Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

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MDS Foundation Forum

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Disclosures

None
Outline

• What is Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
• Transplant Outcomes in MDS
• Selecting a Donor
• HSCT Process
• Risks and Complications of HSCT
Allogeneic vs Autologous Stem Cell Transplant

**Autologous Stem Cell Transplant (ASCT)**

patient’s own stem cells

**Allogeneic Stem Cell Transplant (allo)**

stem cells from a donor

Bone Marrow Transplant = Stem Cell Transplant = Hematopoietic Cell Transplant
What is allogeneic hematopoietic cell transplantation?

- A procedure in which bone marrow that is diseased or damaged is replaced with stem cells from another donor.
- New (transplanted/donor) immune system attacks cancer cells that survived chemotherapy/radiation (graft-versus-tumor effect).
Historical Timeline


Keck Medicine of USC
Number of 1st HCTs reported to CIBMTR in the U.S.
The Hematopoietic Stem Cell

- Stem cells:
  - develop into mature white blood cells, red blood cells, or platelets
  - found in
    - bone marrow, especially in the pelvis, femur, and sternum
    - umbilical cord blood
    - in small numbers, in blood
How do we treat MDS?

• Supportive care:
  – transfusions, growth factors, minimal medical interventions

• Disease Modifying treatments:
  – treatments that may change the natural history of the MDS but don’t “cure” it

• Curative therapy:
  – HCT-hematopoietic cell transplantation
How do we decide which treatment approach is best?

- Patient age/fitness
- MDS risk category
- Risk of treatment
- Patient goals/wishes
**BMT CTN 1102 Study Design:**
Multicenter, biologic assignment study

**Enrollment**

**Inclusion criteria**
- high risk MDS
- 50-75 years
- Any prior therapy
- No prior unrelated donor search
- Eligible for reduced intensity alloHCT from a matched related or unrelated donor

**Donor arm:**
- transplant using lower intensity regimen within 6 months

**No Donor arm:**
- hypomethylating agent or best supportive care

**Primary endpoint:**
- Lived for 3 years

**Secondary endpoints:**
- Lived for 3 years without leukemia
- Quality of life (QoL)
- Cost effectiveness
Clinical outcomes
(Donor arm=260 and No donor arm=124 patients)

Patients who lived for 3 years

Patients who lived for 3 years without leukemia
Risks and Benefits of Transplant

- High risk MDS
- Poor risk genetic mutations
- No response to non-transplant treatments
- Potential cure

High risk of complications from transplant
- Infections
- GVHD
- Organ toxicity

Frailty/ poor functional status
Donor availability
Insurance coverage
Donor Types

- HLA-Matched Related/Sibling Donor
- Matched Unrelated Donor
- Mis-Matched Unrelated Donor
- Haploidentical Donor
- Umbilical Cord Blood
HLA Typing

Separate gene name from HLA prefix

Field 1: Allele group
Field 2: Specific HLA protein
Field 3: Synonymous DNA substitution in coding region
Field 4: Changes in non-coding region
Suffix: Denoted changes in expression

Keck Medicine of USC
Number of Allogeneic HCTs in the U.S. by Donor Type

Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match; CB: Cord blood
Bone Marrow vs Mobilized Peripheral Blood

• Stem cells should be collected prior to exposure to an alkylating agent, as these agents are stem cell toxic
• Collection may be done by bone marrow harvesting or peripheral blood stem cell apheresis following treatment with G-CSF
• Harvested cells are cryopreserved until time of transplant
• Peripheral blood preferred since development of colony stimulating factors and CXC4 inhibitor
• Daily measurement of peripheral CD34 count
• BMT CTN 0201
  • GVHD BM vs PB (41% vs 53%)
  • BM higher incidence of graft failure (9% vs 3%)
  • Donor preference (30% declined BM)
  • No difference in relapse, DFS, OS
Conditioning Regimens

Objective of using a conditioning regimen for hematopoietic stem cell transplantation

• To reduce the bulk of malignant cells
• To decrease the risk of graft rejection via general host immune suppression
• To improve the engraftment of donor HSCs by providing profound immunosuppression of the host
Conditioning Regimens

Intensity classified as
• Myeloablative (MA)
• Reduced intensity (RIC)
• Nonmyeloablative (NMA)
Pre-transplant Process

1. Referral from your treating doctor
2. You meet with a transplant doctor/team
3. Your transplant team works with your treating doctor on a care plan and searches for a donor
4. Best possible donor is chosen and dates for transplant are decided
5. You undergo a comprehensive clinical evaluation
Transplant Process

1. You are admitted to the hospital
2. You undergo conditioning followed by stem cell infusion
3. Your new cells start to grow
4. Early recovery and discharge from the hospital
5. You are followed closely in the outpatient clinic for the first 100 days after transplant
Stem Cell Transplant Phases

- **Phase I: chemotherapy phase**
  - Ends with the infusion of stem cells (Day 0)
- **Phase II: cytopenic phase (+1 to engraftment, usually +14-21)**
- **Phase III: early recovery phase (+14 to +30)**
  - Neutrophil recovery, engraftment syndrome, GVHD can begin to manifest
- **Phase IV: early convalescence phase (+30 to +6-12 months)**
  - Persistent immune-deficiency despite normal peripheral blood counts
  - Antibiotic, antiviral, and antifungal prophylaxis
- **Phase V: late convalescence phase (+12 months)**
  - Near full recovery of immune system
  - Last complications such as organ dysfunction or relapse
Causes of Death after Adult (age ≥18) Unrelated Donor HCT in the US, 2017-2018

