From Clinical Practice to Data Management: An Introduction to HSCT and the MED-A form

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EBMT defines Haematopoietic Stem Cell Transplant (HSCT) as “transfer of stem cells, defined as progenitor cells with repopulating capacity and the potential to sustain long term haematopoiesis, within one person or from one person to another, in a dose that is sufficient to restitute haematopoiesis in all lineages”

…. to repopulate the bone marrow with infused stem cells that will produce new blood
Introduction

- HSCT is an established treatment modality for various malignant and non-malignant conditions

- Since the first human bone marrow transplant in 1959 there have been major landmarks and pioneering work so many patients today can survive lethal diseases.

- Improvements in outcome are due to:
  - Better understanding of the transplant process
  - Improved tissue typing methods
  - Formation of bone marrow registries
  - Improved conditioning regimens
  - Improved supportive care
HSCT Process

1. Decision to Transplant
2. Finding stem cells
3. Transplant procedure
4. After HSCT
Decision to Transplant?
Indications for Autologous HSCT

- Multiple Myeloma
- Non-Hodgkins Lymphoma
  - DLBCL
  - Follicular Lymphoma
  - Mantle Cell Lymphoma
- Hodgkins disease
- Waldenstroms Macroglobulinanemia
- AML
- Germ cell tumours – ovarian, testicular
- Autoimmune disorders – i.e. Crohn’s disease, Multiple Sclerosis
- Ewings sarcoma
- Neuroblastoma
- Myelofibrosis
Indications for Allogeneic HSCT

- AML
- ALL
- CML
- CLL
- Multiple Myeloma
- Hodgkins disease
- Non-hodgkins lymphoma
- Aplastic anaemia
- Myelodysplastic syndromes
- Myelofibrosis
Pre-Transplant Evaluation

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET / CT scans; Bone marrow aspirate / trephine</td>
<td>To assess disease status</td>
</tr>
<tr>
<td>Echocardiogram or MUGA scan</td>
<td>To assess cardiac function</td>
</tr>
<tr>
<td>Lung function tests</td>
<td>To assess pulmonary function</td>
</tr>
<tr>
<td>Blood tests: FBC, ABO, U&amp;Es, clotting screen, syphilis, Viral screen – CMV, VZV, HIV, Hep B, HTLV 1&amp; 2 etc..</td>
<td>To assess suitability for HSCT</td>
</tr>
<tr>
<td>Karnofsky score</td>
<td>To assess suitability for HSCT</td>
</tr>
</tbody>
</table>
Finding Stem Cells
What are Stem Cells?

- Multipotential hematopoietic stem cell (Hemocytoblast)
  - Common myeloid progenitor
    - Erythrocyte
    - Mast cell
    - Myeloblast
      - Megakaryocyte
        - Thrombocytes
      - Basophil
      - Neutrophil
      - Eosinophil
      - Monocyte
      - Plasma cell
      - Macrophage
  - Common lymphoid progenitor
    - Small lymphocyte
      - B lymphocyte
      - T lymphocyte
    - Natural killer cell (Large granular lymphocyte)
Sources of Stem Cells

Bone Marrow

Peripheral Blood

Cord Blood
Sources of Stem Cells

- Autologous – from the patient

- Allogeneic – from another person
  - Unrelated donor – found using a donor registry
  - Sibling donor – HLA matched brother or sister
  - Syngeneic – from an identical twin
  - Haploidentical – half-matched family member

- The choice of graft is dependent on disease type, the availability of a donor and the patient’s condition.
Many factors play a role in how the immune system knows the difference between self and non-self, but the most important for transplant is the human leukocyte antigen (HLA) system. Human leukocyte antigens are proteins found on the surface of most cells. They make up a person’s tissue type, which is different from a person’s blood type.

There are six loci on chromosome 6, where the genes that produce HLA antigens are inherited: HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP.

We inherit one of each of these pairs from each of our parents (and pass one of each pair on to each of our children). Ideally, these antigens should be fully matched when selecting a allogeneic donor.
HLA matches and Tissue Types

Mother

Father

Patient
Sibling 1
Sibling 2
Sibling 3
Sibling 4

HLA matched
Main consideration - Donor preference & age  
Patients disease i.e. preferable to use bone marrow for aplastic anaemia

