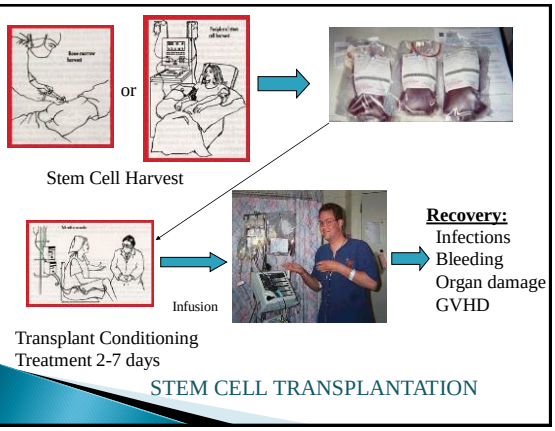
Understanding Bone Marrow Transplant

Where we are now, and What's Coming

AA MDS International Foundation
Indianapolis IN

Luke Akard MD
May 19, 2018



STEM CELL TRANSPLANTATION

What is a marrow stem cell transplant delivering?

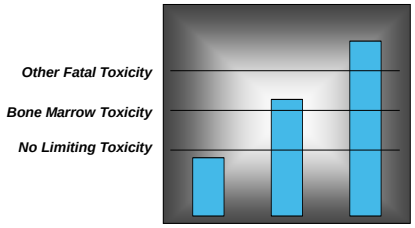
- For many malignancies, there is a dose-response effect for chemotherapy. High doses of treatment can overcome resistance, but at the price of permanent marrow failure. Marrow transplantation overcomes this problem (allogeneic and autologous)
- Allogeneic immune cells have the capacity to attack recipient cells, so establishing donor stem cells in the recipient may well decrease relapse potential (*graft versus leukemia effect*)

What is a marrow transplant delivering? (cont.)

- Bone marrow failure diseases (aplastic anemia) can be cured by providing a source of new marrow
- Certain inherited metabolic diseases can be overcome by marrow transplants from healthy donors by replacing the deficient enzyme

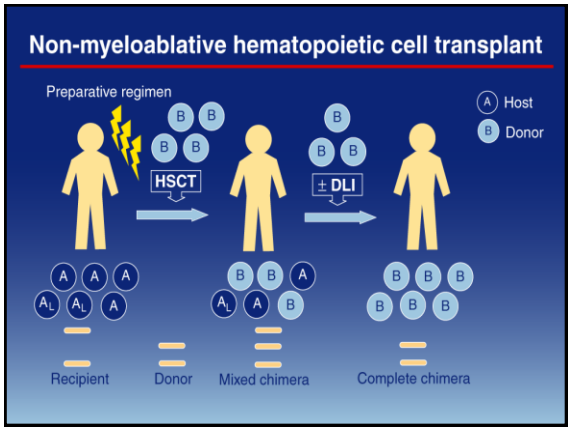
IBMT

DOSE RESPONSE AND CURABILITY OF HEMATOLOGICAL MALIGNANCIES



Transplant conditioning regimen

- High dose treatments-myeloablative
  - Allogeneic and autologous
  - Most common are total body irradiation or busulfan and cyclophosphamide
  - Many other myeloablative alternatives
- Less intensive regimens-NMT or RIT
  - Allogeneic conditioning designed for immunosuppression rather than myeloablation—allow engraftment and graft vs. tumor effect



Applications of SCT

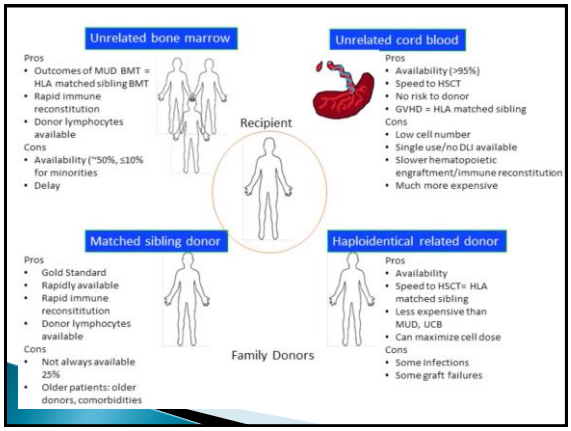
- Replace diseased stem cells (AML, CML, SAA, MDS, Myeloproliferative)
- Repair congenital stem cell defects (SCID, Inborn Errors, Sickle Cell, Thalassemia)
- Overcome chemotherapy cytopenia (AML, NHL, Myeloma, Hodgkins, others)
- Adoptive immunotherapy (GvL, auto-immune Dz)

