Haemopoietic Stem Cell Transplantation

Current Status in Paediatric Disorders
HSCT

- Replacement of recipient HSC and derived lineages, by donor HSC
- Unique organ transplant
  - Regenerative tissue
  - both recipient and donor cells may be immune-competent
    - Recipient lymphocytes mediate graft rejection
    - Donor lymphocytes mediate graft-versus-host disease
Definitions

- **Autologous BMT**
  - BM harvested from patient; reinfused

- **Syngeneic BMT**
  - donor genotypically identical to patient (identical twin)

- **Allogeneic BMT**
  - donor not genetically identical to patient
  - sibling/family mismatch/unrelated donor
Stem Cell Sources

- **BM**
  - Allogeneic
  - Autologous

- **PBPC**
  - Allogeneic
  - Autologous PBPC
    - Mobilisation - G-CSF +/- Chemotherapy

- **Cord Blood**
  - Allogeneic
  - Autologous
Conditions treatable with HSC transplant – Malignant Disease

- ALL / NHL
  - CR1, CR2 or greater
- AML / MDS
  - CR1, CR2
- CML
- Ph’+ve
- JMML
Conditions treatable with HSC transplant - Non Malignant

- Multi-lineage BM Failure Syndromes
  - Severe Acquired Aplastic Anaemia
  - Hereditary Aplasia – Fanconi Anaemia

- Single Lineage BM Failure
  - Pure red cell aplasia – Blackfan Diamond Syndrome
  - Amegakaryocytic thrombocytopenia
Conditions treatable with HSC transplant - Non Malignant

- Abnormal Production
  - Red Cells
    - β thalassaemia major, 4 gene α deletion
    - Sickle cell disease
    - Congenital dyserythropoietic anaemia
  - Granulocytes
    - Kostmann Syndrome
  - Osteoclasts (monocyte derived)
    - Malignant Osteopetrosis
Conditions treatable with HSC transplant - Non Malignant

- Immune Deficiency Disorders
  - Severe combined immunodeficiency
  - Absent ‘T’ cells
  - Wiscott Aldrich Syndrome
  - Chronic Granulomatous Disease
Conditions treatable with HSC transplant - Non Malignant

- Inherited Metabolic Disorders
  - Mucopolysaccharidoses
    - Hurlers Syndrome (MPS I)
    - Marateaux Lamy Syndrome (MPS VI)
  - Leukodystrophies
    - Cerebral X-linked Adrenoleukodystrophy
    - Metachromatic leukodystrophy - ‘Late onset’
    - Globoid cell dystrophy
Donor - Recipient Matching

HLA typing – Each person has 2 Haplotypes

HLA Antigens- A, B, C, DR, DQ, DP

Maternal

A
C
B
DR
DQ

Paternal

Chance of matching

= AxBxCxDRxDQ

K. Tiedemann, August 2001
Donor Selection - HLA Inheritance

Children

K. Tiedemann, August 2001
Donor Identification

- Matched Sib (1:4 chance of match)
- MM related donor - extended family search
- Unrelated donor
  - Volunteer BM donor Registries - BMDWW
    - Almost 9x10^6 donors listed
    - BM, PBSC
  - Cord Blood Banks
    - Approx 180,000 CB units banked

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Donor Identification

- Need for HLA matching at all major histocompatibility loci
  - Class I - A (220), B(460), C(110)
  - Class II - DRB1(360), DQB1(48), DPB1(96)
- Newer tissue typing techniques allow for better typing (allelic level) in unrelated donor-recipient pairs
- The higher the resolution of typing, the less the likelihood of finding a ‘fully matched’ unrelated donor
Cord blood

- Readily available source of haematopoietic stem cells
- Usually discarded
- Immunologic immaturity
  - Potentially less GvHD
  - Crossing of HLA barriers
- ?Decreased GvL effect
Cord blood - potential drawbacks

- Fixed volume
  - Limited no. of progenitor cells
  - ? Adequacy of cell dose for larger patients
- Delayed engraftment
- Infection
- Maternal blood contamination
Advantages of CBB vs BMD Registry

- Increased potential donor pool
  - (HLA MM, increased donor willingness)
- Decreased search time
- Lower risk of viral transmission
- Better ethnic mix of phenotypes
- No donor procedure - no risk
- No donor “loss” with time
The Child Donor

- ‘Tissue Act’ of Victoria allows the donation, by a minor, of regenerative tissue to a sibling or parent only.

