Role of Bone Marrow-Hematopoietic Stem Cell Transplant in Cancer Care And Red Blood Cell Complications

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Annual Numbers of Blood and Marrow Transplantations, 1970-2006
- Worldwide -

![Graph showing annual numbers of blood and marrow transplantations from 1970 to 2006, with separate lines for autologous and allogeneic transplants.](image-url)
Traditional Concept of Transplant

• Administration of Chemotherapy and/or Total Body Irradiation results in lethal damage of hematopoietic stem cells (myeloablative), and allows maximum kill to cancer cells.

• Subsequent Infusion of Hematopoietic Stem Cells (Autologous/Allogeneic) results in reconstitution of blood & immune system, thereby, allowing the patient to survive.
Blood Stem Cells

- Bone graft
- Bone
- Marrow
- Hematopoietic stem cell
- Multipotential stem cell
- Erythrocytes
- Eosinophil
- Basophil
- Megakaryocyte
- Platelets
- Monocyte
- Neutrophil
- Lymphoid progenitor cell
- Myeloid progenitor cell
- T lymphocyte
- B lymphocyte
- Dendritic cell
- Natural killer cell
Stem Cells from Donor to the Rescue

Patient receives chemotherapy or radiation

Stem cells are collected from donor

Stem cells are infused into patient, where they migrate to bone marrow
Allogeneic non-myeloablative stem cell transplantation

Pattern of engraftment vs conventional conditioning
BMT Terminology

• “Stem cell transplantation” has replaced “Bone marrow transplantation”

• Acronym “BMT” = Blood and Marrow Transplantation

• Peripheral Blood is the most common source of stem cells for transplant. Peripheral blood stem cells (PBSCs) are mobilized from the marrow into the bloodstream to collect.
Stem Cell Source (Where)

Peripheral Blood Stem Cell Collection

Bone Marrow Harvest

Umbilical Cord Blood
Donor/Graft Sources

- Autologous - self to self
- Syngeneic - from genetically identical twin
- Allogeneic:
  - Matched sibling or Matched family member
  - Matched unrelated
  - Partially matched and haploidentical family member
  - Umbilical Cord Blood
Tissue Typing Matches Donors to Patients

- **Autologous**
  - Donor
  - Patient
  - No conflict: all marker molecules match

- **Syngeneic**
  - Identical twin donor

- **Allogeneic**
  - Related donor
  - Allogeneic Donor
  - Allogeneic Patient
  - Conflict: only some marker molecules match
  - Unrelated donor
  - Unrelated Donor
  - Unrelated Patient

→ = matches to patient
Allogeneic Stem Cell Transplant

- HLA Matched Donor
  - If not available, then mismatched donor

- Donor Source: Related Sibling, Unrelated, Cord Blood, Haploidentical Parent/Sibling Donor

- Patient/Recipient receives either myeloablative or reduced intensity chemotherapy/radiation

- Administration of Immunosuppressive Therapy (Prograf, CSA) to reduce Graft-vs-Host Disease
Indications for Hematopoietic Stem Cell Transplantation in North America 2005

- Multiple Myeloma: Allogeneic (Total N=7,880) & Autologous (Total N=10,840)
- NHL
- AML
- Hodgkin Disease
- ALL
- MDS/MPD
- CML
- Aplastic Anemia
- Other Leuk
- Other Cancer
- Non-Malignant Disease

Transplant counts for different diseases and transplant types are visualized in the bar chart.
Modern Concept of Transplant

- Adoptive Immunotherapy (Allogeneic only) destroys the residual cancer cells (graft vs tumor/leukemia effect) independent of chemotherapy/radiation effect.
- Graft vs Tumor Effect is a powerful anti-tumor mechanism in patients with leukemia, lymphoma and myeloma.
“Graft vs Leukemia” in Leukemia

Gale et al, Ann Intern Med, 1994
Graft versus Leukemia

3-yr relapse probability

- ALL
- AML
- CML

Matched sibling
Identical twin

Gale, 1994
Who are Allogeneic Stem Cell Transplant Candidates?

- **Acute Myeloid Leukemia**
  - In CR1 with normal or poor risk karyotype up to age 75
  - CR2
  - Primary refractory if <55-60yrs
  - In relapse, best if clinical trial available
  - Refractory relapse patients rarely benefit

- **Acute Lymphoblastic Leukemia**
  - In CR1 Standard/High Risk; Ph+
  - CR2 (any)
  - Relapsed/refractory rarely benefit; only recommend transplant if on clinical trial
Who are Allogeneic Stem Cell Transplant Candidates?

