Milestones in the History of Stem Cell Transplantation

John Barrett MD
Transplant prehistory

The first bone marrow graft

Ulster, Ireland circa 500 BC

Indication: major trauma

Stem cell source: bos taurus xenograft

Outcome: died d+ 7 (major trauma)

Reference: Tain Bo Cuialnghe (The cattle raid of Ulster)
Aspects of stem cell transplant history

Breakthroughs

personalities

immunological science

supportive care

organizations
Introduction of new therapeutic agents

- 1960: Cyclophosphamide, Busulfan, Whole body irradiation
- 1970: Antilymphocyte globulin, Methotrexate, OKT3
- 1980: Cyclosporine, Tacrolimus, Canpath
- 1990: Imidazole antifungals, Acyclovir, Ganciclovir/Foscarnet
- 2000: Fludarabine, Sirolimus, FTY720

Miscellaneous
Organizations

- EBMT
- CIBMTR
- NetCord
- National Marrow Donor Program
- FACT
- ASBMT
- Anthony Nolan Fund
- ISCT
personalities
The chronological history

1940’s  The origins of modern stem cell transplantation

1950’s  The first human marrow transplants

1960’s  Breakthroughs in immunology

1970’s  Clinical bone marrow transplantation takes off

1980’s  Widening indications, widening donor choices, new drugs

1990’s  New stem cell sources, new indications, New conditioning regimens

2000’s  Improved outcomes, older patients, the rise of cord blood, cell therapy
The 1940s

The atomic bomb precipitated research leading to stem cell transplantation.
Jacobsen’s radiation protection experiments

1000 rads

Shield hind limb

Inject spleen cells

Spleen cells

died

protected

protected
Why did the mice survive?  Ford’s experiments

Cellular theory

Inject spleen cells

Chromosome analysis

Surviving mice

marrow cells

With marker chromosome

repopulated marrow

100% marker chromosome
Primary disease and secondary disease

No cells

Death - 7 days: Primary disease

Isologous donor

survival

Secondary disease

Death - 14 days

Homologous donor
**Graft- versus -leukemia (Barnes and Loutit 1956)**

*Isologous marrow*

- Death from leukemia

*Homologous marrow*

- Secondary disease
  - Death d 14 no leukemia!!
Clinical Stem Cell Transplantation and the beginnings of HLA typing

- **1957-Thomas**
  - Safe infusion of marrow into humans

- **1959-Mathé**
  - First bone marrow transplants for radiation accident victims.

- **1958-Dausset**
  - First HLA antigen described (A2)

- **1963-Mathé**
  - First successful complete engraftment and survival of over 1 year, description of acute and chronic GVHD in men

- **1968-van Rood/Terasaki**
  - Modern HLA serologic typing available
  - Secondary disease-running syndrome-GVHD

- **1968-Good (Minneapolis) De Vries (Leiden)**
  - First successful HLA-matched sibling transplant for SCID
Transplanters hall of fame

Georges Mathé  
E Donnall Thomas  
JJ van Rood  

Jean Dausset  
Robert Good  
Paul Terasaki
The 1970’s

Bone Marrow Transplantation takes off!!
Blood. 1977 Apr;49(4):511-33. L

One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation.


94 patients were engrafted and only one patient rejected the graft. ......

Thirteen patients are alive with a marrow graft, on no maintenance antileukemic therapy, and without recurrent leukemia 1-4.5 yr after transplantation.

This observation, coupled with the observation that some patients may be cured of their disease, indicates that marrow transplantation should now be undertaken earlier in the management of patients with acute leukemia who have an HLA-matched sibling.
Tracking and documenting transplants

Europe

1975

2009

EBMT

Survey 2002
Total transplants (1st)
per 10 million

- 0 or no report
- 1-50
- 51-200
- 201-400
- > 400

Israel
Iran
Algeria
Tunisian

Fiorenza
Tracking transplants world-wide
IBMTR - CIBMTR

Mortimer M. Bortin
Scientific Director,
IBMTR 1972-1991

Mary M. Horowitz
Scientific Director,
IBMTR 1991-
IBMTR

- Established in 1972 to monitor and study outcomes of bone marrow transplants; moved to MCW ~1980
- Maintains a database of clinical information on recipients of autologous and allogeneic hematopoietic stem cell transplants in ~450 centers in 47 countries
- Provides scientific and statistical support for analyzing those data

Number of Transplants

Year


0 5,000 10,000 15,000 20,000 25,000 30,000 35,000 40,000 45,000

Autologous

Allogeneic
INDICATIONS FOR BLOOD AND MARROW TRANSPLANTATION (BMT) IN NORTH AMERICA 2002 (IBMTR)