- Proposed donation of BM or PBSC by a minor to a cousin or other relative requires special authorisation through the family court.
The Child Donor – Ethical Issues

- Donor Consent
- Welfare of the donor
  - Medical
  - Psychological
- Donor Conception
- Donor Selection
  - PGD for HLA identity
    - As part of PGD to exclude genetic disease
    - Independent of genetic disease exclusion
Recipient selection – lethal disease

- Disease status should allow ‘reasonable’ chance of successful outcome, from HST
  - Acute leukaemia/lymphoma – in remission/responsive
  - Metabolic disease – as early as possible
    - Hurlers – as soon as donor identified, PIQ > 80
    - ALD – as soon as evident that cerebral progression is occurring (MRI, Neuropsych evaluation)
    - MLD – Presymptomatic
  - Organ function
    - Infection controlled
    - Cardiac, Respiratory
    - Renal
Recipient selection- Non lethal

- **Issues**
  - Quality of standard medical care available
  - Burden of medical care
  - Quality of life
  - Expected disease consequences
  - Type of donor available
The Transplant

- Conditioning
  - Dependent on diagnosis/ co-existing infection, organ dysfunction
  - Nil
  - Myeloablative
    - Chemotherapy +/- TBI +/- ATG
  - Non myeloablative, Immunosuppressive
    - Fludarabine, ATG + Cy / Melphalan / Low dose TBI
The Transplant

- HSC infusion
  - +/- Manipulation
    - Red cell/plasma depletion,
    - CD34+ selection,
    - T cell depletion

- Support during aplastic phase (18-28D)
  - Blood products,
  - Antibiotics

- Engraftment
Transplantation biology

- Host immunocompetent T-cells mediate Rejection

- Donor immunocompetent T-cells mediate
  - graft versus host disease
  - graft versus leukaemia effect
The Transplant

- GVHD
  - Acute (onset < 90 D post Tx)
  - Chronic (persistence, onset >90 D post Tx)
- Immune reconstitution
- Relapse
- Late Effects
  - Chemotherapy
  - XRT
Veno-occlusive Disease

- Clinical
  - Wt gain, ascites, tender hepatomegaly, jaundice

- Pathology
  - Chemotherapy, XRT, pre-existing liver disease
  - Endothelial damage of intra-hepatic venules, obstruction
  - Reversal portal flow, centrilobular necrosis, increased ALT, Bi

- Therapy
  - Prophylaxis- heparin, PG E1, Ursodiol
  - Supportive, t- PA, liver transplant- high mortality
  - Defibrotide – improved response, non toxic
GVHD - Biology

- Haemopoietic SC transplant is unique in that
  - the tissue transplanted is immunologically competent
  - The recipient is immunosuppressed and immunologically incompetent
- GVHD results when the ‘T’ cells in the graft recognise HLA antigens on recipient cells as ‘non self’ and attempt rejection of the recipient tissues
Graft versus Host Disease
Target Organs

- Skin
- Liver
- Gut
Graft Versus Host Disease

- Acute GVHD
  - Onset between 10 and 60 days post transplant

- Chronic GVHD
  - Ongoing GVHD > 90 days post transplant
  - De novo onset > 90 days post transplant
  - Onset > 90 days post transplant after prior resolution of AGVHD

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AGVHD - Mechanism

- Host tissue damage (Drugs, XRT, Viruses)
  - Cytokine production
    - TNF, IL-1
- Donor Lymphocyte stimulation
  - Host Ag’s
  - Cytokine stimulation
- Cytokine storm
  - IFN gamma, IL-2
AGVHD – Clinical

- Skin
  - Rash varying from patchy and limited to generalised erythroderma and bullous formation

- GIT
  - Diarrhoea, electrolyte and fluid disturbance
  - Vomiting, ilius
  - Abdominal pain
  - Bleeding

- Liver
  - Jaundice, enzyme disturbance
GVHD – Risk Factors

- HLA mismatching
  - Greater the degree of HLA MM the higher the risk of acute and chronic GVHD

- Gender mismatch

- Age
  - Younger patients, lower incidence and severity of both acute (20% <20, 30% 20-50, 70% >50) and chronic GVHD (10-50%)
  - Increased donor age increases risk of GVHD

