Paediatric Haemopoietic Progenitor/Stem Cell Transplantation

Karin Tiedemann 2010
Definitions

- **Autologous HPC Transplant**
  - HPC harvested from patient; cryopreserved, reinfused after high dose chemo/irradiation

- **Syngeneic HPC Transplant**
  - donor genotypically identical to patient (identical twin)

- **Allogeneic HPC Transplant**
  - donor not genetically identical to patient
  - matched sibling/family mismatch/unrelated donor
Transplant activity worldwide
1980-2009

[Graph showing the increase in transplant activity worldwide from 1980 to 2009, with two lines representing autologous and allogeneic transplants.]
Allogeneic Haemopoietic Stem Cell Transplantation

- Replacement of recipient haemopoietic progenitor cells (HPC) by donor HPC
- Unique organ transplant
  - Donor tissue is regenerative
  - Both recipient and donor cells may be immune-competent
    - Recipient lymphocytes mediate graft rejection
    - Donor lymphocytes mediate graft-versus-host disease (GVHD) and graft vs leukaemia effect
Haemopoietic Progenitor Cell Sources

- BM
- PB (Mobilised with G-CSF+/- chemo)
- Cord Blood

All may be either

- Autologous
- Allogeneic
  - Related
  - Unrelated
HPC Procurement

- BM Harvest
  - GA
  - Multiple BM aspirates from iliac spines/crests

- PBSC
  - G-CSF Mobilisation
    - Bone pain
    - Splenomegaly
    - Higher yield of CD34+ cells, multiple returns possible in Auto setting
  - Insertion of large gauge cannulae (high flow rates)
    - peripheral in adults
    - CVC, GA in paeds
Leukapheresis
HPC Procurement

- **Cord Blood**
  - N vaginal delivery/ Caesarian section
  - Cord clamped
  - Cord cleansed
  - Umbilical vein cannulated
  - Gravity flow into blood collection bag/CPD
  - Transport to processing laboratory
  - Quality control
    - TNC, TLC, CD34+ cells, virology
    - Tissue Typing
  - Volume/red cell reduction
  - Addition of cryoprotectant – DMSO
  - Rate controlled freeze to -196°C
  - Storage in N₂ vapour phase
  - Registry Listing
Donor – Recipient Matching

- HLA (Human Leukocyte Antigen) System
  - Controlled by genes located on short arm Ch 6
  - HLA loci are part of the genetic region known as the Major Histocompatibility Complex (MHC)
  - MHC molecules control immune response – recognition of self and non self
  - Genes code for **antigens** expressed on cell surfaces (Serology)
  - Each gene is highly polymorphic (**allelic differences**) DNA sequencing
  - Ethnic differences in antigen and allele frequencies ie B 44:04
  - Each parent contributes a haplotype of 3 **Class I** (A, B, C) antigens and 3 **Class II** (DR, DQ, DP) antigens
  - Close matching between recipient and HPC donor is important for transplant outcome
  - Permissive mismatching when CB is donor source

6/01/2011
Donor – Recipient Matching

- HLA system
  - Each individual will have 2 antigens/alleles at each locus (A, B, C, DR, DQ, DP).

Maternal Haplotype:
- A1
- C3
- B4401
- DR4
- DQ3
- DP1

Paternal Haplotype:
- A2
- C8
- B4403
- DR3
- DQ7
- DP2
Donor Selection - HLA Inheritance

Maternal Haplotypes

AB
AC
AD

Paternal Haplotypes

CD
BC
BD

Children
Donor Identification

- Matched Sib (1:4 chance of match) **Best donor!**
- MM related donor - extended family search
  - Search side of family with unusual haplotype/unique antigen
  - Check for consanguinity and sibs partnering sibs
- Unrelated donor
  - Volunteer BM donor Registries - BMDWW
    - Greater $14 \times 10^6$ BM/PBSC donors listed
  - Cord Blood Banks
    - Approx 435,000 CB units banked
HLA-A, -B & -DR Serologically Matched Pairs
number of allele mismatches HLA-A, -B, -C & -DR

