Allogeneic Hematopoietic Stem Cell Transplantation: State of the Art in 2018

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BETHESDA MD
Overview:

• Update on allogeneic transplantation for malignant and nonmalignant diseases: state of the art in 2018
• Choosing the optimal stem cell donor
• New tools to prevent and treat CMV
• First FDA-approved drug approved to treat chronic GVHD
Major Improvements in Transplant Outcomes Over the Past 2 Decades

**Historical Problem**

- Conditioning regimens too toxic
- Older patients ineligible due to prohibitive risk of mortality
- Death from invasive fungus and CMV
- Lack of donors precludes the use of the procedure

**Solution**

- Development of safer conditioning regimens (IV busulfan)/use of lung shielding
- Development of reduced intensity conditioning regimens
- Advent of voriconazole, PCR to detect early CMV reactivation with use of empiric gancyclovir. Letermovir for CMV prophylaxis
- Growth of unrelated registry, increasing use of MUDS, cord transplants and haplo-identical donors
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- Remains only curative modality for certain diseases associated with short survival with conventional therapy
  - Relapsed AML
  - Relapsed ALL
  - High Risk MDS

- Is the only curative modality for many non-malignant debilitating diseases
  - Sickle cell Anemia
  - Aplastic Anemia- Relapsed refractory to IST
We have Made Advances in Diseases Like MDS But Most Patients with High-Risk Disease Will Die from their Disease Without a Transplant
Allogeneic Transplant For AML in CR1 Decreases Relapse Risk and Improves Survival for Select Patients

Outcomes superior for older pts with allogeneic HCT

Stelljes et al JCO 2014:32(4)
Transplant Numbers are Increasing in the U.S.
Most Common Indications for an Hematopoietic Cell Transplant (HCT) in the U.S.
Allogeneic HCT Recipients in the US, by Donor Type

- HLA-iden Sib
- Other Relative
- URD-BM / PB
- URD / UCB

Number of Transplants


Donor Types:
- MUDs
- Sibs
- Haplo
- cords
Donor Sources - who to choose?

1) HLA Identical Sibling (SIB)
2) 8/8 Allele Matched Unrelated Donor (MUD)
3) see below

- HLA-Haploidentical related donor (Haplo)
- 7/8 Allele Matched Unrelated Donor (MMUD)
- Cord Blood transplant

Donor Selection Starts at Referral
Choosing the best donor:

Factors to consider-Urgency of Transplant
- Aggressive disease
- Malignant versus Non-Malignant Disease

Primary Factors
- HLA Match
  - 8/8 allele match still preferred
  - Need to not have Donor-Specific HLA Antibodies in the case of mismatched transplant
  - Availability of Donor in time needed

Secondary Factors (in no particular order!)
- Age
- CMV Status
- ABO Match
- Gender

Other Selection Factors
- DPB1 Matching, NK Alloreactivity, Viral Exposure
Diversity of Adult Donors on the Be The Match Registry® 2014

Minority includes donors who identified their race or ethnicity as:
- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander

Source: National Marrow Donor Program/Be The Match FY 2014

Bone Marrow Donors Worldwide
52 countries
72 Registries
Haploidentical BM Transplants

- Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens

**Advantages:**
- Virtually every patient will have a haplo-identical relative to serve as a stem cell donor

**Disadvantages:**
- Higher incidence of graft versus host disease
- Obligates use of T-cell depleted transplants
- T-cell depletion increases the risk of
  - graft rejection
  - infection
  - disease relapse.
Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC to Prevent GVHD

Fuchs E. et al JHU
Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

Survival

Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.
Haploidentical Transplant With Post-Transplant Cyclophosphamide vs MUD Donors For AML

TRM

Myeloablative vs Reduced Intensity

Figure 1. Nonrelapse mortality. (A) The cumulative incidence of nonrelapse mortality by donor type after myeloablative conditioning regimen, adjusted for performance score. (B) The cumulative incidence of nonrelapse mortality by donor type after reduced intensity conditioning regimen, adjusted for disease risk index.

