The future of HSCT

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Transplants today
Current approaches to improve SCT outcome

1. **Optimize stem cell dose and source**
   - BMT? PBSCT?

2. **Select high risk patients!**

3. **New conditioning regimens**
   - Controlled regimen intensity

4. **Adjusting post transplant I/S to minimize GVHD and preserve GVL**

5. **Better Supportive care**

Graph showing survival and relapse rates over the years.
Roadblocks to successful outcome

- Transplant
- Marrow recovery
- APC recovery
- NK recovery
- T cell recovery
- NK recovery
- B cell recovery

Biological endpoints
- GVL
- aGVHD
- cGVHD

Viral reactivation

Clinical endpoints
- TRM
- Relapse

Statistical endpoints
- OS
- DFS

GVL

Relapse
Preventing GVHD

**Host APC**
- Virus
- Leuk
- mHA
- MHC1
- MHC2
- **CD4**
- **CD8**
- **engagement**
- **Stop activation**
- **CSA/Tacro**
- **Sirolimus**
- **Tregs**
- **ATG**
- **Campath**
- **T cell depletion**
- **Selective T cell depletion**
- **Conditioning**
- **Bortezomib**

**Donor T cells**
- **CD8**
- **CD4**
- **Activation/ expansion**
- **block proliferation**
- **prevent T-cell - target contact**
- **Steroids homing**
- **MTX**
- **Cy**
- **MMF**
- **Steroids**
- **MSC**

**Host target**
- **damage**
- **repair**
- **Tissue repair**
- **Steroids**
- **homing**
- **MSC**
NO CHANGE IN RELAPSE AFTER HLA-IDENTICAL SIBLING
MYELOABLATIVE TRANSPLANTS FOR EARLY LEUKEMIA*
IBMTR, 1975-2002

\[ \text{1975-1984 (1,071) 23\%} \]
\[ \text{1985-1994 (8,989) 22\%} \]
\[ \geq 1995 (9,747) 20\% \]

* 1st CR for AML or ALL
Chronic phase for CML
NO CHANGE IN RELAPSE AFTER HLA-IDENTICAL SIBLING MYELOABLATIVE TRANSPLANTS FOR ADVANCED LEUKEMIA*
IBMTR, 1975-2002

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

PROBABILITY, %

YEARS

1975-1984 (451) 62%
1985-1994 (2299) 60%
≥1995 (2261) 62%

* Not in remission for AML or ALL
Blast phase for CML
Is BMT at an evolutionary dead end?
The challenges ahead

A transplant for every patient that needs one?

Expanding the donor pool

Safer transplants for older patients
Related and unrelated SCT meet less than half the need for donors

Percentage of patients needing donors

100%
21,000 no unrelated donor

42%
4,000 unrelated

30%
11,000 related

CBT
Haplo transplant
Allogeneic Transplants for Age ≤ 20yrs, Registered with the CIBMTR 1992-2009
- by Donor Type and Graft Source -

* Data incomplete
Allogeneic Transplants for Age > 20yrs, Registered with the CIBMTR 1992-2009
- by Donor Type and Graft Source -

Number of Transplants

- Related BM/PB
- Unrelated BM
- Unrelated PB
- Unrelated CB

* Data incomplete
Trend: More patients will have a donor

Umbilical cord and URD
- Increase in banks

Haploidentical donors
- more as the procedure gets safer

Health care delivery
- NMDP approach to increasing SCT availability
- availability increases with socio-economic status
Trend: Older patients will be increasingly transplanted (data shown 1989-2009)

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma
The limits of success today

RELAPSE

GVHD

INFECTION

REGIMEN RELATED MORTALITY
Cell therapy for HSCT – the Vision

- Transplant CD34 cells unmanipulated / T cell depleted
- >90% survival
- DLI, T cells and NK cells
- Virus specific T cells
- MSC
- MSC / Tregs

Sources: Allogeneic
- Marrow
- Blood
- Cord blood

Engraftment
- Relapse
- Infection
- Organ toxicity
- GVHD
Cell therapy complexity