- Allogeneic (Total N = 7,200)
- Autologous (Total N = 10,500)

Transplants for:
- Multiple NHL Myeloma
- AML Hodgkin Disease
- ALL MDS / Other Leukemia
- CML Neuroblastoma
- CLL
- Breast Cancer
- Other Non-Malignant Disease

Breast NHL Hodgkin Multiple Myeloma AML ALL CML Other Leukemia Neuroblastoma CLL Breast Other Non-Malignant Disease
Barriers for stem cell transplantation

The 1980’s: Extending the indications

The 1990’s: Older and debilitated patients

Extending the donor pool

The last decade: Safer transplants

The next decade: More cures
The 1980’s
Extending the indications

1970s | 1980s | 1990s

Acute leukemia

CML

CLL

myeloma

lymphoma

MDS

Cancer

Aplastic anemia and immunodeficiency diseases

Hemoglobinopathies

Inborn errors

Inborn errors
Correction of genetic disorders by replacement with hematopoietic stem cells and their progeny.
Allogeneic SCT for Renal Cell Cancer

Childs et al NEJM 1999
Barriers for stem cell transplantation

The 1980’s: Extending the indications

The 1990’s: Older / debilitated patients

        Extending the donor pool

The last decade: Safer transplants

The next decade: More cures
Limitations to successful cure

Restricts SCT to patients <60y in good condition. How to transplant older people safely?
RIC - a conceptual wavefront of the 90’s

Jerusalem (Slavin)

Houston (Giralt)

Spitzer / Sykes

Bethesda (Childs / Barrett)

Seattle (Storb)

Genova (Carella)
Diversity in 40 published reduced intensity conditioning regimens

Dose variable or not given

Fludarabine
Busulfan
Cyclophosphamid
Melphalan
irradiation
other

Flu/Bu 10

Flu/Cy 9

Flu/Mel 9

TBI-based 12
Busulfan-based regimens look most promising!

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Bu</th>
<th>Mel</th>
<th>TBI</th>
<th>Cy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients</td>
<td>410</td>
<td>612</td>
<td>1052</td>
<td>172</td>
</tr>
</tbody>
</table>

>1.5y PFS

>1yr TRM
Can we make SCT available to more patients who do not have a matched sibling?

- Unrelated
- Cord blood
- Haploidentical
1986 – U.S. government appropriated funds to establish the National Bone Marrow Donor Registry (Donor Panel)

1988 – U.S. Organ Transplant Amendments Act – mandated collecting outcome data (Recipient Registry); also collects donor outcomes

~150 transplant centers and 90 donor centers

Repository with matched recipient/donor blood samples
### Related and unrelated SCT meet less than half the need for donors

Percentage of patients needing donors

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>21,000 no unrelated donor</td>
</tr>
<tr>
<td>42%</td>
<td>4,000 unrelated</td>
</tr>
<tr>
<td>30%</td>
<td>11,000 related</td>
</tr>
</tbody>
</table>

- CBT
- Haplo transplant
Matched Unrelated Donors

Year

1985

1990

1995

2000

2005

2006

Adult

Cord

5,335,465

30,874

50,000

40,000

30,000

20,000

10,000

0

60,000

30,000

20,000

10,000

0
Cord Blood Transplantation

Laughlin M, NEJM 344:1815, 2001
The CBT learning curve

Increase stem cell dose by
double (triple?) CBT
T depleted haplo sibling plus CBT
ex-vivo expansion

Increase immune effect
Salvaged cord lymph expansion
pooled Tregs
antigen-specific T cell expansion

Increase cord banks to provide better matches
Haploidentical transplants

- **Henslee-Downey**
  - n: 72
  - Engraftment: 88%
  - Acute GVHD: 16%
  - Chronic GVHD: 8%
  - 2 year survival:
    - High risk: 27%
    - Low risk: 55%

- **Aversa (NEJM 1998)**
  - n: 43
  - Engraftment: 100%
  - Acute GVHD: 0%
  - Chronic GVHD: 0%
  - TRM: 40%
  - 18 mo F/U: 12/43 alive and well

- **18 mo F/U:** 12/43 alive and well
Barriers for stem cell transplantation

The 1980’s: Extending the indications

The 1990’s: Older and debilitated patients

Extending the donor pool

The last decade: Safer transplants

The next decade: More cures
TRANSPLANTS ARE GETTING SAFER
HLA-IDENTICAL SIBLING MYELOABLATIVE TRANSPLANTS FOR LEUKEMIA Registered with the IBMTR, 1975-2002

- \(\geq 1995\) (15,126) 56%
- 1985-1994 (14,755) 48%
- 1975-1984 (N=2,334) 35%

\[ P = 0.0001 \]
Why are transplants getting safer?

