Introduction to Hematopoietic Stem Cell Transplantation

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Objectives

• Explain the difference between autologous and allogeneic hematopoietic stem cell transplant (HSCT)
• Identify different sources of hematopoietic stem cells (HSC) for transplantation
• Discuss the reasons for choosing a myeloablative vs. a non-myeloablative conditioning regimen
• Recognize those diseases for which each type of HSCT may be indicated

HSCT Timeline

• Days -7 to 0:
  – Conditioning regimen
• Days -3 to -1:
  – Begin immunosuppression (allo)
• Day 0:
  – Infusion of cell product
• Day 0-30:
  – Supportive care while awaiting engraftment

HSCT Timeline

• Day 31-100:
  – Patient remains on immunosuppression (allo)
  – Infection monitoring
  – Acute graft-versus-host-disease (GVHD) monitoring (allo)
• Day >100:
  – Taper immunosuppression (allo)
  – Chronic GVHD monitoring (allo)

The Basics of Stem Cells

• Hematopoietic stem cells (HSC) are cells that can both differentiate into various blood cells and also self replicate
  – These processes are the result of asymmetrical cell division
• These cells are found in the bone marrow but can migrate into the peripheral blood
• True HSC express the CD34 antigen
  – Other markers can be used in addition to identify a HSC

**Stem Cell Transplantation**

- Autologous and allogeneic transplant may both be curative
  - Autologous transplantation has the ability to increase overall survival in certain disease states
- With the use of HSC, much higher doses of chemotherapy may be administered than would otherwise be possible

**Autologous Stem Cell Transplantation**

- Aut- Derived from the word *autos*, means self or same
- The process of an individual’s own, or same, HSC being collected, stored, and infused into him or herself
- A patient’s identical twin may also serve as their donor in an “autologous” transplant
- High-dose chemotherapy with stem cell rescue

**Allogeneic Stem Cell Transplantation**

- Allo- Other, different
- In allogeneic transplantation, stem cells are donated from someone other than the patient being treated
  - This can be a related or unrelated donor or cord blood
- The decision on which donor to choose depends on HLA matching
- These transplants may be curative

**Assess Your Knowledge**

- Which of the following most appropriately describes a difference between autologous and allogeneic transplant?
  a) The stem cell donor for an allogeneic transplant is someone other than the patient, but must be a relative of the patient
  b) The only relative of an autologous stem cell patient that may donate cells is an identical twin, whereas any matching donor can donate cells for an allogeneic transplant patient whether or not they are related
  c) The recovery from autologous transplantation is often longer that the recovery from an allogeneic transplant
  d) Autologous stem cell transplants are rarely curative
Stem Cell Sources

- Bone marrow
  - The historical source for HSC
  - HSC remain primarily in the bone marrow due to their interaction with bone marrow stromal cells

- Peripheral blood
  - HSC not known to be in the peripheral blood until the early 1960s
  - Numbers of HSC in the peripheral blood increase in stressful situations

Bone Marrow Harvest

- Bone marrow harvest is the process of multiple bone marrow aspirations into bones, typically the bilateral iliac crests
- Patients are under general anesthesia during this process
- The process itself can be physically demanding
- Risks to the donor include pain, bruising, and anemia

How are These Stem Cells Obtained?

- There are several methods to mobilize CD34+ cells
  - Colony-stimulating factor used as a single agent
  - Chemotherapy plus a colony-stimulating factor
  - The use of a CXC chemokine receptor type 4 (CXCR4) inhibitor in addition to GCSF may be considered
    - Poor mobilizers
    - Previous failed mobilization attempt(s)

Peripheral Blood Stem Cell Mobilization

- Interactions between stromal cells and stem cells keep the HSC in the bone marrow
- More HSC are found in the peripheral blood after chemotherapy administration
- The use of colony-stimulating growth factor after chemotherapy increases the number of circulating HSC more than chemo alone

Peripheral Blood Stem Cell Mobilization

- Using growth factor alone is another option for stem cell mobilization
- Various doses of growth factor have been used in mobilizing stem cells
  - Both filgrastim and sargramostim are FDA-approved to be used in mobilization

The Apheresis Process

- Stem cells are collected from the peripheral blood through a process known as apheresis
- Apheresis involves a continuous process of filtering blood in order to separate the different blood components
  - This can either be done vein-to-vein or with a double-lumen catheter
### The Apheresis Process

- **Risks to the patient include hypocalcemia, low blood pressure, and bruising**
- More than one apheresis process may be needed to collect the appropriate amount of stem cells
  - The process may take anywhere from 3-5 hours

### Number of HSC Needed

- The minimum number of HSC needed for a successful stem cell transplantation is $2 \times 10^6$/kg.
- These cells must be CD34+
- Patients with more extensive prior therapy may benefit from a higher dose of cells of $>5 \times 10^6$/kg for better platelet recovery.

