.52$, $p=0.03$)
- Reduced risk of overall cGVHD ($\text{HR}=0.61$, $p=0.001$)
- Reduced risk of extensive cGVHD ($\text{HR}=0.4$, $p<0.0001$)
- No effect on relapse ($p=0.27$), LFS ($p=0.7$) and OS ($p=0.16$)
- Increased GRFS ($\text{HR}=0.74$, $p=0.009$)
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Abstract 506: Sirolimus Combined with Mycophenolate Mofetil (MMF) and Cyclosporine (CSP) Significantly Improves Prevention of Acute Graft-Versus-Host-Disease (GVHD) after Unrelated Hematopoietic Cell Transplantation (HCT): Results from a Phase III Randomized Multi-Center Trial

Sandmaier et al
Phase III Randomized Trial – FH2448

Interim analysis: 158 patients

Fludarabine 90 mg/m²

Days -4 -3 -2 0 30 40 56 84 96 150 180

ARM

#1

MMF CSP
BID
TID ... BID

#2

MMF CSP SIR
BID
TID ... BID
QD

MMF: 15 mg/kg p.o. tid
Arm 1: Day 0 until day +30, then bid until day +150, taper to day +180
Arm 2: Day 0 until day +30 then bid until day +40

CSP: 5.0 mg/kg p.o. bid day -3 until day +96, taper until day +150

SIROLIMUS: 2.0 mg p.o. q.d. day -3 until day +150. Taper until day +180 (target 3-12 ng/ml)
Grade II-IV aGVHD

![Graph showing comparison of CSP/MMF vs CSP/MMF + Sirolimus on Days from Transplant for % GVHD Grades II-IV with p=0.0001.](http://localhost:8091/ASH2016/abimages/Paper_90799_abstract_186563_0.jpg)
Grade III-IV aGVHD

p = 0.04

CSP/MMF
CSP/MMF + Sirolimus

Percent Grade III-IV GVHD vs. Days from Transplant

2% at 2 months, 8% at 8 months

p = 0.94

CSP/MMF
CSP/MMF + Sirolimus

Percent Chronic GVHD vs. Years from Transplant

48% at 1 year, 49% at 1 year

p = 0.95

CSP/MMF
CSP/MMF + Sirolimus

Percent Relapse/Progression vs. Years from Transplant

21% at 1 year, 19% at 1 year

Relapse
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Abstract 683 Comparison of Peripheral Blood Stem Cells (PBSC) to Bone Marrow (BM) for T-Replete HLA-Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide.

Bashey et al.

• Selection criteria:
  – First allogeneic HCT (Haplo-HCT with ptCy), US
  – 2009-2014
  – AML, ALL, MDS, NHL, HL
  – Myeloablative and RIC
  – GVHD prophylaxis: post-transplant Cy + CNI + MMF
  – N=671 eligible
    • BM (n=481) and PBSC (n=190)
Acute Graft vs. Host Disease
Adjusted for conditioning regimen intensity

Grade II-IV

HR 0.45, p<0.001

PB: 42% (35 – 50)

BM: 25% (21 – 29)

Grade III-IV

HR 0.61, p=0.06

BM: 7% (5 – 10)

PB: 10% (6 – 15)

Chronic Graft vs. Host Disease
Adjusted for age and performance score

HR 0.35 (95% CI 0.49 – 0.26), p<0.0001

Severity: mild vs. moderate vs. severe (p=0.64)

BM: 62% vs. 28% vs. 10%

PB: 58% vs. 30% vs. 12%

PB: 41% (33 – 48)

BM: 20% (16 – 24)
**Non-relapse Mortality**
Adjusted for age, regimen intensity, CMV serostatus

HR 0.92 (95% CI 0.58 – 1.47), p=0.74

PB: 16% (11 – 22)
BM: 17% (13 – 21)

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**Relapse**
Adjusted for disease risk index

HR 1.45 (95% CI 1.08 – 1.94), p=0.01

BM: 45% (41 – 50)
PB: 28% (22 – 34)

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**Relapse**
Adjusted for disease risk index

**RIC**

HR 1.14, p=0.49

BM: 45% (40 – 50)
PB: 35% (25 – 45)

BM = 396; PB = 87

**Myeloablative**

HR 1.94, p=0.009

BM: 45% (35 – 55)
PB: 22% (15 – 30)

BM = 85; PB = 103
Overall Survival
Adjusted for age, disease risk index, CMV serostatus

Adjusted Probability, %

PB: 57% (49 – 65)
BM: 54% (49 – 59)

HR 1.03 (95% CI 0.77 – 1.36), p=0.86

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Abstract 1165 Use of Bone Marrow or Peripheral Blood Stem Cell Grafts in Non T Cell Depleted Haploidentical Transplants Using Post-Transplant Cyclophosphamide, an ALWP-EBMT Analysis.
Ruggeri et al.

• Design:
  – Retrospective registry-based
  – 451 patients
  – BM in 260 pts, PBSC in 191
  – MAC in 61% of patients receiving BM versus in 49% of PBSC pts
  – GVHD prophylaxis: CNI + MMF + Cy
Multivariate analysis – PB associated with:

- Increased grade II-IV aGVHD (HR=2.2, p=0.005)
- No association with:
  - Grade III-IV aGVHD (HR=2.5, p=0.07)
  - cGVHD (HR=1, p=0.88)
  - Relapse (HR 0.7, p=0.21)
  - NRM (HR 0.80, p=0.4)
  - GRFS (HR 0.90, p=0.56)
  - LFS (HR 0.73, p=0.08)
  - OS (HR 0.79, p=0.23)
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Solomon et al.

New statistical method to determinate the probability of being alive, in remission and without moderate-severe cGVHD

• Death and relapse = terminal event
• cGVHD= dynamic event
• Grade 3-4 aGVHd not included
Gain in GRFS due to the treatment of cGVHD as a dynamic event
Take home messages

- **Age** is no longer a CI to transplantation but GA mandatory
- **Gut GVHD**: importance of *microbiota* and intestinal cells and we can impact with food or antibiotics
- **ATG** still controversial: reduction in aGVHD, cGVHD but decrease DFS and OS? (Soiffer). Increased GRFS in EBMT study
- Addition of *sirolimus* to CSP-MMF in minitransplant decrease aGVHD and TRM and increase OS
- **Haplo**: use of BM decrease acute and chronic GVHD but concern about relapse in myeloablative conditioning
- New **GRFS** as a new endpoint
Thank you for your attention!