Bone Marrow Transplantation and the Potential Role of Iomab-B

Hillard M. Lazarus, MD, FACP
Professor of Medicine, Director of Novel Cell Therapy
Case Western Reserve University
Hematopoietic Cell Transplantation (HCT) Background

• Life-saving art applied for:
  – Hematologic malignancy (most common indication)
    – Goal: eliminate malignancy
  – Acquired and genetic disorders of hematopoiesis and the immune system
    – Goal: restore normal blood production/immunity

• Premise(s):
  – Cytotoxic agents required to turn off recipient’s immune system and allow engraftment (avoid rejection)
  – Increasing doses of cytotoxic agents (chemotherapy, radiotherapy) markedly increase cancer cell kill

• BUT cytotoxics harm blood cell production (marrow injury)

• Leads potentially to fatal infection and bleeding
• Infusion of hematopoietic progenitor cells “rescue” host
• Cells obtained from:
  – patient himself/herself (autologous) or
  – another person (allogeneic)
• Hematopoiesis restored over several weeks by infused cells
• Requires that recipient has been given vigorous supportive care with antibiotics, transfusions, other tools
HCT can be divided into many types; depends on:

- Intensity of chemo-radiation therapy given:
  - myeloablative
  - reduced-intensity conditioning
  - non-myeloablative
• Donor graft, related and unrelated:
  – Autologous (self)
  – Allogeneic (another person)
    – Related: histo-compatible (HLA-identical) sibling
      – Theoretically best donor
    – Related: haplo-identical (“half-match” family member)
      – At present, much less commonly used
    – Alternative donor (not related)
      – Unrelated (but histo-compatible, i.e. HLA-identical) adult
      – Umbilical cord blood (obtained from the placenta after delivery)
Hematopoietic Cell Transplantation (HCT) Background (cont’d)

• Graft source
  – Bone marrow (collected in OR from post-iliac crests)
  – Blood (marrow progenitors mobilized into blood using agents, collected via large catheter (85% of all HCT)
  – Umbilical cord blood (from the placenta after delivery)

• Advantages/disadvantages for these various approaches
  – Depends on disorder affecting recipient
  – Donor availability
  – Age and physical condition of the recipient
  – Planned timing of transplant
  – Many other factors
Autologous Hematopoietic Cell Transplant

Chronology of Approach

Patient Evaluation → Stem Cell: Collection ± Purging Freezing → High-dose Chemotherapy → Infusion of Graft → Vigorous Supportive Care
Allogeneic Hematopoietic Cell Transplant

Chronology of Approach

1. Patient Evaluation
2. High-dose Chemotherapy
3. Infusion of Graft
5. Vigorous Supportive Care

Donor Evaluation

Hematopoietic Cell Collection ± T-cell depletion ± Freezing
## Donor Availability and Transplant Type

<table>
<thead>
<tr>
<th>Donor Type</th>
<th>Match Probability</th>
<th>% All Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-compatible sibling</td>
<td>30%</td>
<td>54%</td>
</tr>
<tr>
<td>HLA-compatible unrelated</td>
<td>35-80%</td>
<td>38%</td>
</tr>
<tr>
<td>Umbilical cord blood (UCB)</td>
<td>10-90%</td>
<td>5%</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>99%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

C Anasetti. BMT CTN State-of-the-Science, June 2007, Ann Arbor, MI
Acute Myeloid Leukemia (AML) Survival by Age

Adapted from Juliusson G et al. Blood 2009;113:4179-4187
Rationale for RIT in HCT Regimens

- AML is highly radiosensitive.
- TBI effective in HCT at high doses.
- TBI cannot be safely dose-escalated because normal organs cannot tolerate more radiation.
- Tradeoff: more killing of leukemia simultaneously destroys normal tissue.

TBI = total body irradiation   RIT = radioimmunotherapy
Conditioning Regimens for Allogeneic HCT

- Myeloablative Conditioning (MA)
- Reduced-Intensity Conditioning (RIC)
- Non-myeloablative Conditioning (NMA)

Efficacy vs. Safety Tradeoff Zone

= Tradeoff Zone; Safety versus Efficacy
Iomab-B combines an anti-CD45 mAb that targets lympho-hematopoietic cells with a radio-toxin, the β-particle emitting radionuclide $^{131}$I.

The mAb does not bind to other normal tissues and directs radiation to only leukemic and immune cells.
Iomab-B is a “guided missile” which selectively ablates bone marrow, killing leukemia cells as well as host immune system cells (the latter prevents rejection of hematopoietic cells from another person).

This therapy is part of the transplant regimen; must be followed immediately by infusion of a hematopoietic graft from another person to restore marrow function.

New marrow grows back over several weeks and blood production resumes.
Iomab-B Phase I/II Results

- Prior data from the Fred Hutchinson Cancer Research Center
- Patients > 50 years old with advanced AML and high risk MDS
- Patients received Iomab-B followed by hematopoietic cell transplant
- N= 21; patients treated at MTD

probability

years after transplant
Iomab-B Phase I/II Results

Definitions:

♦ **Primary Refractory AML:**
  – Leukemia is uncontrolled and resistant to treatment
  – No response seen after two cycles of induction attempts

♦ **Myeloablation**
  – Depletion of bone marrow; carries standard risks of infection and bleeding;
  – Patients are isolated and given vigorous supportive care, i.e. transfusions and antibiotics

♦ **Complete Remission (CR):**
  – No obvious evidence of leukemia
  – Recovery of white blood cells and platelets
Iomab-B Phase I/II Results

- Complete response rate: 100%
- Engraftment by day 28: 100%

Non-relapse mortality (NRM): Day 100<10%, Overall ~20%
(NRM = 46% in comparable patients with conventional myeloablative conditioning transplants*)

All relapsed/refractory AML patients over 50

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iomab-B BMT (N=27)</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Current BMT* (N=10)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Chemotherapy (N=61)</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

N = Number of patients treated. Iomab-B results from FHCRC clinical trials; Current BMT and Chemotherapy results from MD Anderson outcomes analysis
Sources: Blood 2009 114:5444-5453; unpublished FHCRC data
Iomab-B Phase I/II with Poor Cytogenetics

Rel/ref AML patients over 50 w/ poor cytogenetics

N = Number of patients treated  Iomab-B results from FHCRC clinical trials; Current BMT and Chemotherapy results from MD Anderson outcomes analysis
Sources: Blood 2009 114:5444-5453; unpublished FHCRC data
Iomab-B Pivotal Phase III Trial Design

- Single pivotal study, pending trial results
- Patient population: refractory AML patients over the age of 55 years
- Trial arms: study arm and control arm with physician’s choice of conventional care with curative intent
- Trial size: 150 patients total, 75 patients per arm
- Study timeline: enrollment approximately 12 months; primary endpoint additional 8 months; secondary endpoint additional 4 months; follow-up 5 years

*Control arm subjects with no CR are offered crossover to Iomab-B for ethical reasons.

**NMA/RIC = Nonmyeloablative Conditioning/Reduced Intensity Conditioning transplant

1. Based on the End of Phase II meeting and subsequent communications with the FDA.
2. Refractory is defined as either primary failure to achieve a complete remission after 2 cycles of induction therapy; relapsed after <6 months in complete remission; second or higher relapse; or relapsed disease not responding to intensive salvage therapy.
Appendix: Likelihood of Finding an 8/8 HLA Match

In 2015, nearly every patient can have a donor.