<table>
<thead>
<tr>
<th><strong>Bone Marrow Donation</strong></th>
<th><strong>Peripheral Blood Donation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages:</strong></td>
<td><strong>Advantages:</strong></td>
</tr>
<tr>
<td>No G-CSF injections</td>
<td>No general anaesthetic</td>
</tr>
<tr>
<td><strong>Disadvantages:</strong></td>
<td><strong>Disadvantages:</strong></td>
</tr>
</tbody>
</table>
| Requires general anaesthetic Side effects:  
• Side effects of anaesthesia  
• Pain, infections or bleeding at harvest site | G-CSF injections required Side effects:  
• Headaches, bone or joint pains  
• Citrate toxicity  
• Electrolyte imbalances |
| 1-2 nights in hospital | Outpatient procedure takes 4-5 hours |
Bone marrow donation is a surgical procedure done under general or regional anaesthesia in the hospital. While a donor receives anaesthetic, doctors make several small incisions through the skin over the back of the pelvic bones to draw out the marrow.
Collection of Stem Cells
Peripheral Blood

PBSC donation is a non-surgical procedure done in an outpatient clinic. The donor receives daily injections of G-CSF for five days prior to the harvest. This injection increases the number of stem cells in the bloodstream. The stem cell are then collected by a process called apheresis which takes 4 – 5 hours. During apheresis a donor's blood is removed through a needle in one arm and passed through a machine that separates out the blood-forming cells. The remaining blood is returned to the donor through the other arm.
Transplant Procedure
Conditioning Therapy

• The first stage of the transplant. May be given in one dose or over several days.

• Necessary for:
  - Suppressing the patients immune system to lessen the chance of graft rejection
  - Destroying remaining cancer cells
  - Creating room in the bone marrow for the transplanted stem cells

• Conditioning regimen is dependent on the type of disease, the type of transplant, co-morbidities and age.
Low Intensity

- Less regimen related toxicity
- Rely on later graft versus disease effect

High Intensity

- Increase in regimen related toxicities
- Increased level of disease control

Conditioning Regimen Intensity

*Flu / Cy*  
BEAM  
*Cy / TBI*
Conditioning Regimens

• Myeloablative conditioning
  ➢ Irreversibly destroys the haemopoietic function of the bone marrow with high doses of chemotherapy +/- TBI.
  ➢ Higher level of disease control
  ➢ Younger patients with a good performance status
  ➢ Quicker engraftment of donor cells
  ➢ Higher toxicities associated with higher transplant related mortality

• Reduced intensity conditioning
  ➢ Regimens that have been developed to reduce the morbidity and mortality of allogeneic transplant. It aims to use enough immunosuppression to allow donor cells to engraft without completely eradicating the recipients bone marrow.
  ➢ Can be given to older patients
  ➢ Less regimen related toxicities
  ➢ Reduction in morbidity and transplant related mortality
At least 24 hour after the conditioning will be given on Day 0. These are generally given through a central line and takes approximately 30 minutes. Stem cells are either cryopreserved or fresh.

- **Cryopreserved**
  - Usually for autologous transplants
  - Most common side effects are reactions to DMSO

- **Fresh**
  - Usually for allogeneic transplants
  - Administered much like a blood transfusion
  - Generally better tolerated than frozen cells.
Complications of Stem Cell Re-infusions

• Immediate Immunologic complications
  ➢ Acute Haemolytic Reaction
  ➢ Allergic / anaphylactic reactions
  ➢ Transfusion-related acute lung injury

• Delayed Immunologic complications
  ➢ Delayed haemolytic reactions

• Non-immunologic complications
  ➢ DMSO Toxicity
  ➢ Septic infusion reaction
  ➢ Fat emboli
  ➢ Bleeding due to excessive anticoagulation
  ➢ Circulatory overload
  ➢ Hypothermia
  ➢ Non-immunologic haemolysis

• Other issues
  ➢ Rupture of cellular therapy product bag.
### Early Complications of HSCT

<table>
<thead>
<tr>
<th>Early Complications</th>
<th>Acute GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections:</strong></td>
<td></td>
</tr>
<tr>
<td>✓ Major cause of morbidity and mortality</td>
<td>Haemorrhagic cystitis</td>
</tr>
<tr>
<td>✓ Bacterial</td>
<td>Hepatic veno-occlusive disease</td>
</tr>
<tr>
<td>✓ Viral</td>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>✓ Fungal</td>
<td>Diffuse alveolar haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Idiopathic pneumonia syndrome</td>
</tr>
<tr>
<td></td>
<td>Multi-organ dysfunction syndrome</td>
</tr>
</tbody>
</table>
Graft versus Host Disease

- **Acute**
  - Usually occurs before D100
  - Organs affected – skin, gut, liver

- **Chronic**
  - Usually develops after D100
  - Can involve skin, gut, liver, eyes, lungs, connective tissues
  - More prone to opportunistic infections
  - Quality of Life

- **Risk Factors**
  - Prior history of Acute GvHD
  - Unrelated donor
  - Mismatched transplants
  - Male recipients of female donors
  - Older age of recipient or donor
Graft versus Host Disease