0 mismatched loci (n = 791)
1 mismatched locus (n = 394)
2 mismatched loci (n = 172)
3+ mismatched loci (n = 65)

P-value < 0.0001
Allo BM vs PBSC

- PBSC lead to more rapid engraftment
  - N > 0.5x10^9/L 2-3 days earlier
  - Platelet independence (>20x10^9/L) D15 vs D20
- Incidence of AGVHD higher for PBSC
- Incidence of CGVHD higher for PBSC
- Increased GVL effect for PBSC (May be useful in advanced leukaemia)
- Concern re use G-CSF in healthy donors / Children- ? Risk of induction leukaemia
**CB vs UDBM**

- Readily available source of HPC, otherwise discarded
- No donor procedure
- Better ethnic mix of HLA types

- More rapidly available (stored in liquid/vapour $N_2$)
  - Important in rapidly progressive diseases – Relapsed ALL

- Immunologic immaturity
  - Crossing of HLA barriers, > chance of finding donor
  - Less GvHD (Advantage in non malignant disease)

- No decrease in GvL effect
Cord blood - Disadvantages

- Fixed volume
  - Limited no. of progenitor cells
  - ? Adequacy of cell dose for larger patients

- Delayed engraftment

- Delayed Immune reconstitution

- Infection (viral reactivation in recipient)

- Potential genetic disease transmission
Changing donor source

<table>
<thead>
<tr>
<th></th>
<th>'85-89</th>
<th>'90-94</th>
<th>'95-00</th>
<th>'01-04</th>
<th>'05-09</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSib</td>
<td>21</td>
<td>38</td>
<td>38</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SibCB</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MMR</td>
<td>5</td>
<td>12</td>
<td>16</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>UDBM</td>
<td>0</td>
<td>1</td>
<td>35</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>UDCB</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>27</td>
<td>49</td>
</tr>
</tbody>
</table>
Conditions treatable with HSCT
Conditions Treatable by HPC Transplant - Non Malignant

- Immune Deficiencies
- Bone Marrow Failure Syndromes
  - Single lineage
    - Pure rbc aplasia, CAMT, Kostman Syndrome
  - Trilineage (SAA, FA)
- Genetic defects of Hb production
  - Thalassaemias
  - Haemoglobinopathies
  - Congenital Dyserythropoietic Anaemias
- Inherited Metabolic Disorders
Immune Deficiency Disorders

- SCID/CID (T and B cell deficiencies)
- Non SCID PID
  - Wiscott Aldrich Syndrome
  - Di George Syndrome
  - Ataxia Telangiectasia
- Disorders of immune dysregulation
  - Familial HLH
  - XLP
- Defects of phagocyte number/function
  - Chronic Granulomatous Disease
  - Severe Congenital NPA
  - LAD-1
‘Other’ Genetic Disorders affecting haemopoietic lineages

- Abnormal Cellular Production/ Function
  - Red Cells
    - $\beta$ thalassaemia major,
    - $\alpha$ thalassaemia (1-4 gene deletion/ mutation)
    - Sickle cell disease
    - Congenital dyserythropoietic anaemia
  - Osteoclasts (monocyte derived)
    - Malignant Osteopetrosis
Genetic Disorders

- Inherited Metabolic Disorders (Enzyme deficiencies)
  - Mucopolysaccharidoses
    - Hurlers Syndrome (MPS I)
    - Marateaux Lamy Syndrome (MPS VI)
  - Leukodystrophies
    - Cerebral X-linked Adrenoleukodystrophy
    - Metachromatic leukodystrophy - ‘Juvenile onset’
    - Globoid cell dystrophy
Malignant Conditions Treatable by HSC Transplant

- ALL/NHL
  - VHR, CR1
  - CR2
- AML/MDS
  - MDS, untreated
  - HR, CR1
  - CR2
- Ph+ CML
- JMML
# Transplant Indications RCH

**Time period**

1985-2009

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL/NHL</td>
<td>152</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>82</td>
</tr>
<tr>
<td>CML</td>
<td>10</td>
</tr>
<tr>
<td>JMML</td>
<td>12</td>
</tr>
<tr>
<td>SAA/FA</td>
<td>29/8</td>
</tr>
<tr>
<td>SCID</td>
<td>27</td>
</tr>
<tr>
<td>Non SCID ID</td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
</tr>
</tbody>
</table>

