Hematopoietic Cell Transplantation as Treatment for Blood Cancers: The Team Approach

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LEARNING OBJECTIVES

- Describe the types of hematopoietic cell transplantation used in the treatment of blood cancers, including autologous, allogeneic and reduced-intensity allogeneic stem cell transplantation
- Identify the methods of stem cell collection used in patients with blood cancers.
- Explain the overarching goals of hematopoietic cell transplantation for all types of blood cancers
- Explain hematopoietic cell transplantation as a treatment option for blood cancers
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of hematopoietic cell transplantation
- Describe the healthcare professional's role in managing patients with HCT

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FACULTY

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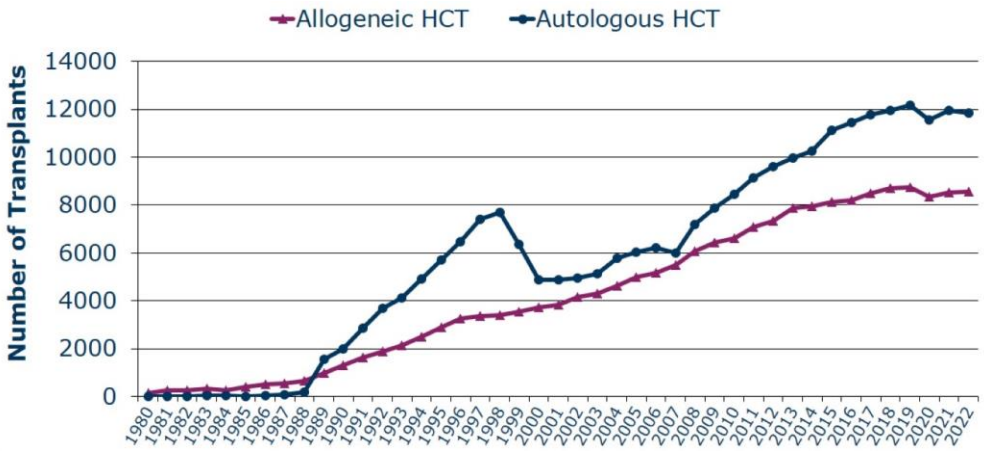
Objectives

- Describe the types of hematopoietic cell transplantation used in the treatment of blood cancers, including autologous, allogeneic, and reduced-intensity allogeneic stem-cell transplantation
- Explain the choice of donor type, graft source and conditioning intensity and how those are tailored to individual patients
- Explain the overarching goals of hematopoietic cell transplantation as a treatment option for blood cancers
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of hematopoietic cell transplantation
- Describe the team-based approach in treating patients with HCT

4

Annual Number of HCT Recipients in the US



Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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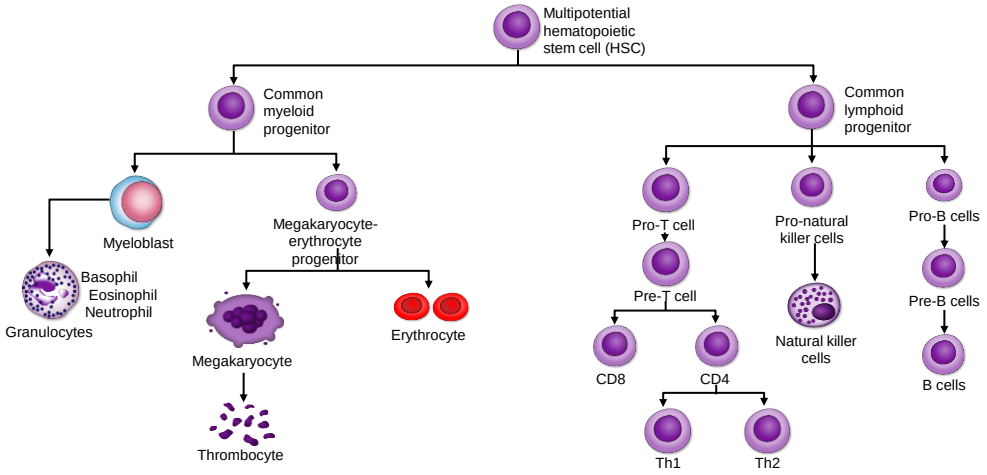
Basic Principle Behind Hematopoietic Cell Transplantation



https://en.wikipedia.org/wiki/Haematopoiesis#/media/File:Hematopoiesis_simple.svg