- Better antifungals
- Better antivirals, pre-emptive treatments
- Treatments for EBV LCL
- Treatments for steroid-resistant GVHD
- Effective antibiotics
- Cell dosing
- Selection of regimen intensity
- Improvement in competence levels worldwide
Improved competence

- Standardized supportive care
  - IV lines, prophylaxis, transfusions
- Standardized treatments of high-risk complications
  - VOD, IP, CMV, EBV, etc
- Education and training widely disseminated and available
- More people doing more transplants!
HD Corticosteroids

≥ 6 days

Cyclosporine IV 12 hour infusion

Infliximab 10mg/kg

Daclizumab 1mg/kg

Amp/Sulbactam

7 11 15 22 29

Lipid Complexed Ampho-B

Voriconazole

Onset Grade 3-4 GI GVHD
Treatment of severe acute GVHD using MSC

Le Blanc et al, Lancet 363, 1439-41, 2004
Barriers for stem cell transplantation

The 1980’s: Extending the indications

The 1990’s: Older and debilitated patients

Extending the donor pool

The last decade: Safer transplants

The next decade: More cures
TRANSPLANTS ARE NOT MORE CURATIVE

HLA-IDENTICAL SIBLING MYELOABLATIVE TRANSPLANTS
ADVANCED LEUKEMIA* IBMTR, 1975-2002

* Not in remission for AML or ALL
Blast phase for CML

YEAR BASED ON:
1975-1984 (451) 62%
1985-1994 (2299) 60%
≥1995 (2261) 62%

NS
GVL comes of age!


Graft-versus-leukemia reactions after bone marrow transplantation.
Blood. 1990 Feb 1;75(3):555-62

DLI


Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients.
Blood. 1990 Dec 15;76(12):2462-5
The GVL effect is T cell linked

<table>
<thead>
<tr>
<th></th>
<th>Allogeneic non T cell depleted</th>
<th>Relapse risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>no GVHD</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>aGVHD</td>
<td>141</td>
<td>17</td>
</tr>
<tr>
<td>cGVHD</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>a+cGVHD</td>
<td>84</td>
<td>15</td>
</tr>
<tr>
<td>Syngeneic</td>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>Allogeneic T depleted</td>
<td>84</td>
<td>34</td>
</tr>
</tbody>
</table>

**NK cells also have a GVL effect**

- Donor-recipient KIR-MHC I mismatch
- Alloreacting NK
- LYSIS
  - Attacks host T cells
  - Attacks host leukemia
  - Attacks host DC
  - BLOCKS GVHD
- ENGRAFTMENT

Ruggeri et al Semin Cancer Biol. 2006
Suicide gene therapy

HSZ-Tk gene inserted into proliferating donor PBMC

transplanted patient

GVHD modulated

ganciclovir

Haplo-identical SCT for advanced leukemia

$10^7$ CD3+TK+ cells/kg
full immune recon broad repertoire
Relapse prevented in 2/3 patients
multiple doses of ganciclovir abrogated GVHD

*Ciceri et al Cytotherapy 2005*
Gene Modified T cells

CMML patient
Leukemia-specific T cell lines

Irrad CML + Donor MNC

restimulate

IL-2

split

10 X 96 well plates

Select and expand growing clones

Test

select

Give DLI to relapsed CML patient

6-8 weeks

Pool active and specific CTL lines

Falkenburg et al
**NK infusions**

Haploidentical NK cells proliferate in recipients and show cytotoxicity

Requirement for lymphodepletion (IL15 driven expansion)

92% of lymphocytes of donor origin and show NK cytotoxicity

*Miller et al Blood 2005*
Selective Depletion

Recipient non-leukemic cells

Donor

Third-party stimulators

Recipient leukemic cells

MLR

CD25

Anti-CD25 immunotoxin

1. Irradiated non-leukemic stimulators: activated/expanded T cells
   - Sufficient numbers
   - Efficient antigen presentation

Non-reactive

Reactive

Reactive

Recipient

1. Irradiated non-leukemic stimulators: activated/expanded T cells
   - Sufficient numbers
   - Efficient antigen presentation
Combined GVL strategies for the perfect stem cell allograft

PBSCT
Selective allodepletion

5 x 10^6 /kg

Block T reg function (Ontacc?)

No immunosuppression!

vaccinate

CD3
CD34

vaccinate

HLA-matched / Mismatched: Select NK alloreactive

vaccinate

Infuse leukemia-specific CTL

survival

relapse

YEARS
The future of allogeneic SCT

- Early chemotherapy
- Combination chemotherapy
- High dose chemotherapy and marrow rescue
- Selective immune reconstitution
- Small molecules
Thanks!

Our patients

Our best friends