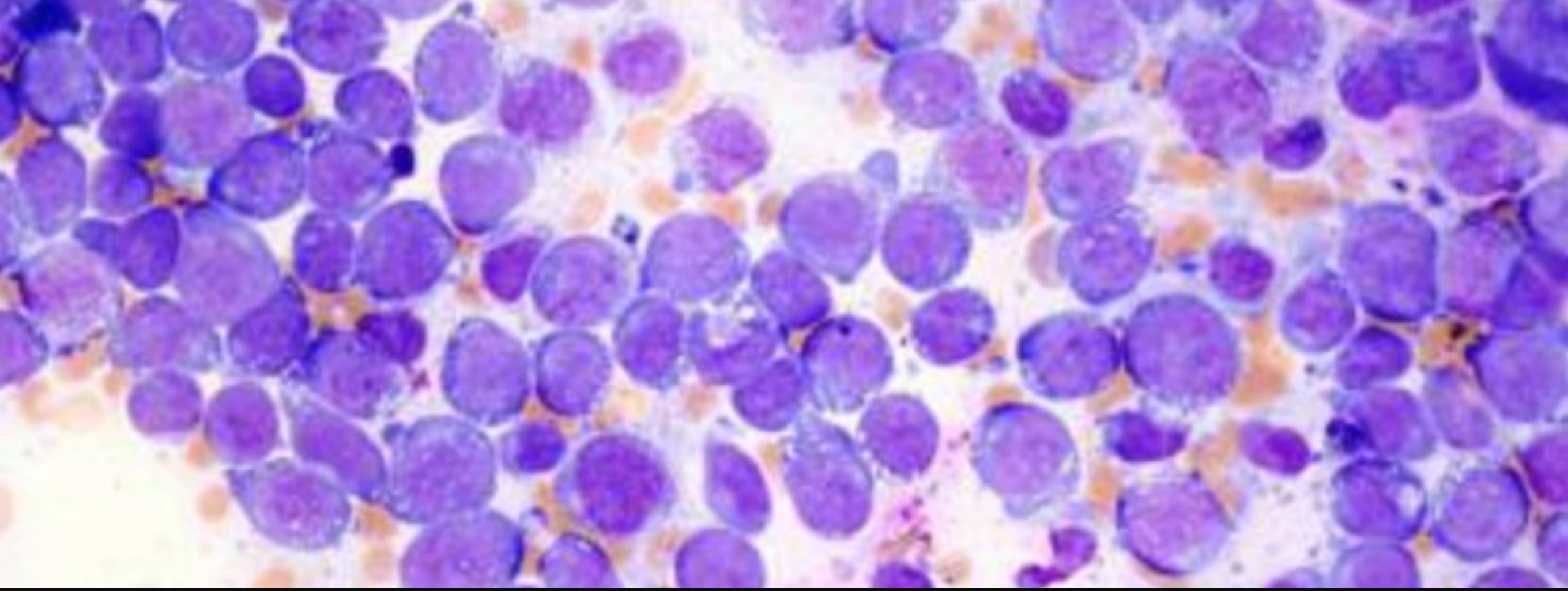

Allogeneic Transplant in MDS

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