- Stem cell product
  - CB < BM < PBSC
AGVHD
## AGVHD Overall Grade

<table>
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<tr>
<th>Grade</th>
<th>Skin</th>
<th>GIT</th>
<th>Liver</th>
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<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>+ - ++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+++ - +++</td>
<td>10-15ml/kg/d Persist. nausea</td>
<td>2-3mg/l</td>
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<tr>
<td>3</td>
<td>++++ - +++++</td>
<td>&gt;16ml/kg/d</td>
<td>&gt;3mg/l</td>
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<tr>
<td>4</td>
<td>As for 3, with</td>
<td>decreased</td>
<td>performance</td>
</tr>
</tbody>
</table>
Graft versus Host Disease

Prevention

- Optimal donor – recipient matching
- Cyclosporin, Methotrexate
  - 2 drugs better than 1
- ‘T’ cell depletion of graft
  - Negative ‘T’ depletion
  - Positive CD34+ selection
Graft versus Host Disease

Treatment
- Steroids, Cyclosporin, Tacrolimus
- ATG
- Monoclonal Ab’s
- PUVA, ECP photopheresis
- Thalidomide
AGVHD - management

- **Prophylaxis**
  - T cell depletion, ex vivo or in vitro (ATG)
  - ‘Short’ MTX, Cyclosporin

- **Standard therapy**
  - Optimise CSA / tacrolimus +/- Mycophenolate
  - Steroids 2 mg/Kg

- **Experimental**
  - Infliximab (anti TNF),
  - Gemtuzumab (anti- IL-2)
Chronic GVHD

- Limited
  - Skin involvement only
  - Hepatic involvement only
  - Both

- Extensive
  - All other extent of disease
Chronic GVHD

- Onset > Day 90
- Target Organs
  - Skin (pigment, moisture, elasticity, )
  - Joints (effusion, stiffness, contracture)
  - GIT (malabsorption, stricture)
  - Liver (chronic change to cirrhosis)
  - Conjunctivae (dry, sicca syndrome)
  - Mucosal surfaces – dry, ulcers, lichen planus
  - Bronchial tree (bronchiolitis obliterans)
CGVHD – Clinical Manifestations

- ‘Autoimmune’ like disorder
- Limited CGVHD
  - Skin or liver involvement only or both
- Extensive CGVHD
  - Other organ involvement
Chronic GVHD
Chronic GVHD
Chronic GVHD

- Risk Factors
  - Pre existing AGVHD
  - HSV infection
  - Age donor

- Treatment
  - CSA, Prednisolone, ATG, Azathiaprine
  - Thalidomide
  - PUVA

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CGVHD - Therapy

- CSA, Steroids
- Azathiaprine
- Thalidamide
- Pentostatin
100-DAY MORTALITY AFTER HLA-IDENTICAL SIBLING TRANSPLANTS 1999-2000

MORTALITY, %

- AML
- ALL
- CML
- MDS
- Aplastic Anemia
- Immune Deficiency

Numbers on bars = numbers of patients evaluable
IBMTR 2002
100-DAY MORTALITY AFTER UNRELATED DONOR TRANSPLANTS 1999-2000

Numbers on bars = numbers of patients evaluable
IBMTR 2002

MORTALITY, %

CR1
CR2+
CP
AP
Other
BP
CAUSES OF DEATH AFTER HLA-IDENTICAL SIBLING TRANSPLANTS 1994-1999

% OF DEATHS

Primary Disease
GVHD
IPn
Infection
Organ Failure
Other

IBMTR 2002
CAUSES OF DEATH AFTER UNRELATED DONOR TRANSPLANTS 1994-1999

% OF DEATHS

100
80
60
40
20
0

Primary Disease
GVHD
IPn
Infection
Organ Failure
Other

IBMTR 2002
Greatest impediment to cure remains relapse despite transplantation

Current intensive 1\textsuperscript{st} line treatment, fewer options post relapse

Strategies

- Early CSA dose reduction/cessation post Tx
- MRD studies to identify patients at risk of relapse early. CR1 transplant may result in improved outcome
PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR ALL, AGE ≤20 YEARS
BY DONOR TYPE AND REMISSION STATUS, 1994-1999