**Malignancy**

69%
Recipient Evaluation

- Issues
  - Expected disease consequences
  - Quality of standard medical care available
  - Burden of medical care
  - Quality of life
  - Chemosensitivity of Malignant disease
  - Type of donor available

- Risk Assessment
  - Disease vs potential TRM
Recipient selection

- Disease status should allow ‘reasonable’ chance of successful outcome from HPCT
  - Acute leukaemia/lymphoma – in remission/responsive
  - Organ function normal/ minimally abnormal
    - Respiratory
    - Cardiac
    - Renal
    - Neurological
  - Infection Controlled
    - Bacterial
    - Fungal
    - Mycobacteria
    - Viral
Pre Transplant Conditioning

Aims

- Disease eradication
  - Malignancy
- Immunosuppression/ Engraftment
  - Malignancy
  - Non Malignant disorders
- Conditioning Regimens
  - Nil (SCID)
  - Myeloablative
    - **Chemotherapy** +/- TBI +/- ATG
  - Non myeloablative, Immunosuppressive, reduced Intensity
    - **Fludarabine, ATG + Cy / Melphalan / Bu/ Low dose TBI**
The Transplant

- HSC infusion (IV via CVC)
  - Cryopreserved (CB)
    - Thaw +/- Wash
  - Fresh Product (BM/PBSC)
  - +/- Manipulation
    - Volume reduction
    - Red cell depletion (Major ABO MM)
    - plasma depletion (Minor ABO MM)
    - CD34+ selection (T/B cell depletion)
    - T cell depletion
The Transplant Course

Transfusion Support
- WCC
- Antibiotics
- VOD

Platelets
- AGVHD

BM infusion
- Chemo

Days post transplant:
- 7
- 14
- 21
- 28
- 35

GVHD Prophylaxis
Post Transplant Care

- Acute chemo-radiation toxicity
  - Marrow Aplasia (18-28D)
  - Mucositis
    - Oral, oesophageal, lower GI
  - Diarrhoea
  - Skin toxicity
    - TBI, Etoposide, Thiotepa

- Supportive Care
  - Blood products (Think of both recipient and donor ABO, Rh groups)
    - May be Major/Minor ABO MM
  - Antibiotics, antifungals
  - Nutritional support

- Engraftment
  - Neutrophils > 0.5x10^9/l
  - Platelets >20x10^9/l sustained >7D post platelet transfusion
Hepatic Veno-occlusive Disease

- ‘Sinusoidal Obstruction Syndrome’
- Onset usually < 21 Days post BMT
- Diagnostic Criteria (Baltimore/Modified Seattle)
  - Obstructive Jaundice,
  - Wt gain (2-5%),
  - Tender hepatomegaly
  - Ascites,
- Risk factors
  - Allogeneic BMT > autologous
  - Prior liver disease
  - Prior Myelotarg
  - Chemotherapy (Cy, Bu, Melphalan)
  - TBI
Pathology of VOD

- Injury to endothelial cells of sinusoids
- Extravasation of rbc into subendothelial space
- Oedema and thickening of wall of central venules
- Narrowing of venular lumen
- Increased resistance to blood flow from portal system to hepatic vein
- Hepatic congestion
- Hepatocyte injury and death
- Thrombus rarely observed in venules or sinusoids.
Histopathology of VOD
Disease Severity

- Mild
  - No therapy required, recovery
  - D 100 mortality 9%

- Moderate
  - Therapy required, recovery
  - D 100 mortality 23%

- Severe
  - Persistent VOD at D100, death from VOD
  - Mortality 98%

- Predictors of severity
  - Maximum Bilirubin < 155mmol/l 5% mort, >255mmol/l, mort 81%
  - Encephalopathy -100% mortality
  - Haemodialysis -14% survival
Prophylaxis against VOD

