Normally....
Genetic mutations alter hematopoiesis

Abnormal (clonal) cells in the bone marrow suppress development of healthy cells in the bone marrow and blood.
Transplant in MDS

• MDS is a clonal **stem cell disorder**
  • Curing MDS = permanently eliminating this clone

• Transplant = replacing the recipient’s stem cells with new stem cells from a donor (allogeneic transplant/HCT)

• Allogeneic transplant is a **potentially curative** treatment

• Allogeneic transplant uses:
  • Chemotherapy to suppress recipient immune system and to reduce disease burden in marrow (both variable)
  • Donor’s immune system develops in the recipient and helps to keep MDS in remission
Use of Allogeneic HCT in MDS

• SEER Database: 10,000 people/year in the US are diagnosed with MDS:
  • Ages 65-69: 13.9 per 100,000 people
  • Age >85: 64 per 100,000 people

• CIBMTR: ~1,000 MDS patients undergo allogeneic transplant/year

• Why do only a minority (10%) of MDS patients receive this potentially curative treatment?

Source:
SEER database
CIBMTR Summary Slides
Two (very) Different People with MDS

Patient #1

Patient #2
Patient #1

• 77-year-old female who lives independently was found on routine bloodwork to have mild, isolated macrocytic anemia (Hgb 10.2g/dl)

• Other medical problems: History of stroke, coronary artery disease with myocardial infarction, high blood pressure, and chronic kidney disease

• Work-up for alternative causes of anemia was negative. Bone marrow biopsy showed mild, single lineage dysplasia with <5% blasts. FISH/cytogenetics are normal.

• Sequencing (NGS) shows mutation in **DNMT3A**

• Revised IPSS score: 1, Category: Very Low

• Expected survival: 8.8 years with low risk of transformation to AML
Patient #2

- 51-year-old female with history of breast cancer six years prior. Treated with surgery/chemo/radiation. No other medical history.
- During follow-up, found to have WBC: 2k, ANC: 800, hemoglobin 8g/dl, and platelet count of 40k
- Bone marrow biopsy showed multilineage dysplasia with 10-15% blasts. Cytogenetics showed complex karyotype
- Sequencing (NGS) shows two mutations in the TP53 gene
- Revised IPSS score: 9, Category: Very High
- Expected survival: 0.8 years
- Median time for 25% of patients to evolve to AML: 0.7 years
Summary: Two Different People with MDS

**Patient #1**
- MDS risk: Low
- Needs Tx: No
- #/severity of other medical problems: High
- ? Die from MDS: Unlikely
- Ability to withstand intensive treatment: Unlikely

**Patient #2**
- MDS risk: High
- Needs Tx: Yes
- #/severity of other medical problems: Low/none
- ? Die from MDS: Likely
- Ability to withstand intensive treatment: Likely
Transplant is not without risk

- **Causes of death within 100 days:**
  - Primary disease (32%)
  - Organ failure (31%)
  - Infection (16%)
  - GVHD (10%)

- **Cause of death between 100 days and 3 years:**
  - Primary disease (53%)
  - Organ failure (14%)
  - Infection (14%)
  - GVHD (12%)

Red text = conditions that can be/are likely worsened by HCT.
Balancing Curative Therapy vs Risks of Curative Therapy

**Risks of Transplant:**
- Infection
- Graft vs. Host Disease
- New/worsening organ dysfunction
- Risk of disease relapse
- Reduced quality of life
- Financial toxicity
- Others

**Benefits of Transplant:**
- Transfusion independence
- Reduced risk of leukemic transformation
- Potential for cure
Disease Biology (Risk) Drives Timing

- Lessons learned from 2004 still guide practice today.

- Patients with lower risk MDS have a survival advantage when transplant is delayed.

- Patients with higher risk MDS benefit from transplant early in their treatment course.

Cutler C, Blood, 2004
Limitations of this work:

• Median age of the cohort was young (<50 years old)
  • Median age of MDS patients is 70
• Patients received high intensity conditioning chemotherapy
  • Reduced intensity conditioning is used more frequently in elderly patients
• Patients were transplanted from Jan 1990 to Dec 1999
  • Transplant is safer/supportive care now
• IPSS has been replaced by newer, more sophisticated scoring systems
• Treatment for MDS/AML has improved since the 90s
Other Factors That Convey Risk

• Molecular mutations (i.e., *TP53*)

• History of prior chemotherapy, radiation therapy, or occupational exposure (i.e., secondary MDS)

• Failure of front-line therapy (?)
Two (very) Different People with MDS

**Patient #1**
- Disease risk: Low
- Molecular Mut: No
- Prior chemo/XRT: No
- Delay Transplant

**Patient #2**
- Disease risk: Very High
- Molecular Mut: TP53
- Prior chemo/XRT: Yes
- Early Transplant
When is it time to prepare for HCT?

- **Some examples of disease progression**
  - A patient who has been transfusion independent begins to need packed red blood cell (PRBC) or platelet transfusions
  
  - A patient who needed PRBC transfusions became transfusion independent with treatment. He/she is now needing them again
  
  - A patient with stable disease has new cytogenetic or NGS abnormalities on a repeat bone marrow biopsy
When is it time to prepare for HCT?

The decision to proceed with allogeneic HCT requires a personalized approach and is based on the disease risk, age and other medical problems, and their beliefs and wishes/desires.

Your physician(s)/APP(s) will help you to weigh the risks and benefits of transplant and make the decision that is right for you or your family member.
A few words about allogeneic HCT

• HLA typing, identifying and evaluating a donor, and collecting the donor’s cells can take several weeks

• Human leukocyte antigen (HLA) typing is performed to profile your immune system so that a match can be identified

• Your doctor may prescribe treatment for MDS prior to transplant to:
  • Reduce your disease burden
  • Reduce the risk of developing acute myeloid leukemia
  • Reduce the number of transfusions you receive prior to HCT
Donors

- Full match = 12/12 (MUD/MRD)
- Haploidentical = 6/12
- Siblings have:
  - 1:4 (25%) chance of being a full match (MRD).
  - 2:4 (50%) chance of being a half match (haplo)
  - 1:4 (25%) chance of not matching.
- Children are almost always haploidentical matches

- Likelihood of identifying an unrelated donor depends on racial/ethnic group

Gragert L, NEJM, 2014
Donors (Cont)

• Centers may use umbilical cord blood units or mismatched unrelated donors (mMUD).
  • Use of these graft types/sources are now safer than ever

• Nearly all patients have a donor and can proceed with allogeneic HCT if needed

• If multiple donors are present, many factors go into selecting the best of these options. This is handled by the transplant team
My advice after 7 years of seeing MDS patients undergoing allogeneic HCT

• If you can safely delay transplant – do it!

• Delays prior to transplant are very common – do your best to roll with them!
  • Donor issues, disease, infections, etc

• Setbacks are a normal part of transplant.

• Exercise, eat well/drink well, and enjoy the journey.
Thank you for your attention!

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