- **Myelodysplastic syndrome**
  - Up front for IPSS Int-2 or High and <65yrs
  - Lower risk IPSS failing other clinical trials

- **CLL**
  - Relapsing after “best” front line therapy
  - 17p deletions

- **Chronic Myelogenous Leukemia**
  - Gleevec failures after 1 year trial still in CP
  - Relapsing on Gleevec in CP
  - Accelerated phase
  - Blast phase, after return to CP or CR
Who are Allogeneic Stem Cell Transplant Candidates?

- **NHL**
  - Relapsed/refractory follicular up to age 75
  - Relapsed diffuse large cell and high LDH at relapse
  - Relapsed T-cell NHL
  - Failure to mobilize auto PBSC

- **Multiple myeloma**
  - Up front on clinical trial
  - Refractory to induction
  - Relapsing after auto transplant

- **Myeloproliferative Disorders**
  - Myelofibrosis up to age 70
  - PV or ET in myelofibrotic phase
Allogeneic HSC Transplantation

• In many instances, represents the only curative therapy for patients with advanced hematological disorders
• Still associated with significant mortality risk due to numerous potential complications
• Many potentially eligible patients do not have a matched sibling donor
Alternative Allogeneic Stem Cell Sources

• Matched Unrelated Donor

• Cord Blood

• Haploidentical Related Donor (3/6 HLA Match)
NMDP Transplants Facilitated by Fiscal Year 1987–2008

![Bar chart showing the number of transplants facilitated by fiscal year, with categories for Cord blood, Peripheral blood stem cells, and Bone marrow. The chart shows an increase in the number of transplants over time, with significant growth in the later years.]
UCBT Compared to Volunteer MUDT

- Immediate availability

- HLA matching Requirements less stringent (4 of 6 match sufficient)

- Limited stem cell dose
UCBT - Graft Availability

• Available immediately
  - Fully HLA matched prior to storage
  - No donor morbidity or attrition

• Search few days vs. few months

• Useful in patients with high-risk malignancies
Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia. NEJM 2004. Rocha et al. EBMT/Eurocord

UBMT

UCBT

35 % ± 2

32 % ± 6

P 0.09

years

0 1 2
Haploidentical Related Donor Transplantation

Collaborative Trial with
Johns Hopkins Oncology Center
Allogeneic BMT is a potentially curative therapy for patients with high risk hematologic malignancies.

Major limitation is the unavailability of matched related or unrelated donors in many patients.

Newer options to widen availability of alternative donor transplantation:
- Double Umbilical Cord Blood Unit Transplantation
- Haploidentical Related Donor Transplantation
Allogeneic Transplant from Partially Matched Related (Haploidentical) Donors

Aversa F and Martelli MF  Springer Semin Immunol 26: 155, 2004
Tony D. 2004

- 44 years old
- Married, 2 children, warehouse manager
- 10/2003 PH-1 Positive ALL
- Hyper-CVAD + Imatinib
- 11/2003 Refractory, 30% Blasts
- HIDAC + MTX + Imatinib
- 12/2003 CR-1
- Completed HCVAD + Imatinib
- Maintenance Imatinib 400mg/day
- No Matched Related Donor
- No suitable donor in registry search
- Continued Imatinib
Reduced Intensity Conditioning + Post Transplant Cyclophosphamide

• Minimized Regimen Related Toxicity

• Post transplant Cy
  – deletes highly alloreactive donor T-cells responsible for GVHD
  – spares other T-cell populations responsible for immune reconstitution
Treatment Schema
Mini-haploBMT with post-transplantation Cy: Summary

• Acceptable toxicity
  – Graft rejection 18%, fatal in 2%
  – aGVHD in 35%, severe in 10%
  – NRM 19% at 1 year

• Relapse is biggest problem: 50% at 1 year

• Donor NK cells may improve outcome
Lymphoid malignancies do better

Event-free survival (%)

Day after BMT

- Lymphoid (n=37)
- Myeloid (n=51)

\[ p = .04 \]
Hodgkin’s Disease: Haploidentical vs. Related vs. MUD Allogeneic Transplant
Incidence of GVHD
BMT Clinical Trials Network (CTN)
Protocol 0603
A Multi-Center, Phase II Trial of Nonmyeloablative Conditioning (NST) and Transplantation of Partially HLA-Mismatched Bone Marrow for Patients with Hematologic Malignancies
Summary