Died within 100 days post-transplant

- Primary Disease: 22%
- GVHD: 27%
- Organ Failure: 2%
- Hemorrhage: 4%
- Unknown: 1%

Died at or beyond 100 days post-transplant

- Primary Disease: 53%
- GVHD: 13%
- Organ Failure: 14%
- Hemorrhage: 11%
- Unknown: 1%

*Data reflects 3-year mortality
Transplant Complications and Outcomes

• Infection
  • PJP, fungal, CMV, VZV, HSV, EBV

• Myelosuppression

• Graft failure

• Hepatic Sinusoidal Obstruction Syndrome (SOS), previously VOD
  • Severe liver injury can result from cellular injury and obstruction in hepatic vein sinuses, results in elevated levels of bilirubin, hepatomegaly, fluid retention
  • Treatment: anticoagulants/defibrotide may reduce severity of hepatic SOS
  • Ursodiol can prevent SOS

• Pulmonary toxicities
  • Idiopathic pneumonia syndrome
  • Diffuse alveolar hemorrhage

• Thrombotic microangiopathy
Transplant Complications and Outcomes

• **Mucositis**
  - Injury to oropharyngeal mucosa commonly associated with conditioning regimen
  - Treatment: pain medications and IVF/TPN

• **Engraftment syndrome**
  - Rash, fever, capillary leak, pulmonary edema, renal failure

• **GVHD**
  - Rare occurrence post autologous transplant
  - Usually mild and self-limiting

• **Secondary malignancies**
  - Increased incidence of skin cancer, other solid tumors, acute leukemias, MPNs
  - Increased risk in TBI based preparations
  - Post-HSCT oropharyngeal cancer may have more aggressive behavior with poorer prognosis
Engraftment and Graft Failure

Chimerism Analysis: STR-PCR: CD3, CD33
Primary Graft Failure: >95% recipient CD3 or CD34 after engraftment
Secondary Graft failure: loss of previously functioning graft by at least two cytopenic lines

Factors associated with Graft Failure
- Quantitative progenitor issues
- Immunologic issues
- Viral infections
- Others (Drugs)
Graft versus host disease (GVHD)

- Occurs because of differences between the cells of your body and the donor cells
- Severity ranges from mild to life-threatening
- Two types:
  - Acute:
    - Develops in the first 100 days after transplant but can occur later
    - Usually involves skin rash, nausea/diarrhea or liver issues
  - Chronic GVHD:
    - Usually develops 3-6 months after transplant, but can appear earlier or later
    - Can involve most organ systems like skin, eyes, lungs, joints etc
    - Adversely impacts long term quality of life
Acute GVHD (aGVHD) and Chronic GVHD (cGVHD)\textsuperscript{1,2}

- **CLASSIC ACUTE**
  - Day 0
  - Skin (erythema)
  - Gastrointestinal (secretory)
  - Liver

- **LATE ACUTE**
  - Day 100
  - Skin (lichenoid, sclerotic...)
  - Mouth
  - Nails and hair
  - Eyes
  - Lung
  - Musculoskeletal

- **OVERLAP**
  - Hematopoietic
  - Gastrointestinal (esophageal)
  - Liver
  - Other

- **CLASSIC CHRONIC**
  - Subsequent episode
    - Recurrent
    - Persistent
    - New onset or late acute
  - First episode: classical

- Any sign of acute GVHD?

- **No = classic chronic**
- **Yes = overlap syndrome**

Post-Transplant Vaccinations

- Non-live vaccinations begin at 1 year
- Non-live influenza vaccine can be given after Day +60
- Live vaccines administered after 2 years if off immunosuppression
- Can monitor CD4 and/or CD19 as surrogate for lymphocyte recovery

What determines the success of transplants?

• In general, transplants are most successful if:
  • MDS is in remission at the time of transplant and has not transformed to leukemia
  • Good organ function
  • Optimum functional status
  • No major uncontrolled infections
  • Good psychosocial support
How to prepare for transplant and improve chances of a successful outcome

• Get information about risks and benefits of transplant
• Explore non-transplant options such as clinical trials
• Select a transplant center
  • Live within about an hour of transplant center for at least 100 days after allogeneic HCT
• Continue to optimize your functional status and nutrition
• Select/decide about caregiver plan
• Plan your finances
What can I do as a potential transplant caregiver?

• 3 main areas of support:
  • Medical – gather information, talk to doctors and help care for the patient
  • Financial – talk to the insurance company and help manage transplant costs and daily household finances
  • Emotional and social – listen and support the patient
• Taking care of yourself while caring for your loved one
  • Many resources available for supporting caregivers
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<tr>
<th>Patient perceived</th>
<th>Provider perceived</th>
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<td>• Perceptions about high risks of transplantation</td>
<td>• Lack of awareness of the process of transplant among community hematologists/ oncologists</td>
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<td>• Social barriers</td>
<td>• Potential revenue loss</td>
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<td>• Need for transportation and lodging benefits</td>
<td>• Lack of care coordination</td>
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<tr>
<td>• Lack of caregiver</td>
<td>• Financial barriers to HCT/need for in-network insurance</td>
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<td>• Lack of insurance/ undocumented patients</td>
<td>• Lack of clarity on post-transplant care</td>
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<td>• Lack of optimal donors</td>
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