IBMT

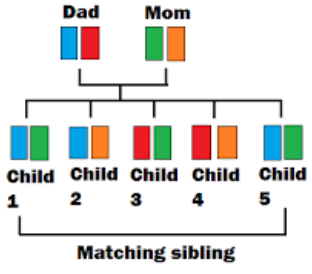
Sources of HSC – The Donor

- Autologous – from the patient
- Syngeneic – from the patient's identical twin
- Allogeneic – from a HLA tissue-matched donor –
  - MSD – matched sibling donor – full brother / sister
  - MUD – matched unrelated donor – a volunteer identified as compatible with the patient – a specific type of allogeneic donor
  - PMRD – partially matched related donor
  - Haploidentical – Half matched family (parent, sibling, child)
  - UCBD – umbilical cord donor (matched or mismatched)

IBMT



HLA Typing



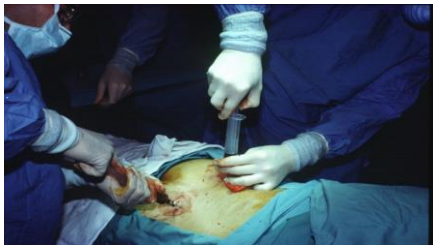
HLA Typing

- HLA system located on chromosome 6
  - Class 1: HLA A, B, C
  - Class 2: DR, DQ, DP
  - With smaller family size, the likelihood of having a sibling match is about 30%
- Molecular diagnostic methods allow improved matching outside of the family
- Alternative donors—matched unrelated donors about 70% find a match
- Alternative donor—umbilical cord donor can find about half the time for adults

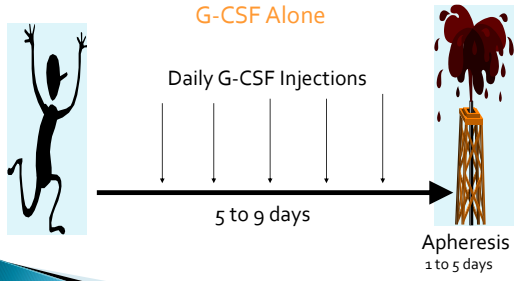
Source of Stem Cells

- Bone Marrow
  Surgical procedure, rapid, not complex, some discomfort
- Peripheral blood
  IV access issues, time consuming, more complex, less discomfort

Iliac Crest BM Aspirations



Mobilization Schema



Peripheral blood stem cell collection by apheresis

Bone marrow vs. Blood stem cells

- Compared to marrow harvest, blood has
  - 10 times more mononuclear cells
  - 5.5 times more CD3+ T-cells
  - 3 times more CD19+ B-cells
  - Similar numbers of CD4+ T-helper cells
  - Higher percentage of CD8+ T-suppressor cells

Hassan HT et al Transpl Immunol 4:319-23, 1996

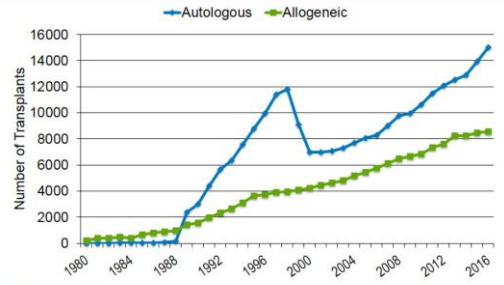
Source of Stem Cells

- Recovery of blood counts is more rapid following peripheral blood stem cell transplants (autologous and allogeneic)
- Probably less chance of tumor contamination with peripheral blood stem cell transplants (autologous)
- More chronic graft versus host disease with peripheral blood transplants (allogeneic) Does this matter?