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History of HCT

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

E. Donnall Thomas, M.D.,† Harry L. Lochte, Jr., M.D.,‡ Wan Ching Lu, Ph.D.,§ and Joseph W. Ferrebee, M.D.¶

Cooperstown, New York, and Boston, Massachusetts

After a lethal dose of radiation in rodents,[1] canines[2] or primates,[3] the destroyed bone marrow may be repopulated by intravenous infusion of cellular suspensions of marrow taken from healthy isologous, homologous[4] and, in some cases, heterologous[5] donors. Effective cells for these infusions may be stored by the Polge technic of freezing to −80°C. in glycerol.[6] Hosts seeded with donor marrow have some of the immunologic characteristics of the donors, and in some circumstances will take and hold homografts of other organs from them.[7]

Since cases of radiation disaster may occur, and since bone-marrow deficiency from radiation or chemotherapy does occur in the normal course of clinical medicine, an effort has been made to determine the availability and usefulness of bone-marrow infusions for the treatment of these conditions in man.

*From the Mary Imogene Bassett Hospital (affiliated with Columbia University), Cooperstown, and the Children's Cancer Research Foundation, Children's Medical Center, Boston, and Harvard Medical School. Supported by research grants (C-2643 and H-607) from the United States Public Health Service and by contract AT (30-1)-2005 from the United States Atomic Energy Commission.

†Associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; physician-in-chief, Mary Imogene Bassett Hospital.

‡Public Health Service Research Fellow, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

§Research assistant, Department of Pathology, Harvard Medical School; research assistant, Division of Laboratories and Research, Children's Medical Center.

¶Associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; research physician, Mary Imogene Bassett Hospital.

Experimental Considerations

Bone marrow was collected from fetal and adult cadavers, from ribs removed at surgery and from aspiration biopsy of the ilium. Irrespective of source, it was passed repeatedly through a stainless-steel screen[8] and broken into a smooth cellular suspension, and the fat, as a rule, removed by centrifugation. The cells, resuspended in tissue-culture fluid and serum, were administered intravenously or frozen in glycerol and stored at −80°C.

One may assess permissible periods of post-mortem

Thomas E et al. *N Engl J Med.1957*;257:491-496.

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Types of HCT – Autologous vs Allogeneic

Distinct Therapies:

1. Autologous HCT (patient's own stem cells) = High-dose chemotherapy with stem-cell rescue
   - Purpose is to allow administration of high-dose chemotherapy
   - Benefit relies on chemo-sensitivity of cancer
   - Curative in aggressive lymphoma; extends survival in myeloma
2. Allogeneic HCT (donor stem cells)
   - Combines chemotherapy/radiotherapy and immunotherapy
   - Purpose is **curative** by combining chemotherapy/radiotherapy with immunotherapy
   - Effective across multiple blood cancers, including in patients with chemo-refractory disease
   - Immunotherapeutic effect induced by donor T cells in the stem cell graft:
     - Graft-vs-tumor (GVT) → Prevents relapse
     - Graft-vs-host (GVH) → Toxicity (GvHD)
3. Syngeneic HCT – From identical twin; similar to autologous transplant (no GVT, no GVH)

Appelbaum F. *N Engl J Med.* 2007;357:1472-1475.