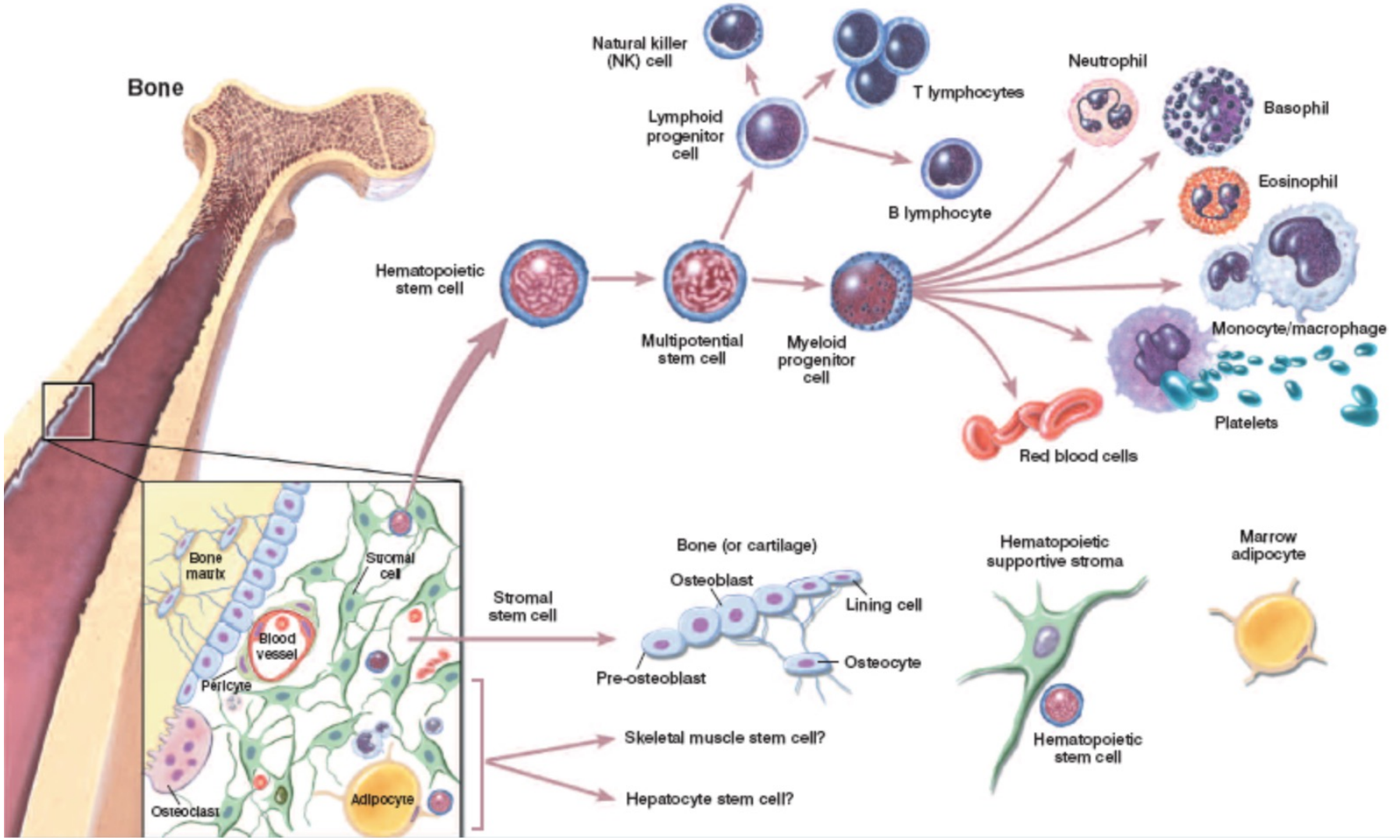
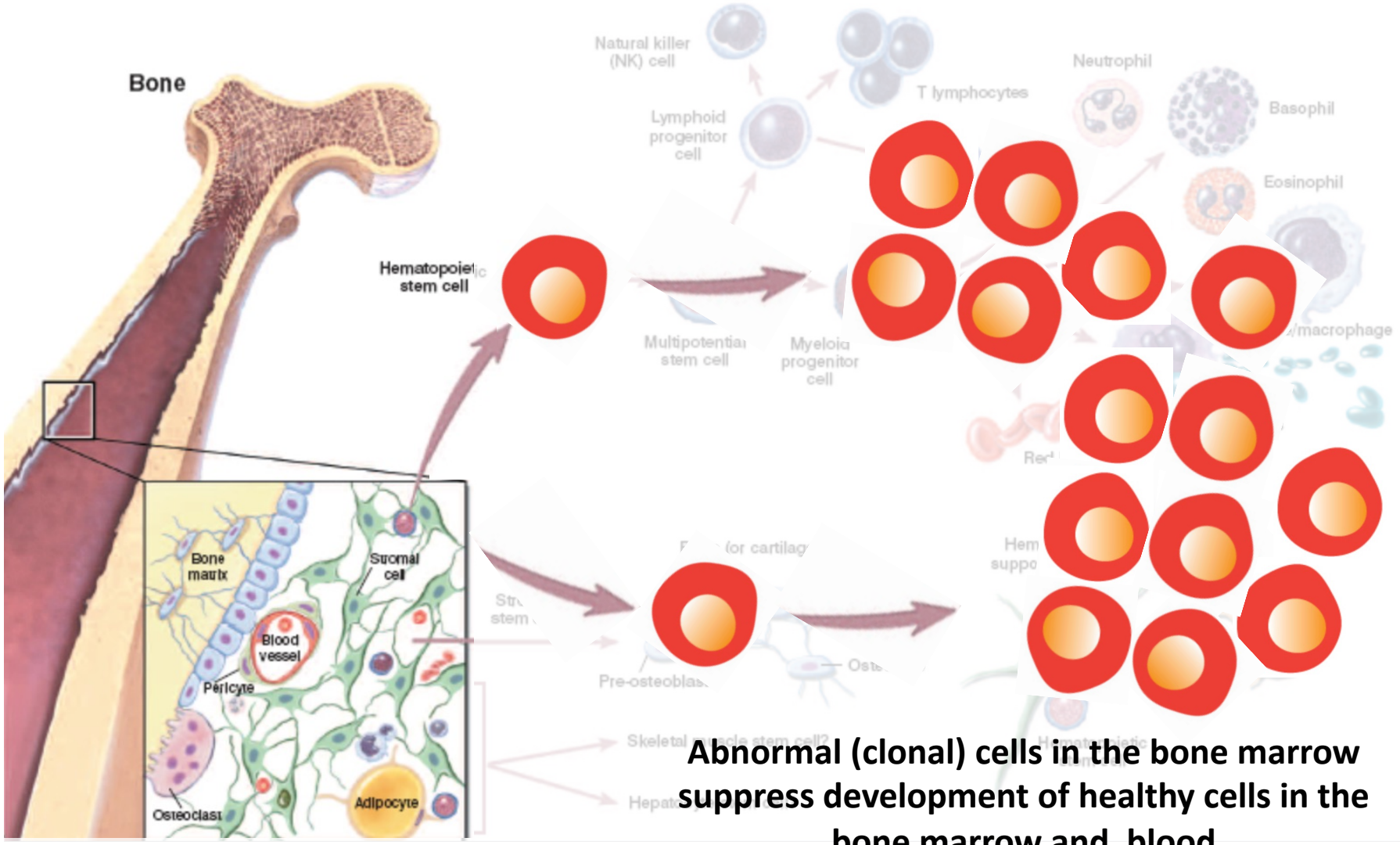
Nashville