- Minimal manipulation
- Minimal cell sorting
- Culture expansion
  - Adjuvants selection
  - Feeder cells
- Gene insertion

Level 1
- Marrow
- UCB
- G-PBSCT
- G-Marrow
- DLI

Level 2
- CD34 selection
- CD4 selection
- Memory cell selection
- T reg selection
- NK selection

Level 3
- Selective immunodepletion
- Virus specific T cells
- Tumor-specific T cells
- TIL, MIL
- NK cells
- MSC
- DC

Level 4
- CAR cells
- TCR insertion
- Suicide genes
- TGFβ resistance
- Cytokine secreting

Frequency of use
The long winding road to successful T cell therapy

- Improved growth conditions
- Multi-virus specific T cells in the clinic
- Improved APC generation
- Low volume GMP grade culture systems
- Target antigen identification
- Incorporating CD4 and CD8 responder
- Proof of principle: Virus specific T cells, Leukemia-specific T cells
- 1995: Proof of principle
- 2000: Incorporating CD4 and CD8 responder
- 2000: Improved APC generation
- 2000: Tumor specific T cells in the clinic
Multivirus-specific CTL Protect against EBV after HSCT

- 9/40 patients had EBV reactivation
- 9/9 patients had decrease in EBV viral load with corresponding elevation in EBV-specific CTL detected in PB
- No antiviral therapy required

Diagnosis of PTLD 2 months later

Nat Med. 2006;12(10):1160-1166
Making LMP1 and LMP2 T cells to treat Hodgkin's disease

Adherent PBMC
GM-CSF
IL-4
IL-1β
IL-6
TNF-α
PGE-2

rAd6F35

LCL
IL-15
IL-2
IL-2

PBMC

More recently
Substituting ad
vector for
pepmixes

LMP-specific
Cytotoxic T
Lymphocytes
(CTL)

Bollard et al, JIT 2004, Straathof et al, JJ 2005
Clinical Responses post LMP-CTL
Relapsed Disease Arm (n=23)

- No toxicity
- 12 CR (1 also given Rituximab) (includes 1PR→CR)
- 2 very good partial responses (up to 36 mths)
- 9 progressive disease (2-8 wks)

Median clinical response: 1.5y (range: >6 to >40 mths)
In Girl’s Last Hope, Altered Immune Cells Beat Leukemia

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children’s Hospital of Philadelphia. More Photos »
## Progress in the general application of cell therapy

<table>
<thead>
<tr>
<th>Technology</th>
<th>Clinical trials</th>
<th>Acceptance</th>
<th>Commercialization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34 cell products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dendritic cells</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MSC</td>
<td></td>
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<tr>
<td>Gene modified T cells</td>
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<td>Virus-specific T cells</td>
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<td>NK cells</td>
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<td>CAR-trans T cells</td>
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<tr>
<td>Tumor specific T cells</td>
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<td>T regs</td>
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“Black Box” The future for commercial cell therapy?

- Apheresis lymphocytes
- Apheresis monocytes
- Add growth factors
- Add peptides
- Controlled sterile environment
- Cell product: Virus specific T cells
- Cell product: Virus specific T cells
2043

Transplants in 30 years time?

Some predictions
PREDICTION: APPROX 5% IMPROVED SURVIVAL / DECADE

(URD myeloablative SCT shown)

\[ P = 0.0001 \]
PREDICTION: IMPROVED CURE RATES

(HLA-ID Sib SCT for advanced disease shown)

1975-1984 (451) 62%
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≥1995 (2261) 62%

2045 – 5%??

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Blast phase for CML
Unpredictables

Graph showing the number of transplants over years from 1980 to 2010 for autologous, related donor, and unrelated donor categories.
Unpredictables: combinations that work

- Surgery radiation
- Chemotherapy
- Cell therapy, SCT
- New agents
- Cytokines
- Monoclonals
- Small molecules
Unpredictables: new treatments change indications for HSCT

another imatinib

cell therapy without HSCT

gene therapy
The future evolution of allogeneic SCT

Early chemotherapy

Combination chemotherapy

High dose chemotherapy and marrow rescue

Small molecules

Cell therapy
Cytokines
New drugs