PROBABILITY, %

0 1 2 3 4 5 6
YEARS

P = 0.0001

HLA-identical sibling, CR2+ (N = 962)
HLA-identical sibling, CR1 (N = 561)
Unrelated, CR1 (N = 280)
Unrelated, CR2+ (N = 805)

IBMTR 2002
PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR AML BY DONOR TYPE AND REMISSION STATUS, 1994-1999

**Probability, %**

- HLA-identical sibling, CR1 (N = 3,298)
- HLA-identical sibling, CR2+ (N = 837)
- Unrelated, CR2+ (N = 567)
- Unrelated, CR1 (N = 424)

**P = 0.0001**

**Years**

IBMTR 2002
PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR CML IN CHRONIC PHASE BY DONOR TYPE AND DISEASE DURATION, 1994-1999

- HLA-identical sibling, <1y (N = 2,876)
- HLA-identical sibling, ≥1y (N = 1,391)
- Unrelated, <1y (N = 61)
- Unrelated, ≥1y (N = 936)

P = 0.0001

IBMTR 2002
Acquired Severe AA

- Matched sib Tx vs Immunosuppressive therapy (ATG)
  - Msib Tx 86%
  - IS 78%

- Unrelated Donor Tx
  - Poor survival pre 1995 (35%)
    - Graft failure, regimen related toxicity, GVHD
  - Non myeloablative, IS regimen (Flu, ATG, Cy)
    - 65-75% S
PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR SEVERE APLASTIC ANEMIA BY DONOR TYPE AND AGE, 1994-1999

- HLA-identical sibling, ≤20y (N = 844)
- HLA-identical sibling, >20y (N = 845)
- Unrelated, ≤20y (N = 244)
- Unrelated, >20y (N = 114)

P = 0.0001
Fanconi Anaemia

- Marked susceptibility to tissue damage in response to alkylating agents and XRT
  - 80’s-90’s - Conditioning with reduced dose Cy and T-A XRT 5Gy
    - Survival 2yrs approx 70%
    - **BUT** Late oral SCC’s (Baseline increased malignancy risk)
  - Current - Elimination of XRT - replace with Fludarabine, ATG, +/- Cy
    - Small nos but 75% + S
PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR FANCONI ANEMIA BY DONOR TYPE AND AGE, 1994-1999

- **HLA-identical sibling, \( \leq 10\) y (N = 109)**
- **Unrelated, \( \leq 10\) y (N = 36)**
- **HLA-identical sibling, >10 y (N = 100)**
- **Unrelated, >10 y (N = 58)**

\( P = 0.0001 \)
β Thalassaemia Major

Lucarrelli (1990)

- **Class I pts** <17yrs, no hepatomegaly or portal fibrosis
  - S 94%, EFS 90%

- **Class II** <17yrs, hepatomegaly or portal fibrosis
  - S 80% EFS 77%

- **Class III** <17yrs, hepatomegaly and portal fibrosis
  - S 60% EFS 53%

- >16yrs No DFS>100D (Ceased 1986)

- **Modified conditioning, Class III -<17,>16 (1997)**
  - Class III S 97%, EFS 90% : Adult S 70%, EFS 57%

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Sickle Cell Disease

- Indications for HSCT
  - Prior Stroke, Chest syndrome, recurrent painful crises (shift to earlier intervention)

- Transplants
  - Myeloablative 80-85% DFS, 90-95% S
  - Non myeloablative
    - Minimally toxic 20% EFS, 100% S
    - Reduced intensity 57% EFS, 72% S
How can a BMT help in the Storage Disorders?

HSC → rbc → neutrophil → Monocyte

Substrate Breakdown → Enzyme Diffusion → CNS Macrophage

K. Tiedemann, August 2001
HCT for Hurler Syndrome

- Donor-derived monocytes/macrophages produce enzyme and cross-correct recipient cells

- Early* major limitation of HCT:
  - High disease- and regimen-related mortality
  - High frequency of failed donor-derived engraftment

* first 5 to 10 years of HCT experience
HCT for Hurler Syndrome (MPS IH)

High frequency of failed donor-derived engraftment

**HLA-identical donor:** 15%


**Unrelated donor:** 37%

HCT for Hurler Syndrome
Univ. of Minnesota (N=88, >30% High Risk)

- Donor Type: RD: N=31 (35%)  
  URD: N=57 (65%)
- Median follow-up: 5.6y (0.2-17.7y)
- HCT’s performed: 9/83 – 9/2002
- Overall survival: 59%  
  (RD=67%, URD=54%)
- Overall engraftment 53%  
  (RD=68%, URD=47%)