• Hematopoietic Stem Cell Sources Include
  – Autologous
  – Allogeneic
    • Related HLA Matched Donor
    • Unrelated HLA Matched Donor
    • Cord Blood Donor
    • Mismatched Haploidentical Related Donor
Summary

• Allogeneic Hematopoietic Stem Cell Transplant therapy results in eradication of hematological malignancies both by the action of the preparative chemotherapy agent and from the effect of “Graft vs. Tumor/Leukemia”
Summary

• With advances in donor sources including cord blood and haploidentical related donors, most patients with poor risk blood cancers are able to proceed with allogeneic transplant therapy
ABO Incompatible Transplant Donor – Recipient Pairs

- **ABO Major Incompatible**
  - Recipient Antibody directed against Donor red cells (e.g. A donor, O Recipient)

- **ABO Minor Incompatible**
  - Donor Derived Antibody directed against Recipient red cells (e.g. O donor, A Recipient) (Acute and Delayed)

- **ABO Bidirectional Incompatible**
  - A Donor, B Recipient
Problems in ABO Incompatible Transplant Donor – Recipient Pairs

1) Acute Hemolysis when Graft (Donor Bone Marrow) infused: Major ABO Incompatible
2) Delayed Erythrocyte engraftment
3) Increased Transfusion Requirements
4) Passenger Lymphocyte Syndrome—Delayed Hemolysis
5) Pure Red Cell Aplasia (PRCA)
Hemolysis in ABO Incompatible Bone Marrow/Stem Cell Transplants

- **ABO Major Incompatible**
  - Bone Marrow Products: High Risk for acute hemolysis: RBC 25% – 35% of product infused
  - PBSC Apheresis Products: Low Risk for acute hemolysis: RBC 2% – 5% of product infused
  - Risk of Hemolysis reduced by RBC Removal
  - Depletion of isoagluttinin titer

- **Minor ABO Incompatible**
  - Risk is Delayed Hemolysis
Figure 1 Shown are suggested algorithms for the management of major red cell-incompatible transplants (a) and minor red cell-incompatible transplants (b). These algorithms are based on the experience of the author and are not tested in prospective studies of transplantation immunohematology.
Table 2  Transfusion support for recipients of ABO-incompatible HSC components

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor</th>
<th>Red blood cell and granulocyte components</th>
<th>Platelet and plasma components</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO major</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>A</td>
<td>0</td>
<td>A, AB</td>
</tr>
<tr>
<td>0</td>
<td>B</td>
<td>0</td>
<td>B, AB</td>
</tr>
<tr>
<td>0</td>
<td>AB</td>
<td>0</td>
<td>AB</td>
</tr>
<tr>
<td>A</td>
<td>AB</td>
<td>A, O</td>
<td>AB</td>
</tr>
<tr>
<td>B</td>
<td>AB</td>
<td>B, O</td>
<td>AB</td>
</tr>
<tr>
<td>ABO minor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>O</td>
<td>0</td>
<td>A, AB</td>
</tr>
<tr>
<td>B</td>
<td>O</td>
<td>0</td>
<td>B, AB</td>
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<tr>
<td>AB</td>
<td>O</td>
<td>0</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>A</td>
<td>A, O</td>
<td>AB</td>
</tr>
<tr>
<td>AB</td>
<td>B</td>
<td>B, O</td>
<td>AB</td>
</tr>
<tr>
<td>ABO major and minor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>0</td>
<td>AB</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>0</td>
<td>AB</td>
</tr>
</tbody>
</table>

Red cell components should be packed or washed to reduce plasma volume, or components from donors with low isoagglutinin titers. Shown are the first choice for platelet support; platelets from other blood groups can also be infused but should similarly be concentrated to reduce plasma volume.
Recipient ABO Isoagglutinins persist after BMT

Usually clear after 6 – 8 weeks with conversion to donor chimerism

Longer duration to clear with Reduced Intensity Transplants
Persistence of Recipient ABO Isoagglutinins may result in Red Blood Cell Aplasia (PRCA)