- Ursodeoxycholic Acid
  - possible benefit on overall hepatic toxicity

- PGE1
  - vasodilator, cytoprotective effect on endothelium – toxic, no benefit

- ATIII
  - no reduction in incidence of VOD

- Low dose continuous infusion Heparin
  - Benefit not proven but single R study showed benefit. Low incidence toxicity

- Defibrotide (Novel polydeoxribonucleotide -, no intrinsic anticoagulant activity)
  - Marked reduction in incidence/severity of VOD in small, non randomised studies.
  - R study now confirmed risk reduction by 40% when used prophylactically
Treatment of VOD

- Supportive care
  - Fluid restriction, diuretics, platelets
  - Correction of coagulopathy

- Specific therapy
  - Defibrotide – 42% survival in severe VOD
  - Recombinant tPA – ‘unacceptable’ incidence of bleeding problems but up to 45% response in severe VOD
  - Liver transplant
GVHD

- **Target Organs**
  - Skin
  - GIT
  - Liver

- **Onset**
  - AGVHD D12-D100
  - CGVHD >D100
GVHD – Risk Factors

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

- **Gender of donor**
  - Female donor, male recipient
  - Female (previous preg) to female recipient

- **Age**
  - Younger patients, lower incidence and severity of both acute and chronic GVHD

- **Stem cell product**
  - CB < BM < PBSC
  - T cell dose
AGVHD - Mechanism

- **Host tissue damage** (Drugs, XRT, Viruses)
  - Antigen exposure
  - Cytokine production
    - TNFα, IL-1
- **Donor Lymphocyte stimulation**
  - Host Ag’s
  - Cytokine stimulation
- **Cytokine storm**
  - IFN gamma, IL-2
AGVHD - Onset D12-100

- Skin
  - Rash - patchy and limited, to generalised erythroderma with bullae formation, desquamation

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

- Liver
  - Jaundice, enzyme disturbance
## AGVHD Overall Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>GIT</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>M-P rash involving up to 50% body</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>&gt;25% MP rash (+++) generalised erythroderma (+++)</td>
<td>10-15ml/kg/d Persist. nausea</td>
<td>Bi 34 -53umol/l</td>
</tr>
<tr>
<td>3</td>
<td>++ - ++++ (bullous formation)</td>
<td>&gt;16ml/kg/d Abdo pain/ileus</td>
<td>&gt;53umol/l</td>
</tr>
<tr>
<td>4</td>
<td>As for 3, with</td>
<td>decreased</td>
<td>performance</td>
</tr>
</tbody>
</table>
Acute Graft versus Host Disease

- **Prophylaxis**
  - CSA/MTX
  - T-Cell Depletion
    - CD34 Selection
    - In vitro T depletion - Anti CD3 Ab
    - In vivo T depletion - Campath

- **Treatment**
  - Steroids, Cyclosporin, Tacrolimus, MMF
  - ATG
  - Monoclonal Ab’s
  - Extra corporeal photopheresis
Acute GVHD
100-day mortality after HLA-identical sibling transplantation 2007-2008

- Early Disease: 60%
- Intermediate Disease: 20%
- Advanced Disease: 20%
- Chronic Phase: 0%
- Accelerated Phase: 40%
- Blast Phase: 20%
- Other: 20%
100-day mortality after unrelated donor transplantation 2007-2008

- Early Disease: 60%
- Intermediate Disease: 40%
- Advance Disease: 20%
- Chronic Phase: 20%
- Accelerated Phase: 0%
- Blast Phase: 0%
- Other: 0%

Diseases:
- AML
- CML
- MDS/MPS
- ALL
- Aplastic Anemia
- Immune Deficiency
Causes of death after transplantations done in 2003-2008

HLA-identical sibling

- Primary Disease (43%)
- GVHD (10%)
- Infection (14%)
- Other (22%)
- Organ Failure (8%)

Unrelated donor

- Primary Disease (35%)
- GVHD (12%)
- Infection (17%)
- Other Cause (19%)
- Other (22%)
- Organ Failure (12%)

Autologous

- Primary Disease (73%)
- IPn* (1%)
- Infection (5%)
- Organ Failure (4%)
- Other Cause (17%)