Relapse

Myeloablative vs Reduced Intensity

Figure 2. Relapse. (A) The cumulative incidence of relapse by donor type after myeloablative conditioning regimen, adjusted for disease risk index. (B) The cumulative incidence of relapse by donor type after reduced intensity conditioning regimen, adjusted for performance score, disease risk index, and secondary AML.
GVHD Remains a Major Contributor to Transplant Related Mortality

Acute GVHD
1. GI Tract: Diarrhea
2. Liver: Jaundice
3. Skin: Rash
Causes of Death after Unrelated Donor HCT done in 2013-2014

Died within 100 days post-transplant
- Primary Disease: 34%
- Graft Rejection: 23%
- Infection: 10%
- Hemorrhage: 18%
- Organ Failure: 11%
- GVHD: 2%
- Other: 2%

Died at or beyond 100 days post-transplant
- Primary Disease: 27%
- GVHD: 46%
- Organ Failure: 6%
- Secondary Malignancy: 10%
- Hemorrhage: 9%
- Infection: 1%
- Other: 1%
Classical treatment approach for GVHD prevention

Zeiser and Blazar, NEJM 2017
Multivariate Analysis Identifies ATG in Conditioning as Reducing Risk of grade 2-4 acute and chronic NIH GVHD (N=2941)

Flowers et al BLOOD, 2011
Antilymphocyte Globulin for Prevention of Chronic Graft-versus-Host Disease

Nicolaus Kröger, M.D., Carlos Solano, M.D., Christine Wolschke, M.D., Giuseppe Bandini, M.D., Francesca Patriarca, M.D., Massimo Pini, M.D., Arnon Nagler, M.D., Carmine Selleri, M.D., Antonio Risitano, M.D., Ph.D., Giuseppe Messina, M.D., Wolfgang Bethge, M.D., Jaime Pérez de Oteiza, M.D., Rafael Duarte, M.D., Angelo Michele Carella, M.D., Michele Cimminiello, M.D., Stefano Guidi, M.D., Jürgen Finke, M.D., Nicola Mordini, M.D., Christelle Ferra, M.D., Jorge Sierra, M.D., Ph.D., Domenico Russo, M.D., Mario Petrini, M.D., Giuseppe Milone, M.D., Fabio Benedetti, M.D., Marion Heinzelmann, Domenico Pastore, M.D., Manuel Jurado, M.D., Elisabetta Terruzzi, M.D., Franco Narni, M.D., Andreas VölP, Ph.D., Francis Ayuk, M.D., Tapani Ruutu, M.D., and Francesca Bonifazi, M.D.

Kroger et al,
NEJM, 2016
GVHD prophylaxis in allo PBSCT MRD: ATG added to myelo-ablative regimen. Phase 3 RCT. N=155. Patient with AML/CLL.

Cumulative incidence of cGVHD at 2 years.

Conditioning regimens:
1. TBI (12gy)+Cytoxan
2. Busulfan + Cytoxan
3. Etoposide+ TBI
4. ATG

P<0.001

Kroger et al, NEJM, 2016
GVHD prophylaxis in MRD HSCT: ATG

Kroger et al, NEJM, 2016
GVHD prophylaxis in MRD HSCT: ATG

Kroger et al,
NEJM, 2016
GVHD prophylaxis in MRD HSCT: ATG

- This randomized trial defines a clear role for the use of ATG in conditioning regimens to prevent cGVHD.
Graft Source

- PBSC is the most common graft source
- BM is associated with a lower risk of GVHD compared to PBSC
- Cord Blood transplants, despite HLA mismatching, are associated with a low incidence off GVHD
Peripheral Blood Stem Cell Transplants (PBSCs) are the Most Utilized Graft Cell Source for Allogeneic Transplants

Pros of PBSCs:
1. Easy to collect
2. Higher CD34+ Cell dose
3. Lower graft rejection rate

Cons of PBSCs
1. Higher cGVHD risk
PBSCs Associated with Higher Incidence of cGVHD than BM Transplants

- Extensive chronic GVHD 32% BM vs 48% PBSC (p=0.001)

Anasetti et al; NEJM 2012: 367:1487
What Transplant Stem Source is Optimal for Haplo-Transplants Using Post Transplant Cyclophosphamide: Bone Marrow vs. PBSC?
Mobilized Peripheral Blood Stem Cells Versus Unstimulated Bone Marrow As a Graft Source for T-Cell–Replete Haploidentical Donor Transplantation Using Post-Transplant Cyclophosphamide


**ABSTRACT**

**Purpose**
T-cell–replete HLA-haploidentical donor hematopoietic transplantation using post-transplant cyclophosphamide was originally described using bone marrow (BM). With increasing use of mobilized peripheral blood (PB), we compared transplant outcomes after PB and BM transplants.

**Patients and Methods**
A total of 681 patients with hematologic malignancy who underwent transplantation in the United States between 2009 and 2014 received BM (n = 481) or PB (n = 190) grafts. Cox regression models were built to examine differences in transplant outcomes by graft type, adjusting for patient, disease, and transplant characteristics.
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

681 haplo-transplant pts
N=481 bone marrow
N=191 PBSC

Bashey et al. JCO 2017
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

Transplant Related Mortality

Relapse

Bashey et al. JCO 2017
PBSC vs BM Following Haplo-Transplantation with Post-transplant Cytoxan

Survival

Survival curve showing adjusted probability (%).