Normally….


Bone
Natural killer (NK) cell
T lymphocytes
Neutrophil
Basophil
Lymphoid progenitor cell
B lymphocyte
Eosinophil
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelets
Red blood cells
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

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

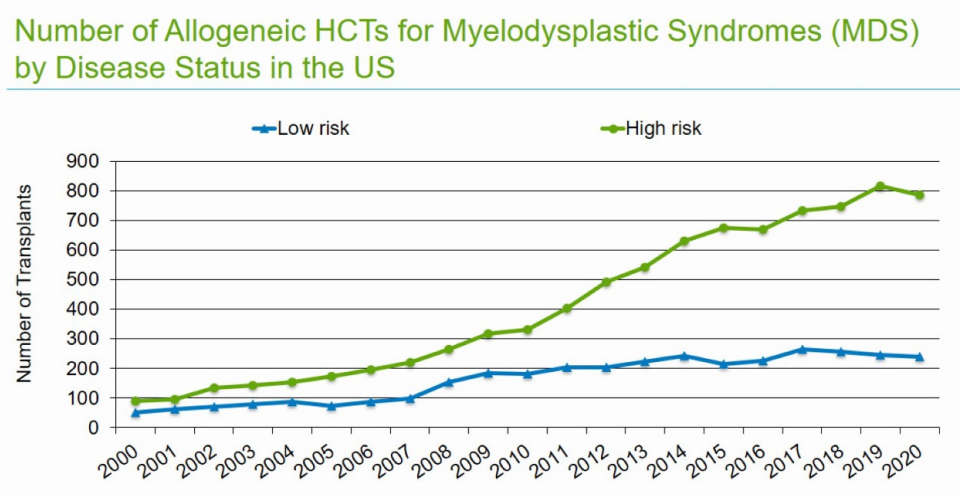
- MDS is a clonal stem cell disorder
  - Curing MDS = permanently eliminating this clone
- Transplant = replacing the recipient's stem cells with new stem cells from a donor (allogeneic transplant/HCT)
- Allogeneic transplant is a potentially curative treatment
- Allogeneic transplant uses:
  - Chemotherapy 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