• Prevention
  - HLA matching
  - Reduced intensity conditioning regimens
  - Drugs – Ciclosporin, Methotrexate, Mycophenolate mofetil
  - T-cell depletion (i.e. Campath)

• Treatment
  - Steroids with ciclosporin
  - ATG
  - Extracorporeal photopheresis (ECP)
After HSCT
Neutrophil engraftment occurs when neutrophils ≥ $0.5 \times 10^9$

Platelet engraftment occurs when platelets ≥ $20 \times 10^9$

Phases of Immune Recovery

- **Neutropenic Phase**
  - From conditioning to engraftment

- **Intermediate phase**
  - Neutrophil engraftment until D100

- **Late phase**
  - D100 +
Infections

(Tomblyn, Blood Marrow Transplant. 2009; 15(10):1143-1238)
Infection Prophylaxis

- Encapsulated bacteria
- Viruses
- PCP
- Fungal

- Infection prophylaxis will vary from centre to centre, but in general:
  - Until neutrophil recovery
  - Until the patient is off immunosuppressive therapy
  - Until the patient does not have GvHD

- Patients will require a vaccination schedule after transplant
Management of Patients until D100

- Risk of Infection
- Risk of Thrombocytopenia and Bleeding
- Nutrition
- Fatigue
- Graft versus host disease
- Routine investigations – Blood Tests, CMV monitoring, monitoring of immunosuppressive medication levels, disease assessment
### Late Effects

<table>
<thead>
<tr>
<th>Late Effects</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic GvHD</td>
<td>Back to work issues</td>
</tr>
<tr>
<td>Late infection and immune defects</td>
<td>Secondary MDS / leukaemia / malignancy</td>
</tr>
<tr>
<td>Pulmonary late effects including restrictive lung diseases and COPD</td>
<td>Late graft failure</td>
</tr>
<tr>
<td>Late liver complications (i.e. Hepatitis B,C and iron overload)</td>
<td>Relapsed disease</td>
</tr>
<tr>
<td>Late ocular effects including cataracts</td>
<td>Infertility / sexual dysfunction</td>
</tr>
<tr>
<td>QoL and neuropsychological functioning including intellectual and / or concentration issues</td>
<td>Endocrine abnormalities e.g. hypothyroidism</td>
</tr>
<tr>
<td>Emotional issues</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Dental late effects</td>
</tr>
</tbody>
</table>
Patient Outcomes

- Disease status after HSCT – best response and at last contact?
- First relapse or progression?
- Patient outcome?
  - D100 TRM
  - 1, 2 and 5 year TRM
  - Most transplant related deaths occur within the first year of transplant
- TRM is likely to increase with
  - Allogeneic transplant
  - Advanced disease status at time of transplant
  - Type of donor
  - Intensity of conditioning regimen
  - Patient age
The MED-A form
Introduction

• **Minimum Essential Data**

• Completion of the MED-A form is a requirement for all EBMT members.

• **JACIE requirement**
  
  - B 9.1 - The clinical programme shall collect all the data necessary to complete the Transplant Essential Data forms of the CIBMTR or the Minimum Essential data-A forms of the EBMT

• First report should be submitted as soon as possible after D100

• Follow up report should be submitted annually

• Patient must give consent for data submission
Which forms should be completed?

- The first report consists of a common set of data that allows registration of the patient, the summary of the procedures and the status at 100 days, and a series of disease specific forms one of which must always accompany the submission (HSCT).

- After the patient has died if this occurs any time after the patient has started conditioning
MED-A: First report – 100 days after HSCT
Patient Identification

- Unique patient number
- Initials
- Date of Birth
- Gender
• Date of initial diagnosis
  - Usually taken from bone marrow or PET/CT scan results
  - Sometimes difficult to establish if the patient is diagnosed locally – no original patient results
  - Write the date of diagnosis, for the indication of the transplant (i.e. if the disease is of secondary origin)
## Performance Score

- **Karnofsky Performance Scale Index (1949)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

- **Lansky Score is used for paediatric patients**
Donor Information

Type of HSCT:
- Autologous
- Allogeneic
- Patient CMV status: [ ] Negative, [ ] Positive, [ ] Not evaluated, [ ] unknown
- Multiple donors/products: [ ] No, [ ] Yes: Number
- (including multiple CB units or different stem cell products from same donor)

Stem Cells (autograft or allograft):
- [ ] Peripheral Blood
- [ ] Cord Blood
- [ ] Other: ____________________________

Donor ID: ____________________________ [ ] N/A (autograft, go to graft manipulation below)