- PB: 57% (95% CI, 49% to 65%)
- BM: 54% (95% CI, 49% to 59%)

No. at risk:
- BM: 496
- PB: 191
- 327: 105
- 192: 42

$P = .52$
BM and PBSC both viable stem cell options post Haplo transplant
Longer follow-up needed to discern if PFS advantage with PBSC improves survival
New Tools To Treat Transplant Related Complications
Letemovir- a non-nucleoside CMV inhibitor targeting viral terminase complex preventing viral replication

Randomized trial n=570 patients
- n=376 received prophylactic letemovir
- n=192 received placebo
- 14 weeks of study drug
- Dose 480 mg/day off CSA
- Dose 240 mg/day on CSA
- Study endpoint- CMV reactivation week 24
## OUTCOMES

<table>
<thead>
<tr>
<th>End Point</th>
<th>Letemovir Group (N=325)</th>
<th>Placebo Group (N=170)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point at wk 24 after transplantation</td>
<td>122 (37.5)</td>
<td>103 (60.6)</td>
<td>-23.5 (-32.5 to -14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically significant CMV infection</td>
<td>57 (17.5)</td>
<td>71 (41.8)</td>
<td></td>
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<tr>
<td>Initiation of preemptive therapy</td>
<td>52 (16.0)</td>
<td>68 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV disease†</td>
<td>5 (1.5)</td>
<td>3 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued trial before wk 24</td>
<td>56 (17.2)</td>
<td>27 (15.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to adverse event</td>
<td>6 (1.8)</td>
<td>1 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to death without CMV</td>
<td>28 (8.6)</td>
<td>12 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to other reason‡</td>
<td>22 (6.8)</td>
<td>14 (8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing outcome in wk 24 visit window</td>
<td>9 (2.8)</td>
<td>5 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key secondary end point at wk 14 after transplantation</td>
<td>62 (19.1)</td>
<td>85 (50.0)</td>
<td>-31.3 (-39.9 to -22.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinically significant CMV infection</td>
<td>25 (7.7)§‡</td>
<td>67 (39.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of preemptive therapy</td>
<td>24 (7.4)</td>
<td>65 (38.2)</td>
<td></td>
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</tr>
<tr>
<td>CMV disease†</td>
<td>1 (0.3)</td>
<td>2 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued trial before wk 14</td>
<td>33 (10.2)</td>
<td>16 (9.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to adverse event</td>
<td>5 (1.5)</td>
<td>1 (0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to death without CMV</td>
<td>14 (4.3)</td>
<td>6 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to other reason‡</td>
<td>14 (4.3)</td>
<td>9 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing outcome in wk 14 visit window</td>
<td>4 (1.2)</td>
<td>2 (1.2)</td>
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</table>
OUTCOMES

- FDA approves letermovir Nov 2017 for CMV prophylaxis post transplant
  - Letermovir is well tolerated
    - No marrow suppression unlike ganciclovir
    - No renal toxicity unlike foscarnet
  - Use of drug to treat CMV reactivation being studied
Ibrutinib for chronic GVHD after failure of prior therapy

Miklos, D et al, Blood-Sept 2017
cGVHD

- No standard 2\textsuperscript{nd} line therapy for cGVHD (after corticosteroids)

- Ibrutinib inhibits BTK (which regulates B-cell survival)

- Ibrutinib also inhibits ITK (IL-2 inducible T-cell kinase, which drives immune reactivity toward healthy tissues)

- po daily dosing

- T ½ = ~5 hrs
Ibrutinib improved clinical manifestations of cGVHD in pre-clinical studies
Study Design

• Phase 1b/ Phase 2
• Multicenter, Open Label
• Pharmacyclics company sponsored
• Enrollment 7/2014, Last follow-up 9/2016
• Sample size 40; assuming cGVHD response rate of 50%; Power 90% to show efficacy
Inclusion Criteria

- Adult
- Steroid dependent OR refractory cGVHD
  - Dependent = >0.25mg/kg/d Prednisone for ≥ 12 wks
  - Refractory = despite >0.25mg/kg/d Prednisone for ≥ 4 wks
Methods

