The future of HSCT

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Current approaches to improve SCT outcome

- Optimize stem cell dose and source
- BMT? PBSCT?
- Select good risk patients!
- New conditioning regimens
- Controlled regimen intensity
- Adjusting post transplant IS to minimize GVHD and preserve GVL

Roadblocks to successful outcome

- Transplant
- Marrow recovery
- Biological endpoints
- Biological endpoints
- NK recovery
- Relapse
- G cell recovery
- aGVHD
- cGVHD
- Viral reactivation
- Infection
- GVL
- TRM
- OS
- DFS

Preventing GVHD

Host APC

- Remove APC
- Block APC
- Conditioning
- Bortezomb
- Virus
- Leuk
- mHAG
- MHC1
- MHC2

Donor T cells

- CD8
- CD4
- CD3
- CD28
- Engagement
- Activation
- Proliferation
- Block proliferation
- Prevent T-cell contact
- Tissue repair
- ATG
- Depletion
- Selective T cell depletion
- STSMX
- Drugs
- Steroids
- MTX
- Cyc
- Bortezomb

Host target

- Damage
- Repair
- Steroids
- Stroma
- MSC
- Prevent T-cell contact
- Tissue repair
- MSC
- HLA
- Other

Biological endpoints

- GVL
- cGVHD
- aGVHD
- Viral reactivation
- Infection
- GVL
- TRM
- OS
- DFS

Statistical endpoints

- Relapse
- TRM
- OS
- DFS

Graphs showing no change in relapse after HLA-identical sibling myeloablative transplants for early leukemia:

- 1975-1984 (1,071) 23%
- 1985-1994 (8,589) 22%
- ≥1995 (9,747) 20%
The challenges ahead

A transplant for every patient that needs one?
Expanding the donor pool
Safer transplants for older patients

Is BMT at an evolutionary dead end?

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

Allogeneic Transplants for Age \leq 20yrs, Registered with the CIBMTR 1992-2009 - by Donor Type and Graft Source -

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

**The limits of success today**

- RELAPSE
- GVHD
- INFECTION
- REGIMEN RELATED MORTALITY

**Cell therapy complexity**

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

**The long winding road to successful T cell therapy**

- Improved APC generation
- Improved growth conditions
- Low volume
- GMP grade culture systems
- Multi-virus specific T cells in the clinic
- Tumor specific T cells in the clinic
- Proof of principle
- Target antigen identification
- Incorporating CD4 and CD8 responder

**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
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

Clinical Responses post LMP-CTL

- 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)

Progress in the general application of cell therapy

- CD34 cell products
- Dendritic cells
- MSC
- Gene modified T cells
- Virus-specific T cells
- NK cells
- CAR-trans T cells
- Tumor specific T cells
- T regs
"Black Box" The future for commercial cell therapy?

Apheresis lymphocytes

Add growth factors

Add peptides

Cell product: Virus specific T cells

Controlled sterile environment

2043

Transplants in 30 years time?

Some predictions

PREDICTION: APPROX 5% IMPROVED SURVIVAL / DECADE

(URD myeloablative SCT shown)

PREDICTION: IMPROVED CURE RATES

(HLA-ID Sib SCT for advanced disease shown)

Unpredictables: combinations that work

Surgery radiation chemotherapy

Cell therapy, SCT

New agents
Cytokines
Monoclonals
Small molecules

Unpredictables
Unpredictables: new treatments change indications for HSCT

- another imatinib
- cell therapy without HSCT
- gene therapy

The future evolution of allogeneic SCT

- Combination chemotherapy
- Small molecules
- Early chemotherapy
- High dose chemotherapy and marrow rescue
- Cell therapy
- Cytokines
- New drugs