Therapy: Immune Suppression Modulation, Plasma Exchange, Rituximab (CD20+ Mab), Donor Lymphocyte Infusion to promote Full Donor Chimerism
Table 4. Relationship of Pretransplant Hemagglutinin Titers to Recovery of Peripheral Blood Reticulocytes Following ABO Blood Group Incompatible Bone Marrow Transplantation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pretransplant Hemagglutinin Titer</th>
<th>Days to Reticulocyte Count &gt; 1%</th>
<th>Hemagglutinin Titer When Reticulocyte &gt; 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-A</td>
<td>Anti-B</td>
<td></td>
</tr>
<tr>
<td>129</td>
<td>1:64</td>
<td>1:256</td>
<td>266</td>
</tr>
<tr>
<td>87</td>
<td>1:64</td>
<td>—</td>
<td>42+</td>
</tr>
<tr>
<td>88</td>
<td>1:32</td>
<td>—</td>
<td>60</td>
</tr>
<tr>
<td>133</td>
<td>1:32</td>
<td>—</td>
<td>64</td>
</tr>
<tr>
<td>170</td>
<td>1:16</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td>168</td>
<td>1:16</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>188</td>
<td>1:8</td>
<td>—</td>
<td>49+</td>
</tr>
<tr>
<td>254</td>
<td>1:8</td>
<td>—</td>
<td>41</td>
</tr>
<tr>
<td>126</td>
<td>1:8</td>
<td>—</td>
<td>39</td>
</tr>
<tr>
<td>221</td>
<td>1:8</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td>82</td>
<td>1:8</td>
<td>—</td>
<td>26</td>
</tr>
<tr>
<td>252</td>
<td>1:8</td>
<td>—</td>
<td>17</td>
</tr>
<tr>
<td>132</td>
<td>1:4</td>
<td>1:2</td>
<td>18</td>
</tr>
<tr>
<td>103</td>
<td>1:4</td>
<td>—</td>
<td>42+</td>
</tr>
<tr>
<td>78</td>
<td>1:4</td>
<td>—</td>
<td>35+</td>
</tr>
<tr>
<td>118</td>
<td>1:2</td>
<td>—</td>
<td>59</td>
</tr>
<tr>
<td>186</td>
<td>1:2</td>
<td>—</td>
<td>34</td>
</tr>
<tr>
<td>230</td>
<td>1:1</td>
<td>—</td>
<td>17</td>
</tr>
</tbody>
</table>

*Patient died prior to attaining >1% reticulocytes.
Hematopoietic stem cell transplantation between red cell incompatible donor-recipient pairs

Figure 2 Shown is the titer of anti-A isoagglutinin (IgG) over time for one patient who underwent allogeneic bone marrow transplantation from an HLA-compatible but ABO-major incompatible (A donor, O recipient) donor. This patient received erythropoietin supplementation for two periods of 6 and 3 months (EPO) and underwent plasmapheresis using protein fractions for replacement fluid on five occasions over 10 days (TPE). Red blood cell transfusion requirements persisted until the anti-A titer became undetectable.
1) Delayed Hemolysis of Recipient’s Red Cells from ABO Minor Incompatible Donor Antibodies produced from Donor B–cell Lymphocytes

2) Passenger Donor Lymphocytes are restimulated by the Host (Recipient) Red Cell Antigens (A, B, Rh, non–ABO red cell Ag)

3) Delayed hemolysis occurs typically 9 – 16 days following transplant

4) May result in life–threatening hemolysis
Passenger Lymphocyte Syndrome
Passenger Lymphocyte Syndrome
Rh Incompatible

Figure 1  Laboratory values showing rapid worsening of anemia and increase in transfusional requirement (a). Laboratory values consistent with intravascular hemolysis (b-d).
Passenger Lymphocyte Syndrome

- Treatment Options
  - Rituximab (Anti–CD20+ MAb)
  - Red Cell Apheresis Exchange with compatible ABO Red Cells to donor and recipient
  - Steroids, Immune suppression
Non-ABO Red Cell Antigen Incompatible Donor-Recipient Delayed Hemolysis Due to Passenger Lymphocytes

Table 1. Non-ABO red blood cell group antigen systems involved in the development of post-BMT alloimmune hemolytic anemia