Blood versus bone marrow

- The incidence of chronic GVHD and chronic infections is higher after peripheral blood transplants.
- This decreases the success rate of low risk leukemia: childhood acute leukemia, first remission AML, and chronic phase CML
- Greater graft vs. disease effect from blood stem cell transplants may increase the success rate of 2nd remission leukemia and other diseases in adults

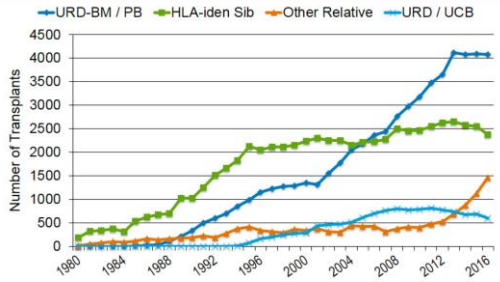
Annual Number of HCT Recipients in the US by Transplant Type



CIBMTR

3

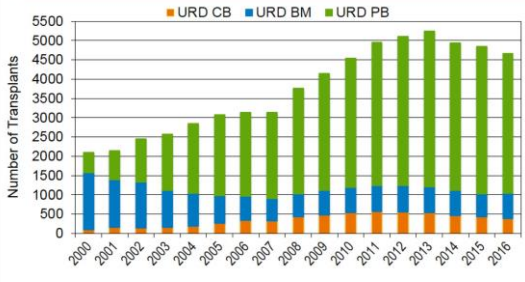
Allogeneic HCT Recipients in the US, by Donor Type



CIBMTR

4

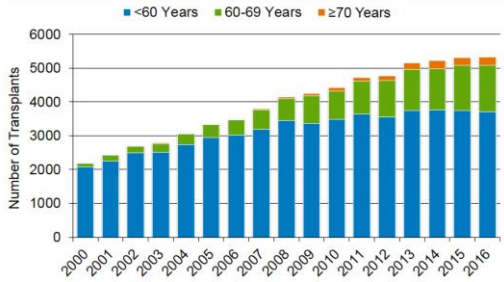
Unrelated Donor Allogeneic HCT in Patients Age ≥18 years



CIBMTR

10

Trends in Allogeneic HCT in the US by Recipient Age^

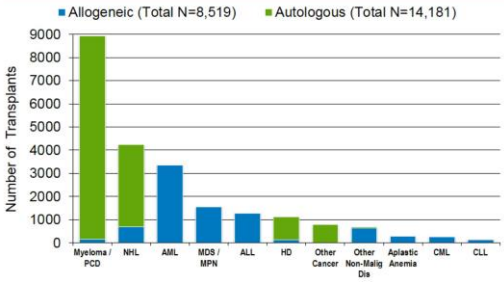


CIBMTR

^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

12

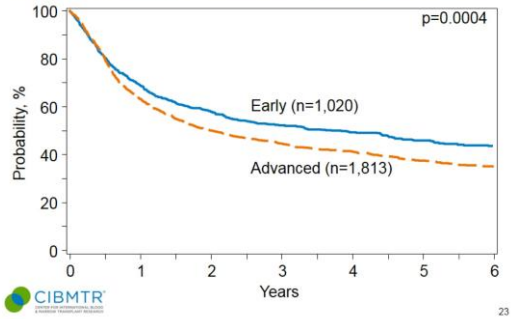
Indications for Hematopoietic Cell Transplant in the US, 2016



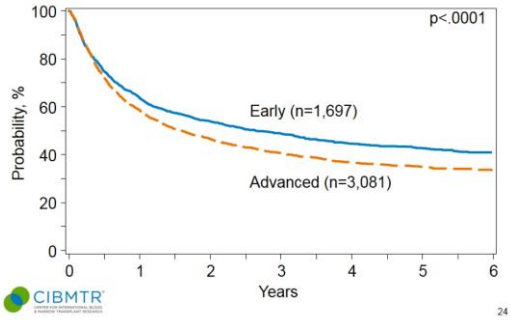
CIBMTR

13

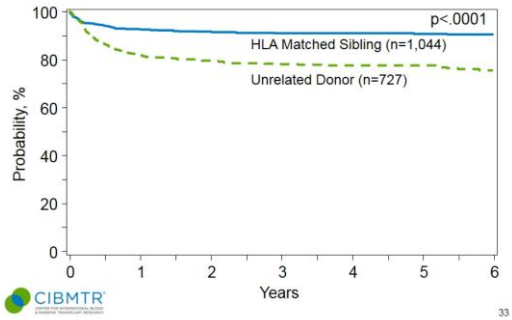
Survival after HLA-Matched Sibling HCT for Myelodysplastic Syndrome (MDS), 2005-2015