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Hurler Syndrome: Lessons Learned

- Ongoing efforts to optimize engraftment while minimizing toxicity
- Investigate use of various stem cell sources
- Orthopedic surgeries required in the first 2 to 5 years after transplant to optimize outcomes and QOL
- Intensive PT/OT/Speech Therapy are critical to optimizing post-HCT outcomes
X-ALD: Phenotypes and Estimated Relative Frequencies

- Childhood onset cerebral (CALD): 31-35%
- Juvenile onset cerebral: 4-7%
- Adult onset cerebral: 2-5%
- Adrenomyeloneuropathy (AMN): 40-46%
- AMN + cerebral disease: ~40% of AMN
- Adrenal insufficiency alone: varies w/ age

HCT for X-ALD

HCT rationale:

- Biochemical defect expressed in WBC
- Brain microglia are monocyte-derived
- Cerebral disease characterized by an inflammatory process with accumulation of macrophages
Long-term beneficial effect of HCT for CALD

- 12 engrafted pts evaluated by MRI, neurological, neuropsych, electro-physiological, and VLCFA
  - MRI--reversal/improved/no change: 4
  - MRI--dysmyelination then stability: 8
  - Motor--NL or improved: 10
  - VIQ--NL: 11
  - PIQ--improved/stable: 7
  - PIQ--decline then stable: 5

Shapiro EG et al. Lancet 2000;356:713
University of MN - Experience with HCT in ALD (N=51)

23 had mild/moderate disease with PIQ>80 (Loes score 0.5 -14)
- 15 are alive (65%)
- Most function independently; none are blind
- 7 died from HCT complications; only 1 from ALD

28 had severe disease with PIQ ≤ 80 (Loes score 5-20)
- 12 are alive (43%) 3 are recent transplants
- All are very low functioning; 5 of 12 are blind
- Most died from disease; HCT may accelerate disease progression
MLD Clinical Presentations

- Late infantile: death after a few years of rapid and sustained neurologic degeneration during infancy and early childhood

- Juvenile: begins after ~5 years of age with minimal neurologic deficits followed by major cognitive deficits
MLD Clinical Presentations

- Adult: can begin during early to late teenage years and presents as severe neuropsychological deficits

- Severe neurological and cognitive deficits lead to demise over a longer period of time in juvenile and adult forms vs. late infantile form
MLD HCT: Summary

HCT arrests the course of the central dysmyelinating process in patients with MLD treated early.

- HCT does not influence the course of the dysmyelinating peripheral neuropathy.
- Alternative stem cells may provide effective enzyme activity peripherally as well as centrally.
MLD HCT: Conclusions

Late onset-MLD: cognitive function has typically declined during the first 1 to 2 years after HCT but remained stable as long as 9 y post-HCT
# Immunodeficiency – 3yr Survival

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Msib</th>
<th>MMR</th>
<th>UD</th>
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<tr>
<td><strong>European Data (1968-‘99)</strong></td>
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<tr>
<td>SCID</td>
<td>77%</td>
<td>54%</td>
<td>62%</td>
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<tr>
<td>Non SCID</td>
<td>71%</td>
<td>42%</td>
<td>59%</td>
</tr>
<tr>
<td>WAS</td>
<td>81%</td>
<td>41%</td>
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<tr>
<td><strong>Duke University(1982-’98)</strong></td>
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<tr>
<td>SCID</td>
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### Late Effects of BMT

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<th>Chemotherapy</th>
<th>TBI</th>
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<tr>
<td>Growth</td>
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<td>+</td>
</tr>
<tr>
<td>Cataracts</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Infertility</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↓ Sex hormone secretion</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>↓ Thyroid hormone</td>
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</tr>
<tr>
<td>↓ Cognitive Function</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>(Age / Underlying Disease Dependent)</td>
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</tr>
<tr>
<td>↑ Risk of malignancy</td>
<td>+</td>
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K. Tinday, Aug 4, 2001
Summary

- HSCT offers a chance of cure to many
- There is a price to pay
- Risks versus benefits must be weighed
- Quality of life may decrease post Tx
  - GVHD, BO
- QOL may increase markedly
  - ie Hurlers Syndrome