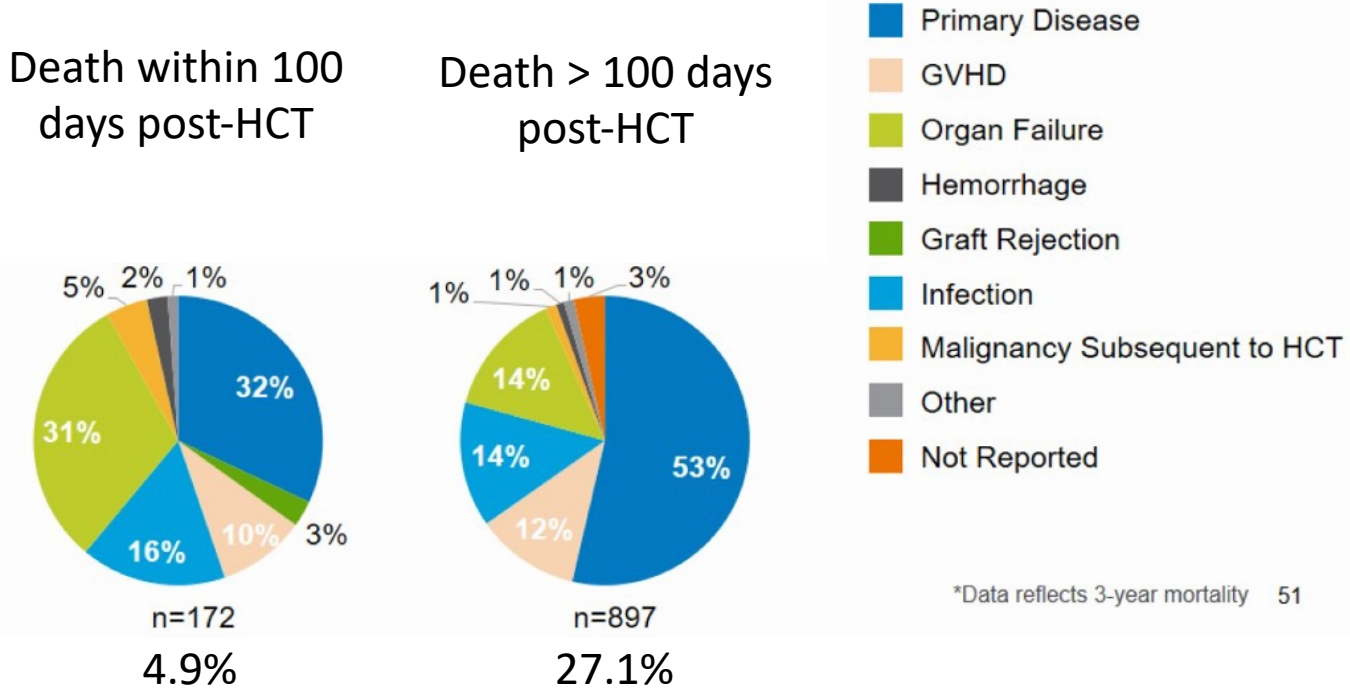
? Die from MDS: Likely

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%)