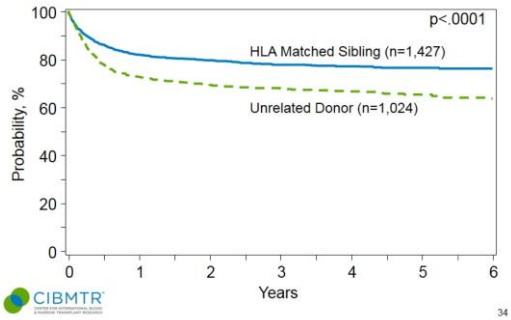
Survival after Unrelated Donor HCT for Myelodysplastic Syndrome (MDS), 2005-2015



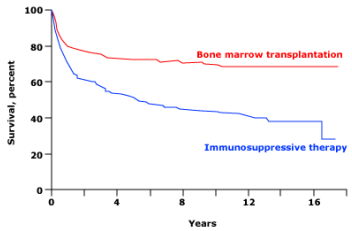
Survival after Allogeneic HCT for Severe Aplastic Anemia, <18 Years, 2005-2015



Survival after Allogeneic HCT for Severe Aplastic Anemia, ≥18 Years, 2005-2015



Aplastic Anemia: Survival after treatment– Bone marrow transplant vs. immunosuppression



Aplastic anemia allogeneic transplantation: haploidentical donor

- Limited number of HLA identical family donors
- Alternative donors include unrelated, umbilical cord blood, and haploidentical related donors
- Few transplants using umbilical donor cells have been performed in adults.
- Most patients will have a haploidentical related donor without HLA sensitization.

Reduced intensity haploidentical BMT with post-transplant cyclophosphamide

- In the USA most people have over 3 potential haploidentical relatives
- Post transplant cyclophosphamide decreases the risk of GVHD
- Engraftment and the risk of GVHD appears acceptable

Johns Hopkins Alternative donor BMT using post transplant cyclophosphamide in SAA

- **·21 patients with refractory SAA (median f/u 24 mos (range 3-72)**
- –Median age: 33 years (range 5-69)
- –15/21 had evidence of clonality (PNH and/or cytogenetic abnormality)
- –18 haplo 1 mmURD(9/10) 2 URD (10/10)
- **·Rapid and consistent engraftment**
- –ANC 15 days Reds 25 days Platelets 28 days
- –Day 60 chimerism 100% in 20/21 patients
- ·One primary graft failure (engrafted with 2nd BMT from different donor)
- **·Excellent Disease Free Survival**
- –All 21 alive, transfusion-independent, without clonality (KPS 100)
- –Acute GVHD grade II-IV 2/21 (9.5%)
- –Extensive chronic GVHD 0/21
- –All off IST

DeZern et al BBMT 2017

Post allogeneic transplant recovery

Complications – Allo BMT

- 1st three weeks (D+21):
  - Anorexia, nausea, vomiting, diarrhea
  - Mucositis
  - Pancytopenia – RBC & platelet transfusions
  - Neutropenic fever
  - Infection – bacterial, viral, fungal
  - Veno-Occlusive Disease (VOD)
  - Graft versus Host Disease (GvHD)

IBMT

Engraftment after SC infusion (days)

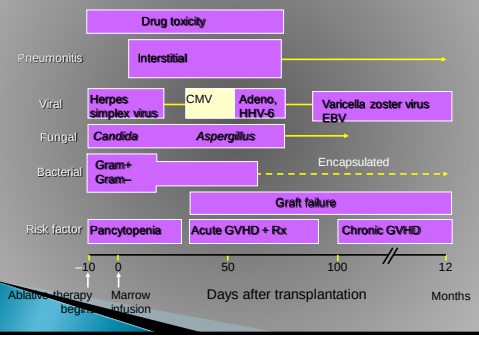
	AGC>500	Plat>20k
Autologous BM (w/o GF)	24	20
Autologous BM (w/ GF)	20	19
Autologous PBSC (w/o GF)	11	11
Autologous PBSC (w/ GF)	10	11
Allogeneic BM (w/o GF)	17	22
Allogeneic PBSC (w/o GF)	14	13