<table>
<thead>
<tr>
<th>RBC antigen system</th>
<th>Antibodies</th>
<th>Mechanism of hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh system</td>
<td>Anti-D, -C, -c, -E</td>
<td>Delayed hemolytic anemia,\textsuperscript{13,21,32} which may be severe after major Rh-mismatched grafts.\textsuperscript{15} Passenger lymphocyte syndrome\textsuperscript{7} and chronic hemolysis (in the case of persistence of mixed chimerism)\textsuperscript{8} have also been described</td>
</tr>
<tr>
<td>Kell system</td>
<td>Anti-Kell</td>
<td>Delayed hemolytic anemia\textsuperscript{25,28}</td>
</tr>
<tr>
<td>Kidd system</td>
<td>Anti-JK\textsuperscript{a}, -JK\textsuperscript{b}</td>
<td>Severe acute hemolytic anemia with intravascular hemolysis (passenger lymphocyte syndrome),\textsuperscript{6,29} delayed hemolytic anemia\textsuperscript{25}</td>
</tr>
<tr>
<td>MNSs system</td>
<td>Anti-M, -N, -S, -s</td>
<td>Delayed hemolytic anemia\textsuperscript{6,25}</td>
</tr>
<tr>
<td>Lewis system</td>
<td>Anti-Lewis\textsuperscript{a}, -Lewis\textsuperscript{b}</td>
<td>Passenger lymphocyte syndrome\textsuperscript{26}</td>
</tr>
</tbody>
</table>
Pure Red Cell Aplasia

- **Risk Factors**
  - High initial ABO anti-Donor Isoagglutinin titer, or persistently elevated anti-Donor Isoagglutinin titer that persist following transplant
  - RBC Incompatibility involving the A antigen
## Risk factor analysis for Pure Red Cell Aplasia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95%-CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO incompatibility</td>
<td></td>
<td></td>
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<tr>
<td>Major</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>1.97</td>
<td>1.26-3.06</td>
<td>0.003</td>
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<tr>
<td>Isoagglutinin titer reduction¹</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Yes</td>
<td>1.57</td>
<td>1.05-2.35</td>
<td>0.029</td>
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<tr>
<td>Acute GvHD²</td>
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<tr>
<td>Grade 0-I</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade II-IV</td>
<td>1.79</td>
<td>1.19-2.70</td>
<td>0.050</td>
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<tr>
<td>Stem cell source</td>
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<tr>
<td>Bone marrow</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>2.18</td>
<td>1.41-3.38</td>
<td>&lt;0.001</td>
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<tr>
<td>Conditioning</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Myeloablative</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Reduced intensity</td>
<td>1.81</td>
<td>1.08-3.03</td>
<td>0.025</td>
</tr>
<tr>
<td>Age at H SCT³</td>
<td>0.99</td>
<td>0.97-1.00</td>
<td>0.032</td>
</tr>
</tbody>
</table>

¹Anti-donor isoagglutinin titer reduction: in vivo adsorption, plasmapheresis, or both methods. ²Acute GvHD was analyzed as a time-dependent covariate. ³Increment=1 year.

Cumulative incidence of PRCA and RBC engraftment (A)

Incidence of PRCA

Pure Red Cell Aplasia
Treatment Options

- **Pre-emptive**
  - Plasmapheresis of Recipient to reduce Anti-Isoagglutinin titer

- **Treatment**
  - Rituximab (Anti-CD20+ Mab)
  - Erythropoietin
  - Donor Lymphocyte Infusion (Promote Graft vs. Host Disease and full donor chimerism)
  - Withdrawal of immune suppression to promote donor chimerism
Pure Red Cell Aplasia

Donor lymphocyte infusions for refractory pure red cell aplasia relapsing after both autologous and nonmyeloablative allogeneic peripheral stem cell transplantation

M Musso, F Porrett, A Cresciimanno, V Polizzi and R Scalone

Figure 1.

Figure and tables index

- PDN+EO
- PDN+CYA+
- ATG+EO
- Auto
- Allo
- CY 4g/m²
- DLI
- Hb

Auto: autologous transplant conditioning regimen comprised Cy, 50 mg/kg day -6,-5; 6-methyl prednisolone, 1 g+anti-T-globulin 10 mg/Kg day -4,-3,-2; allogeneic transplant conditioning regimen comprised Cy, 60 mg/kg/day x 2 days; Fluorara, 30 mg/m² x 4 days; CY: cyclophosphamide; DLI: donor lymphocyte infusion; PDN: methylprednisolone; CYA: cyclosporine; EPO: erythropoetin; ATG: anti-T-globulin. Hb: haemoglobin.
The Blood and Marrow Transplant Program at Northside Hospital

Transplant Team

The Transplant Team consists of 170 experienced professionals dedicated to the care of patients.