HLA Match type (for allografts):
- [ ] Syngeneic (monozygotic twin)
- [ ] HLA-identical sibling (may include non-zygotic twin)
- [ ] HLA-matched other relative
- [ ] HLA-mismatched relative:
  - Degree of allele mismatch: [ ] 1 HLA antigen mismatch
  - [ ] 2 HLA antigen mismatch
- [ ] Unrelated donor
- Name of donor registry/CB Bank: ____________________________

MBMDW/WMAD code (up to 4 characters)
- [ ] B
- [ ] C
- [ ] DRB1
- [ ] DQB1
- [ ] DPB1

Antigen
- [ ] A
- [ ] B
- [ ] C
- [ ] DRB1
- [ ] DQB1
- [ ] DPB1
- HLA code is 2 digits
- HLA code is 4 digits
- Female: 1 mismatch; 2-2 mismatches; ND not done

Graft manipulation ex-vivo (including T-cell depletion)
- [ ] Male
- [ ] Female
- [ ] Donor CMV status: [ ] Negative, [ ] Positive, [ ] Not evaluated, [ ] unknown

EBMT MED-4 2010 - 21/02/2011 - p. 1
Donor Information

- HLA match type
  - Syngeneic (identical twin)
  - HLA identical sibling
  - HLA mismatched relative
  - Unrelated donor

- Donor sex – M / F

- CMV status
HSCT Procedure

• Chronological number of HSCT for the patient – include date and type of transplant

• Part of a planned multiple graft protocol?
Conditioning Regimen

• Will be found on the Transplant protocol / Prescription chart
• Often a combination of different drugs given over a several days
• Total prescribed cumulative dose
  
  - e.g. Fludarabine – given at 25mg/m² over 5 days will be written as 125mg/m² on the Med-A form

• Total prescribed dose of radiation
After HSCT - GvHD

- GvHD prophylaxis
  - Immunosuppressive drugs e.g. Ciclosporin, methotrexate, campath, sirolimus, tacrolimus
  - For allografts – Presence and grade of acute GvHD
### Consensus Conference on aGvHD

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stage 1-2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>Stage 3 or</td>
<td>Stage 1 or</td>
<td>Stage 1</td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>Stage 2 - 3 or</td>
<td>Stage 2 - 4</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4 or</td>
<td>Stage 4</td>
<td>-</td>
</tr>
</tbody>
</table>

### IBMTR Severity Index for aGvHD

<table>
<thead>
<tr>
<th>INDEX</th>
<th>Skin</th>
<th>Liver</th>
<th>GI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage (max)</td>
<td>Extent of rash</td>
<td>Stage (max)</td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>&lt; 25%</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>25–50% or</td>
<td>1 - 2</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>&gt; 50% or</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>Bullae or</td>
<td>4</td>
</tr>
</tbody>
</table>
After HSCT

- Absolute neutrophil count (ANC) recovery - “Neutrophil Engraftment”
  - Date
  - Lost graft?
  - Never Below

- Additional treatment
  - May be planned before the transplant i.e. maintenance chemotherapy
  - May be unplanned – i.e. chemotherapy for relapsed or persistent disease; DLI

- Disease status
  - Continued complete remission
  - CR achieved? – date assessed
  - Never in CR – date assessed
  - Not evaluated
After HSCT

• Date of last contact
  - Use the actual date – not the date nearest to 100 days

• First relapse or progression
  - Clinical / Haematological
  - Cytogenetic – Bone marrow reports / FISH
  - Molecular i.e. BCR/ABL

• Disease presence at last contact

• Patient status at last contact
  - Alive
  - Dead - cause of death
MED-A: Follow up

- Every year for transplants performed less than 10 years ago
- Every 2 years for transplants performed between 10 and 20 years ago
- Every 5 years for transplants performed more than 20 years ago
- At time of death
MED-A: Donor Cell Infusion form

Up to 4 Donor Cell Infusions given in the follow up period can be reported on this form

Make as many copies as necessary
Complications of HSCT

- Chronic GvHD
  - Usually after D100
  - Date of diagnosis – clinical picture / Biopsy results
  - Recurrence
  - Extent of GvHD – limited / extensive / unknown
  - Resolved since it was last reported?

- Graft failure
  - Chimerism

- Secondary Malignancy
  - Lymphoid / myeloid disorders possibly caused by treatment for the original disease
  - Solid tumours
Disease and Survival Status

- First relapse or progression
- Disease presence at last contact
- Pregnancy
  - Rare but it does happen
  - Many patients are infertile at the time of transplant due to the chemotherapy / radiotherapy for disease control or conditioning
  - All patients are advised to use contraceptives during and after chemotherapy – causes birth defects and miscarriage
  - Sperm banking / embryo and oocyte storage
- Patient survival status
Acknowledgements

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Any Questions?

Thank you!