### Overcoming Mobilization Failure

- Failure can be due to several factors, both patient related and therapy related
- Giving chemotherapy plus a growth factor can increases success of mobilization
- Increasing the dose of growth factor can increase the chances for a successful mobilization

### Plerixafor

- A CXCR4 chemokine receptor inhibitor approved in 2008
- Plerixafor has been shown to successfully mobilize stem cells in those patients who have previously failed
  - $0.24 \text{ mg/kg}$ given as a subcutaneous injection
  - Given 11 hours prior to planned stem cell collection
- Side effects include diarrhea, injection site erythema, bone pain, and nausea

### Umbilical Cord Blood

- A 3rd source of stem cells is the umbilical cord
- Umbilical cord blood (UCB) is usually reserved for those patients who do not have a matched donor
- Amount of HSC is expressed as total nucleated cells, or TNC
- Cells are collected from blood from the umbilical vein

### Cord Blood as Source of Stem Cells

- HLA-matching and cell dose are two important factors in determining the outcome of a transplant using cord blood
- Some centers are using 2 cord blood units to try and optimize cell dose
  - Matching each cord blood unit to the patient is important
  - These may be infused together or within 6 hours of each other
Preferred Stem Cell Source

- Autologous transplant
  - Stem cells vs. bone marrow
- The stem cell source for an allogeneic transplant has become more controversial
  - First randomized trial comparing BM vs. PB just published in October 2011
  - Lower incidence of chronic GVHD in BM recipients
  - PB should be reserved for those with certain circumstances


Comparison of Stem Cell Sources

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Blood</th>
<th>Bone Marrow (BM)</th>
<th>Umbilical Cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to neutrophil engraftment</td>
<td>Shortest (11-29 days)</td>
<td>Moderate (13-36 days)</td>
<td>Longest (3-6 weeks)</td>
</tr>
<tr>
<td>Time to platelet engraftment</td>
<td>Shortest</td>
<td>Moderate</td>
<td>Longest</td>
</tr>
<tr>
<td>Incidence of acute graft-versus-host disease (GVHD)</td>
<td>No difference</td>
<td>Least</td>
<td></td>
</tr>
<tr>
<td>Incidence of chronic graft-versus-host disease (GVHD)</td>
<td>Most</td>
<td>Moderate</td>
<td>Least</td>
</tr>
<tr>
<td>Risk of graft failure or graft rejection</td>
<td>Lowest</td>
<td>Moderate</td>
<td>Highest</td>
</tr>
<tr>
<td>Risk of relapse</td>
<td>No difference</td>
<td>Least</td>
<td>Highest</td>
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Selecting a Donor

- The critical factor in determining a suitable donor for an allogeneic transplant patient is the human leukocyte antigen (HLA) matching
- HLA are proteins that are encoded by the major histocompatibility complex (MHC)
- MHC is a complex of genes found on the long arm of chromosome 6
- The MHC is divided into 2 classes, Class I and Class II

Class Matching

- Class I HLA are found on all nucleated cells
  - Class I = HLA-A, HLA-B, & HLA-C
- Class II HLA are found on certain immune cells
  - Class II = HLA-DR, HLA-DQ, & HLA-DP
- The nomenclature of the classes involves the loci (A, B, C, DR, DQ, & DP) and the antigen, which is the number expressed after the loci
  - Ex.: HLA-A2
- Allogeneic transplants may either be matched or mismatched based on HLA matching

Importance of Matching

- Matches (or mismatches) are based on alleles or antigens
- Offspring get 1 allele from each parent; an antigen is comprised of 2 alleles
  - Allele mismatch vs. antigen mismatch
- Mortality is increased as the number of mismatches increases

Assess Your Knowledge

- What is the least likely scenario below involving stem cell donors?
  a) A patient’s own cells are stored then used for his autologous transplant
  b) Cells from 2 different umbilical cords are donated to the same patient
  c) A autologous transplant patient receives stem cells from her identical twin
  d) Stem cells from a 3 antigen mismatch are donated for an allogeneic transplant patient

Conditioning Regimens

- The therapy given immediately prior to transplantation
- Chemotherapy or radiation, or a combination of both
- Some regimens ablate the entire marrow whereas other regimens do not
  - True even for autologous transplants

Non-Myeloablative Conditioning Regimens

- Graft-versus-tumor effect
- Lower early treatment-related mortality
- Can be used in a wider patient population

Assess Your Knowledge

- A 69 year-old patient with AML in 2nd remission has come to your transplant center for a consultation. His 1st remission lasted only 6 months. He has no other comorbidities. Your physician recommends a transplant using a reduced-intensity regimen. Which patient characteristics is the likely reason for recommending a reduced-intensity regimen?
  a) Age
  b) Disease state
  c) Lack of comorbidities
  d) Male sex

Who Gets an Autologous Transplant?