IBMT (JCMM 9: 37, 2005)

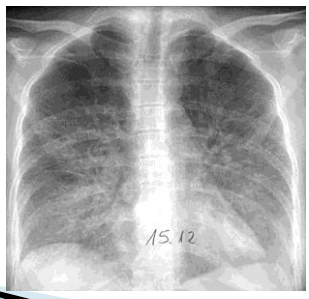
Factors determining immune reconstitution after allogeneic SCT

- Source of stem cells
- Age of donor and recipient
- Numbers of progenitors
- Donor matching
- Bone marrow manipulation/purging
- Intensity of prior treatment
- Presence of GVHD
- GVHD prophylaxis

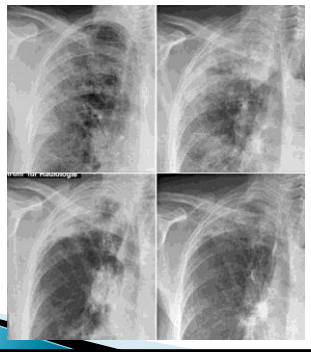
Complications Following Allogeneic BMT



Viral pneumonia



Fungal pneumonia post transplant



Complications – Allo BMT

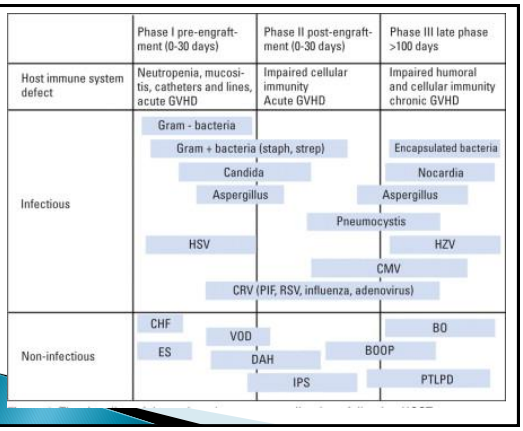
- 1st three months (D+100):
  - Anorexia
  - Cytopenias – RBC & platelet transfusions
  - Infection – viral, fungal
  - Renal insuffuciency
  - High blood pressure
  - Edema
  - Graft versus Host Disease (Acute GvHD)
    - skin, gut, liver

IBMT

Complications - Allo BMT

- Beyond 1st three months (>D+100):
  - Infection – viral
  - Renal insuffuciency
  - High blood pressure
  - Graft versus Host Disease (Chronic GvHD)
    - skin, gut, liver, lungs, joints
  - Relapse of disease

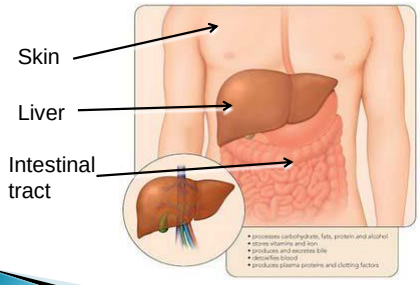
IBMT



Graft versus host disease

- Immune cells transplanted from a donor (graft) recognize the transplant recipient (host) as foreign causing an immune attack that causes disease in the transplant recipient.
- Acute: usually during the first 3 months, skin, liver, gastrointestinal targets
- Chronic: chronic reactions of the skin, GI tract, liver, mouth, eyes, joints usually after 3 months
- Methods to prevent GVHD are always used and include medications such as cyclosporine, tacrolimus, methotrexate, and mycophenolate

Targets of Acute Graft vs. host disease



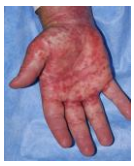
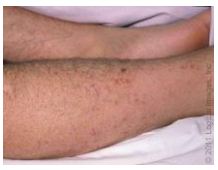
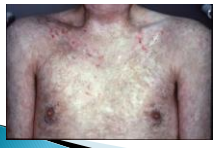
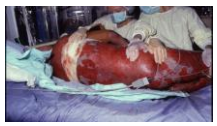
GVHD Risk Factors