*IPn = Idiopathic pneumonia syndrome
Chronic GVHD

- Risk Factors
  - HLA MM
  - Pre-existing AGVHD
  - HSV, VZV infection
  - Age of donor: Adult > Child
  - Donor Source: PBSC>BMD>CDB
CGVHD – Clinical Manifestations

‘Autoimmune’ like disorder

- Limited CGVHD
  - Skin or liver involvement only, or both
- Extensive CGVHD
  - Other organ involvement
Chronic GVHD

- Onset > Day 100
- 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)
Chronic GVHD
Chronic GVHD
Chronic CGVHD

- Treatment
  - CSA, Tacrolimus, Prednisolone, ATG, Azathiaprine
  - Thalidomide
  - PUVA
  - ECP
Immune reconstitution

- Donor type
  - Msib PBSC/ BM > MUD> UDCB
- Graft Manipulation
  - T cell replete > T cell depleted
- CGVHD
  - Immunosuppressive therapy
Important milestones

- Cessation of GVHD prophylaxis
  - Decreased immunosuppression
    - Decreased risk of relapse
    - Increased risk of CGVHD

- Early as Possible for Malignant Disease (1-6 months post Tx)
  - M sib donor, earlier than matched UD, earlier than MMUD
  - Young children earlier than older patients (increased risk CGVHD)
  - Delay if severe AGVHD

- Later for patients with non malignant disease
  - no benefit from CGVHD
  - no GVL effect
  - risk of graft rejection

- Return to school (4-12M post Tx)
Post Tx Re-immunisation

- Full re-immunisation required
- Inactivated vaccines 6-12M post transplant, timing dependent on B cell recovery
  - Prevenar, Fluvax from 6 months
  - DPT, inactivated polio, Haemophilus influenzae, HBvax, meningococcal vaccine from 12months
- Annual Influenza vaccine
- Live vaccines
  - Off all immunosuppression
  - Recovering cellular immunity
  - Generally not before 2 yrs post Tx
Relapse Risk post BMT

- Diagnosis
- Stage of disease at time of transplant
  - CR1, CR2, MRD, Relapse
- Graft source
- T cell depletion
- Type/duration of post graft immunosuppression
Survival

- Disease
  - Malignant
  - Non Malignant
- Donor source
- Age
- Stage of disease at time of transplant
Probability of survival after allogeneic transplant for severe aplastic anemia, by donor type and age, 1998-2008
One-year survival after myeloablative conditioning for acute leukemias in any remission phase, CML or MDS, age <50 years, by year of transplant and graft source, 1988-2008
Probability of survival after HLA-matched sibling donor transplant for ALL, age <20 years, by disease status, 1998-2008

Early (N=915)
Intermediate (N=1,313)
Advanced (N=243)

P < 0.0001

Years
Probability of Survival, %
Probability of survival after unrelated donor transplant for ALL, age <20 years, by disease status, 1998-2008

P < 0.0001

CIBMTR
Probability of survival after HLA-matched sibling donor transplant for AML, age <20 years, by disease status, 1998-2008
Inherited Immune Syndromes
Survival of Pediatric (Age < 18 Years) Marrow Recipients with All Preparative Regimens, by Disease 1998–2006

- WAS (n = 48)
- SCID (n = 35)

Years After Transplant
Survival
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
0 1 2 3 4 5

NATIONAL MARROW DONOR PROGRAM®
Inherited Metabolic Disorders
Survival of Pediatric (Age < 18 Years) Marrow Recipients with Myeloablative Preparative Regimens, by Disease 1998–2006

NATIONAL MARROW DONOR PROGRAM®
# Late Effects of BMT

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>+/-</td>
<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>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>↓ Cognitive Function</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>(Age / Underlying Disease Dependent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Risk of malignancy</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Summary

- HSCT offers a chance of cure to many
- Risks versus benefits must be weighed
- Long term surveillance for late effects of therapy
- Quality of life may be compromised post Tx
  - GVHD, BO
- Survival & QOL may increase markedly
  - ie ALL, Hurlers Syndrome, SAA