- All received CS before and during study + other IS allowed (as long as stable doses 14d prior to study) – drugs could be tapered
- 3+3 design
- Phase 1b: Started at dose 420mg; if DLT could reduce to 280mg or 140mg
  - N=6, No DLT, RP2D = 420mg
- Phase 2
  - N=42
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(N = 42)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior lines of treatment for cGVHD (range)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Mean prednisone dose at enrollment (range), mg/kg/d</td>
<td>0.31 (0.1–1.3)</td>
</tr>
</tbody>
</table>

### Prior therapies for cGVHD

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Extracorporeal photopheresis/PUVA photochemotherapy</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Other immunosuppressants</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>
- Steroid dependent: ORR 75%, CR 25%
- Steroid refractory: ORR 50%, CR 17%
## Response Rates

<table>
<thead>
<tr>
<th>Sustained response of ≥ 20 weeks</th>
<th>No. of responders</th>
<th>Sustained response rate n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28</td>
<td>20 (71)</td>
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</table>

<table>
<thead>
<tr>
<th>Organ</th>
<th>No. of responders with organ involvement at baseline</th>
<th>Best overall response rate, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Mouth</td>
<td>24</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>11</td>
<td>10 (91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organs showing response</th>
<th>No. of patients with ≥ 2 involved organs at baseline among responders</th>
<th>Best overall response rate, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 organs</td>
<td>25</td>
<td>20 (80)</td>
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</tbody>
</table>
Ibrutinib Reduced Corticosteroid (CS) Usage

- Among responders, median CS use from 0.29 to 0.12 mg/kg/d
- 5 completely stopped CS
Ibrutinib Reduced GVHD Symptoms

- Lee GVHD Sx scale improved significantly in 61% of responders
Conclusion

• Ibrutinib demonstrated ORR 67% (CR=21%, PR=45%)
  – FDA approved for cGVHD – first drug approved for this indication

• Ibrutinib was largely safe to use, though:
  – 1/3 discontinued due to AE, though in a low PS population

• Phase 3 study underway for further validation
The Future of Allogeneic BMT

• Success of haplo-transplants:
  – Will lead to more annual transplants world-wide

• Reduced mortality of allotransplants
  – Better drugs to prevent and treat GVHD (i.e. Ibrutinib/ruxolitinib for cGVHD)
  – Better drugs to prevent CMV reactivation
  – Transplants performed earlier in disease course- (i.e AML)- will reduce risk of disease relapse

• More studies exploring investigational cellular therapies to improve transplant outcomes will be forthcoming
  – Viral reactive T-cells
  – Leukemia reactive T-cells
271 patients hematological malignancies – Transplanted single center 2005-2010

- 53 Haploidentical donors
- 117 MRDs
- 101 MUDs

Grade II-IV GVHD

NRM

Relapse

Bashley et al; JCO 2013
Is the patient a good candidate for a transplant?

- Age-no longer limiting
- Medical co-morbidity- less limiting with RIC transplants
- Donor availability- no longer limiting

- Disease Status as a critical determinant for transplant eligibility.
  - Guiding principle- if the disease has a bad prognosis with conventional therapy then the risks of a transplant may be justifiable
    - This is a moving target for some diseases- i.e. P53 mutated CLL
    - This is easy for other diseases
      - Therapy related MDS/AML
      - AML in second CR
      - ALL in second CR
Single-agent cyclophosphamide: GVHD prophylaxis
N=117 pts.  78 MRD, 39 URD. MAC: BuCy. Advanced hem malignancies

DAY 100:
Grade 2-4 aGVHD: 43%
Grade 3-4 aGVHD: 10%

Luznik et al. Blood 2010
## Results

<table>
<thead>
<tr>
<th></th>
<th>(N = 42)</th>
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</thead>
<tbody>
<tr>
<td>Median time on study (range) —</td>
<td>13.9 (0.5–24.9)</td>
</tr>
<tr>
<td>months</td>
<td></td>
</tr>
<tr>
<td>Median time on treatment (range)</td>
<td>4.4 (0.2–24.9)</td>
</tr>
<tr>
<td>months</td>
<td></td>
</tr>
<tr>
<td>Patients still on treatment —</td>
<td>12 (29)</td>
</tr>
<tr>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Reasons for treatment</td>
<td></td>
</tr>
<tr>
<td>discontinuation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Adverse events (including death)*</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Patient decision†</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Progression of cGVHD</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Recurrence or progression of</td>
<td>2 (5)</td>
</tr>
<tr>
<td>original malignancy</td>
<td></td>
</tr>
<tr>
<td>Investigator decision†</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Noncompliance with study drug</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
Likelihood of finding matched unrelated adult donor

Range 66-97%: Available suitable match, by race/ethnic group, Be The Match Registry®

Race or ethnic group of searching patient for hematopoietic cell transplantation