Total HCTs: 3,484

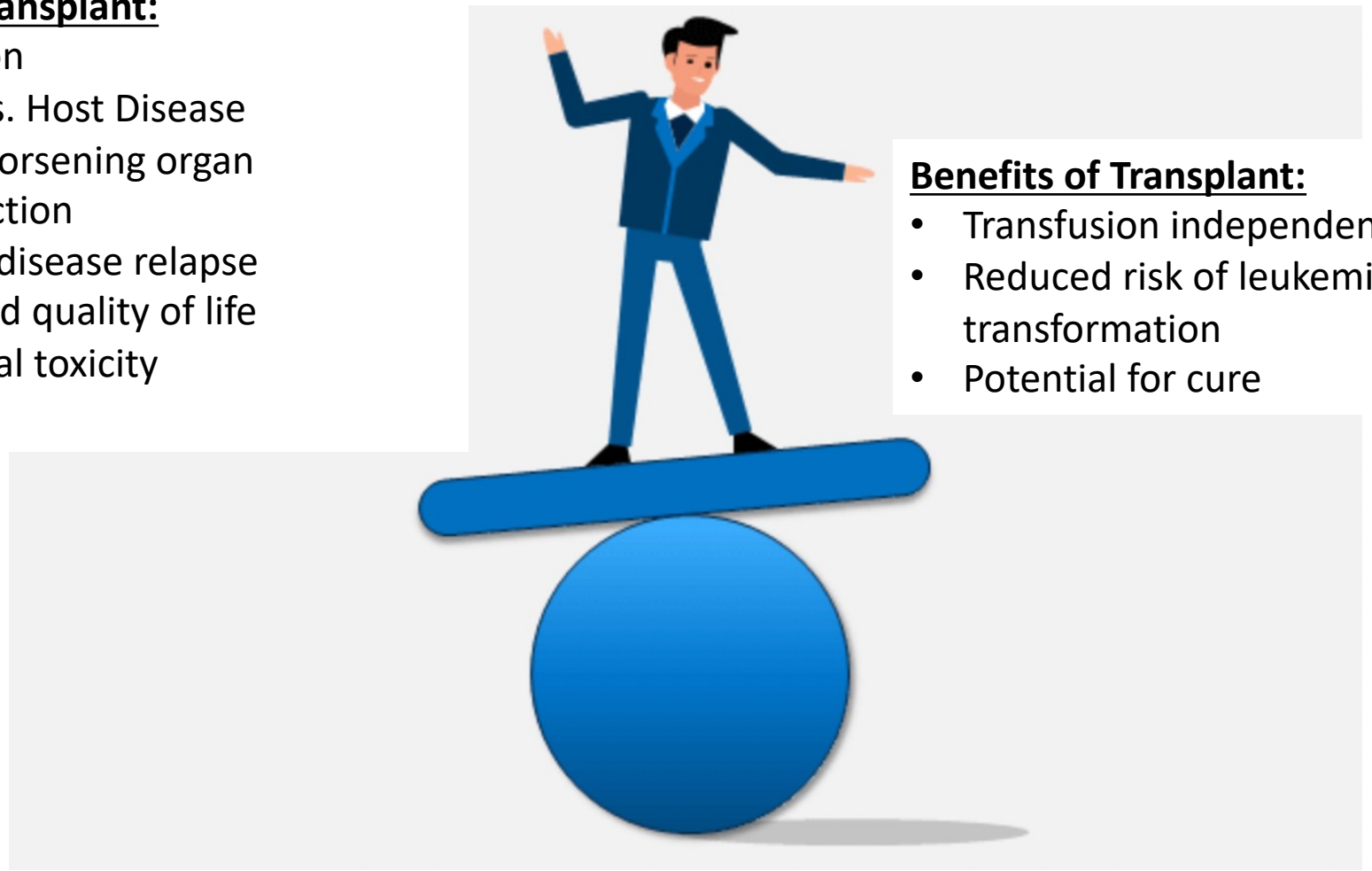
Red text = conditions that can be/are likely worsened by HCT.

CIBMTR Summary Slides
2018-2019 MRD HCTs

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



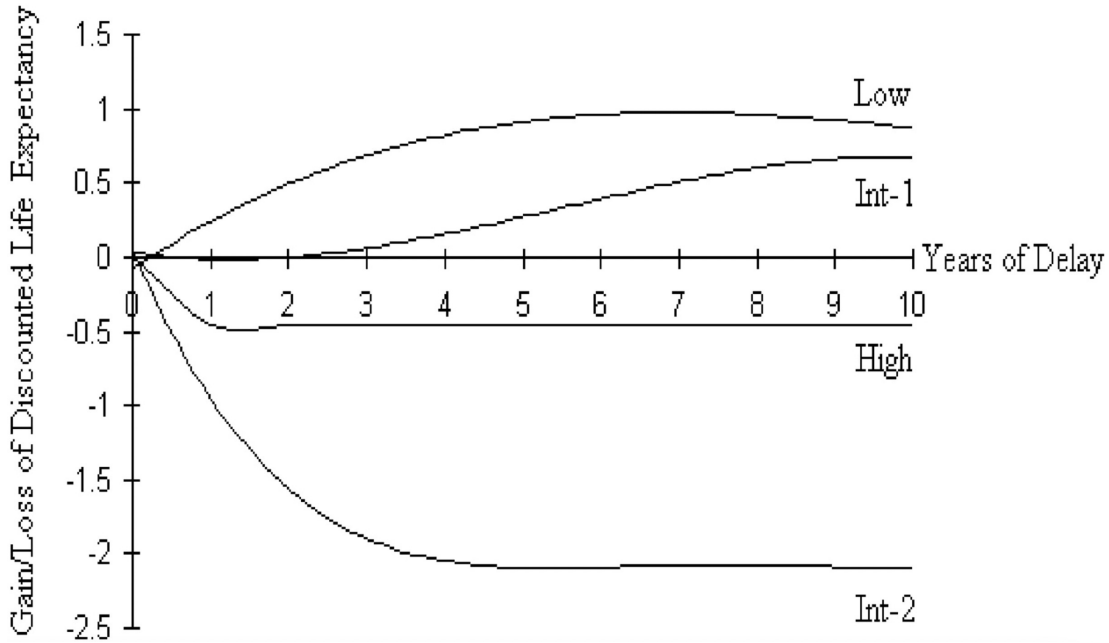
Benefits of Transplant:

- 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

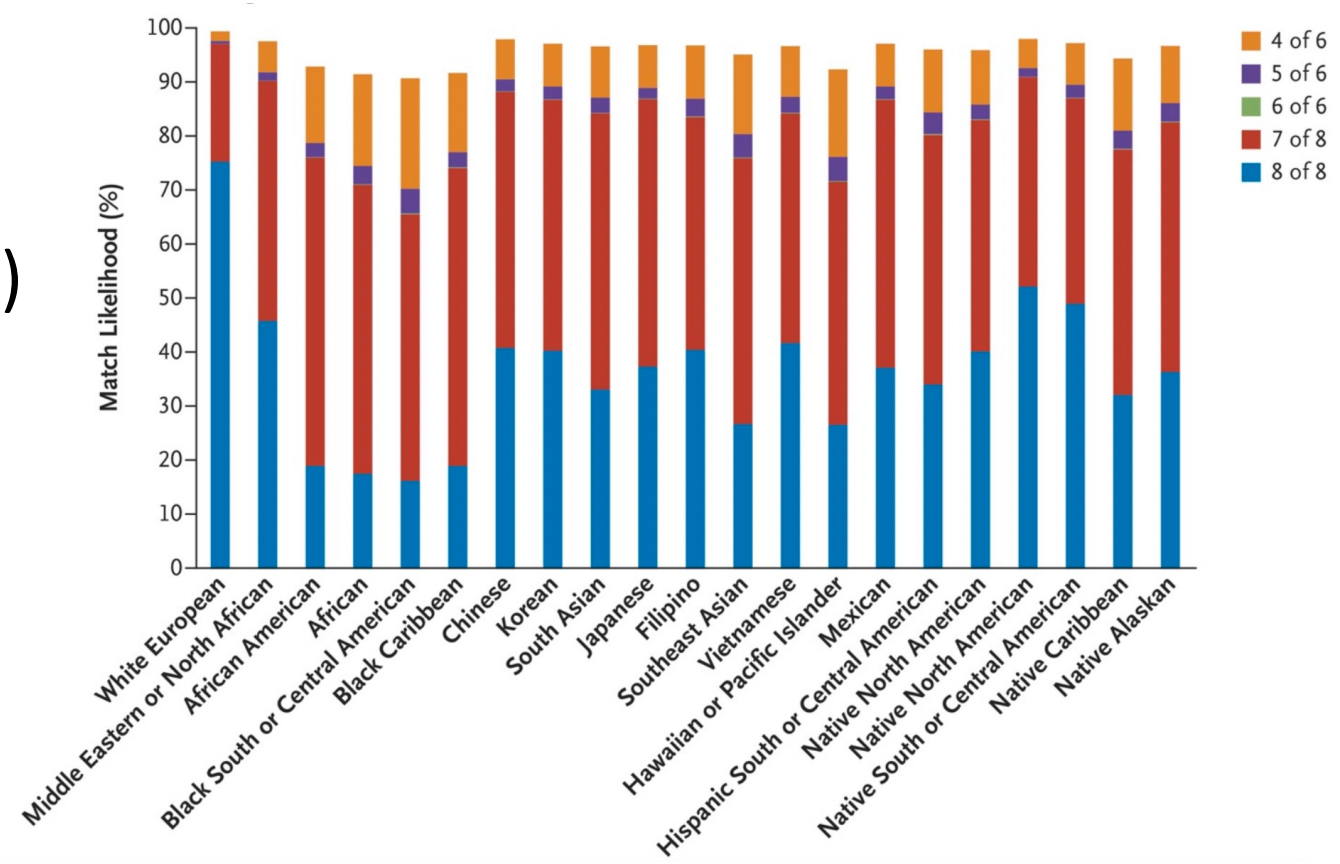
- HLA typing, identifying and evaluating a donor, and collecting the donor's cells can take several weeks

- 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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