- Decision for transplant must be made based on type of disease, stage of disease, and patient-specific factors
- Several diseases, both hematologic and non-hematologic can be cured by an autologous transplant

<table>
<thead>
<tr>
<th>Malignancies</th>
<th>Non-Malignancies</th>
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</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td></td>
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<tr>
<td>Glioblastoma</td>
<td></td>
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<tr>
<td>Germ cell tumors</td>
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Autologous Transplantation for Hematologic Malignancies

- Multiple Myeloma
  - Not curative
  - Every patient should be considered for a transplant ; Stem cell harvest is recommended after initial therapy for those that are transplant candidates
  - If there is a response after primary therapy, autologous transplant is one of the 3 treatment recommendations
- Amyloidosis


Autologous Transplantation for Hematologic Malignancies

• Diffuse Large B-Cell Non-Hodgkin Lymphoma
  – Curative
  – Consider for relapsed or refractory disease
  – First attempt to achieve a 2nd complete remission prior to transplantation

• Mantle Cell Lymphoma
  – Consider for later stage disease (II(bulky), III, IV)
  – May be used as consolidation therapy after first CR

Autologous Transplantation for Hematologic Malignancies

• Burkitt Lymphoma
  – For low or high risk patients, used in relapsed disease

• Follicular lymphoma (FL)
  – Consider transplantation for FL with histological transformation to DLBCL
  – Used most often for disease still responsive to other therapies

Autologous Transplantation for Hematologic Malignancies

• Peripheral T-cell Lymphoma
  – Can be considered as consolidation or additional therapy

• Hodgkin Lymphoma
  – Remains a disease often cured with initial therapy
  – Transplantation reserved for relapsed or refractory disease
  – At least 1 study has shown that imaging showing no evidence of disease predicts for a better event free survival

Autologous Transplantation for Solid Tumors and Non-Malignant Diseases

• Testicular Cancer
  – For metastatic germ cell tumors if patient achieves an incomplete response after 2nd-line therapy or if relapse occurs

• Glioblastoma

• Autoimmune Disorders
  – Multiple sclerosis, systemic sclerosis may benefit from an auto transplant

Which of the listed disease states would not be cured by an autologous transplant?

a) Germ cell tumor
b) Multiple myeloma
c) DLBCL
d) Hodgkin’s disease

Who Gets an Allogeneic Transplant?

<table>
<thead>
<tr>
<th>Good-risk Candidates</th>
<th>High-risk Candidates</th>
</tr>
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<tbody>
<tr>
<td>Young age</td>
<td>Older age</td>
</tr>
<tr>
<td>No comorbid conditions</td>
<td>With comorbid conditions</td>
</tr>
<tr>
<td>No active infections</td>
<td>Refractory/relapsed disease</td>
</tr>
<tr>
<td>Disease in remission/no refractory disease</td>
<td>Aggressive prior therapy</td>
</tr>
<tr>
<td>HLA-matched donor</td>
<td>High-risk/complex karyotype</td>
</tr>
<tr>
<td>Low risk of relapse post-transplant</td>
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Who Gets an Allogeneic Transplant?

- Those patients in which the benefits of transplantation outweigh the risks or outcomes of other therapy
  - This is based on studies in various disease states comparing transplantation to no transplant
- Those who will benefit from graft-versus-tumor effect

Allogeneic Transplant for Hematologic Malignancies

- Leukemias
  - Myeloid
    - Most patients should be transplanted in 1st remission
  - Lymphoid
    - Only certain factors predispose patients to needing a transplant in 1st remission
      - Ph+, complex karyotype, high WBC, time to CR >4wks.

- Myelodysplastic syndrome
  - Those with a high-risk karyotype, ≥5% myeloblasts
- Myeloproliferative neoplasms
  - If peripheral blood disease or leukemic transformation


Allogeneic Transplant for Hematologic Malignancies

- Non-Hodgkin Lymphoma
  - May be used for patients who have relapsed after an auto transplant
  - Consider a non-myeloablative conditioning regimen
- Multiple Myeloma
  - May be curative for MM
  - Treatment-related mortality is much higher
    - Only non-myeloablative conditioning used
    - Reserve for patients with high-risk cytogenetics


Allogeneic Transplant for Non-Malignant Diseases

- Aplastic Anemia
  - Upfront therapy if patient has a HLA-matched donor
- Disorders of the immune system
  - Transplants for this indication performed in both adults and children


For which disease would you more likely perform an allogeneic transplant?

a) Multiple myeloma
b) DLBCL
c) AML
d) Germ cell tumor
## Important Transplant Facts to Remember

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<thead>
<tr>
<th></th>
<th>Autologous</th>
<th>Allogeneic</th>
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</thead>
<tbody>
<tr>
<td>Need to be able to collect stem cells</td>
<td>Need to locate donor</td>
<td></td>
</tr>
<tr>
<td>Toxicity - mainly regimen-related</td>
<td>Toxicity - regimen-related, GVHD</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
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<tr>
<td>Financial situation</td>
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