- Degree of HLA match, sibling vs. unrelated
- Donor/recipient gender difference
- Transplant regimen intensity/TBI
- Method used to prevent GVHD
- Cell source: bone marrow, peripheral blood, umbilical cord blood
- Age of the donor/recipient

GVHD management

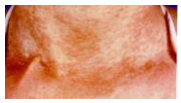
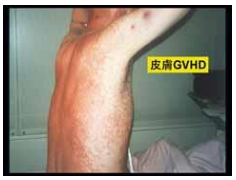
- In spite of preventative efforts, many patients develop acute GVHD and need treatment.
- Treatment can be directed at both the target organ (topical steroids to the skin, oral non-absorbable steroids to the gastroinestinal tract) and be systemic either IV or oral medications. Steroids such as prednisone are the backbone of all GVHD treatments
- Many responses are only partial, and additional drug treatments or non-drug treatments such as photopheresis are used.

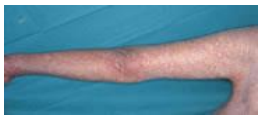
Acute Graft vs Host Disease

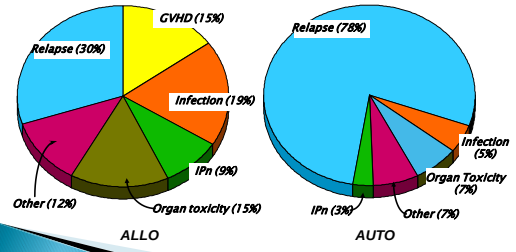
IBMT

Chronic GVHD

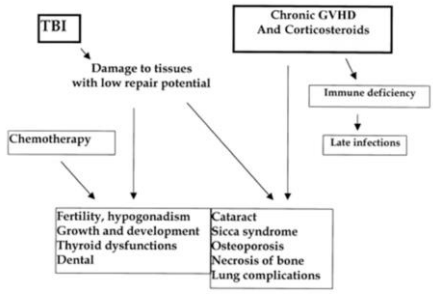



CAUSES OF DEATH AFTER TRANSPLANTS



Late Effects after Allogeneic BMT



Long term follow-up: Allogeneic

- Immunizations starting at 1 year if off immunosuppression
- Relapse
- GVHD and complications
- Hormone issues
  - Thyroid, estrogen deficiencies
  - Osteopenia/porosis
- Secondary malignancies
  - Skin cancer, head and neck cancer, breast cancer, lymphoma
- Coronary artery disease?

TABLE 2. Screening and Preventive Practices for Long-Term Survivors After AHSCT

Organ	Screening Consideration
Cardiac or vascular	Education of heart-healthy lifestyle Endocarditis prophylaxis Early interventions for cardiovascular problems Monitor ferritin at one year for iron overload.
Endocrine or fertility	Monitor thyroid function test. Referral to appropriate specialist Birth control if indicated
Immune system	Immunization *Pneumocystis jirovci* pneumonia and antiviral prophylaxis Monitor for encapsulated organisms.
Liver	Monitor liver function tests. Consider liver biopsy if indicated. Viral load monitoring and liver biopsy in patients with known hepatitis B or C Monitor serum ferritin at one year.
Musculoskeletal	Consider chronic graft-versus-host disease changes. Encourage activity. Vitamin D and calcium replacement Consider bisphosphonate therapy. Consider dual photon densitometry at one year.
Respiratory	Constant physical examination for pulmonary complications Smoking cessation
Ocular	Schedule regular ophthalmology examinations.
Oral	Schedule regular dental examinations. Ongoing oral examinations
Renal	Aggressively manage hypertension. Monitor renal function.
Secondary malignancies	Educate patients regarding risks adding to cancer diagnosis (e.g., smoking, sun exposure). Follow general population recommendations for cancer screening. Consider second malignancies based on symptoms. Monitor blood work on a regular basis, specifically complete blood cell levels.

AHSCT—autologous hematopoietic stem cell transplantation
Note. Based on information from Majhail & Rizzo, 2013; Savani et al., 2011.

Best Transplant Outcome