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Sources of Hematopoietic Stem Cells

Bone Marrow (BM)

↓

Stem cells removed from pelvic bone under general anesthesia

Peripheral Blood Stem Cells (PBSC)

↓

Stem cells mobilized with growth factors and collected by apheresis

Umbilical Cord Blood (UCB)

↓

UCB contains stem cells and naive T cells

- Graft contains stem cells, lymphocytes (primarily T cells) and other cell types (e.g., dendritic cells, NK cells)
- Choice of graft is based on disease type, disease status, and donor availability

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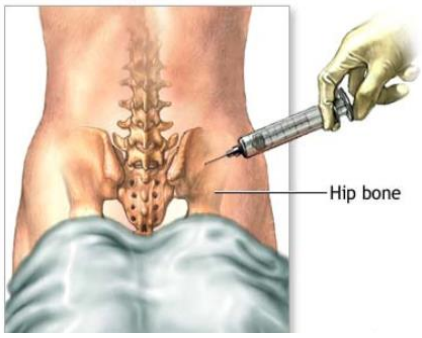
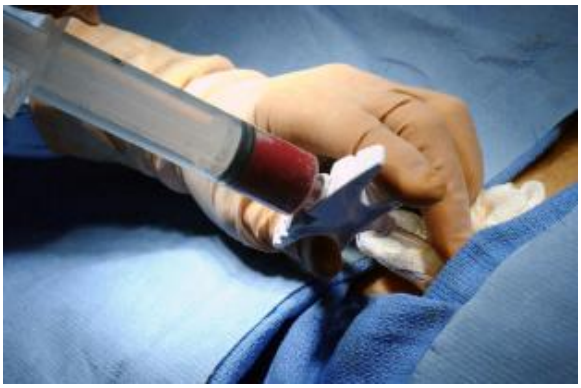
Graft Sources

Bone Marrow Harvest





- Despite high volume (up to 2L), stem-cell and T-cell numbers are generally low
- Requires operating room procedure and general anesthesia

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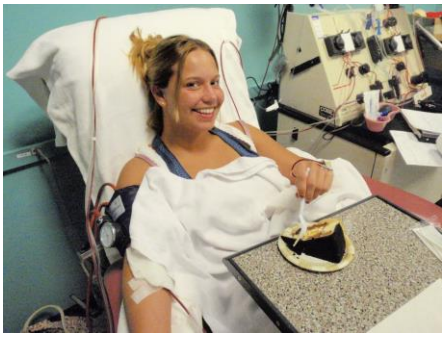
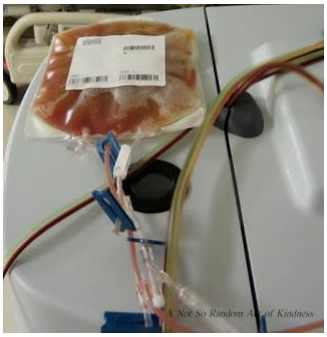
Graft Sources

Peripheral Blood Stem Cells





- High numbers of stem cells and T-cells can be collected
- Requires mobilization with high-dose granulocyte-colony stimulating factor (G-CSF) and other mobilizing agents

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Graft Sources

Umbilical Cord Blood

- HLA matching criteria are liberal
- Stem-cell numbers are low
  - Requires 2 UCB units to engraft an adult safely
- Potent GvT effect
- Low risk for chronic GvHD
- Slow engraftment
- Slow immune reconstitution

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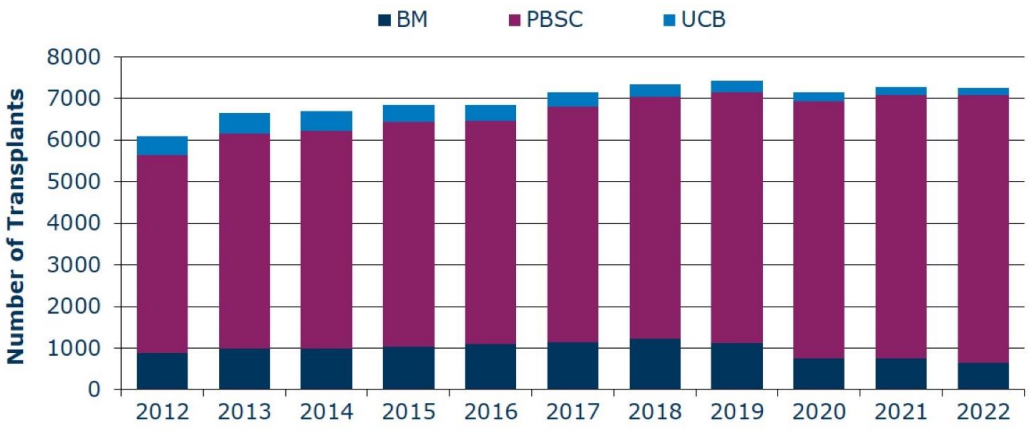
Trends in Allogeneic Transplants by Graft Source - Adults



Abbreviations: BM, bone marrow; PBSC, peripheral blood stem cells; UCB, umbilical cord blood.

Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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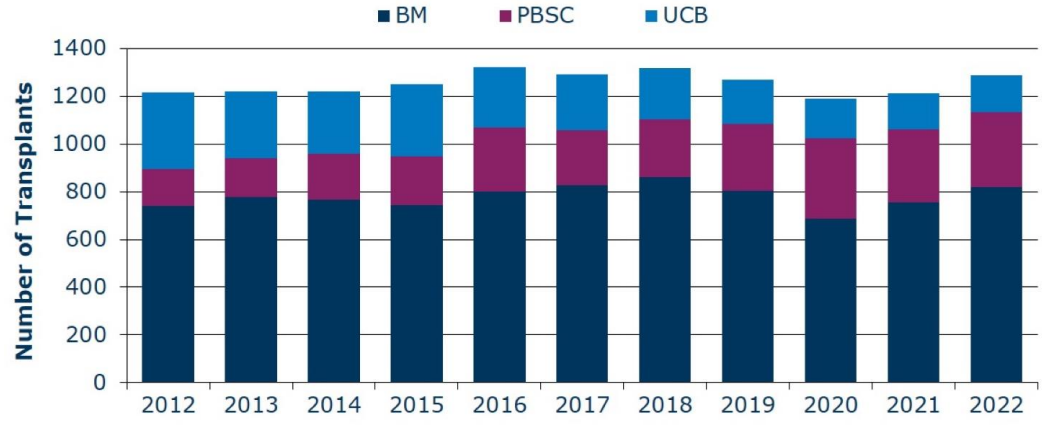
Trends in Allogeneic Transplants by Graft Source - Pediatrics



Abbreviations: BM, bone marrow; PBSC, peripheral blood stem cells; UCB, umbilical cord blood.

Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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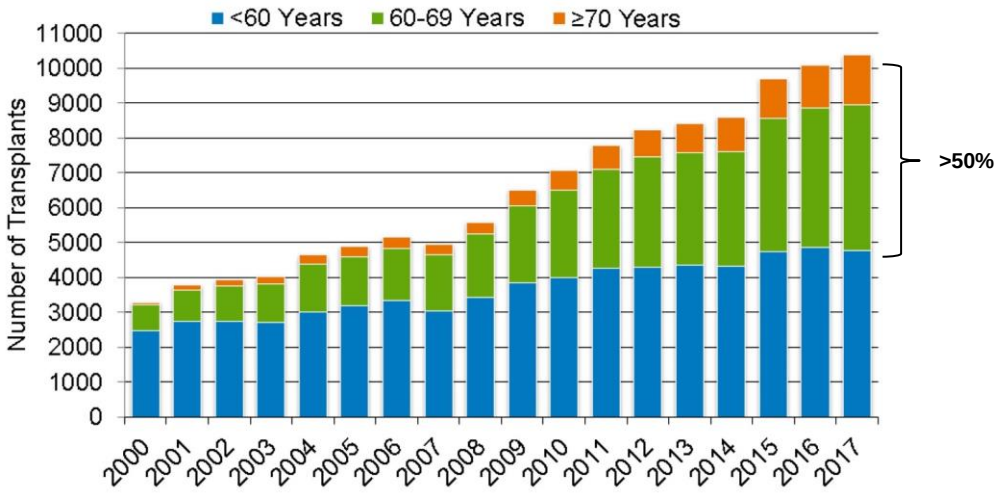
Trends in Autologous HCT for Blood Cancers by Age



D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2018. Available at https://www.cibmtr.org

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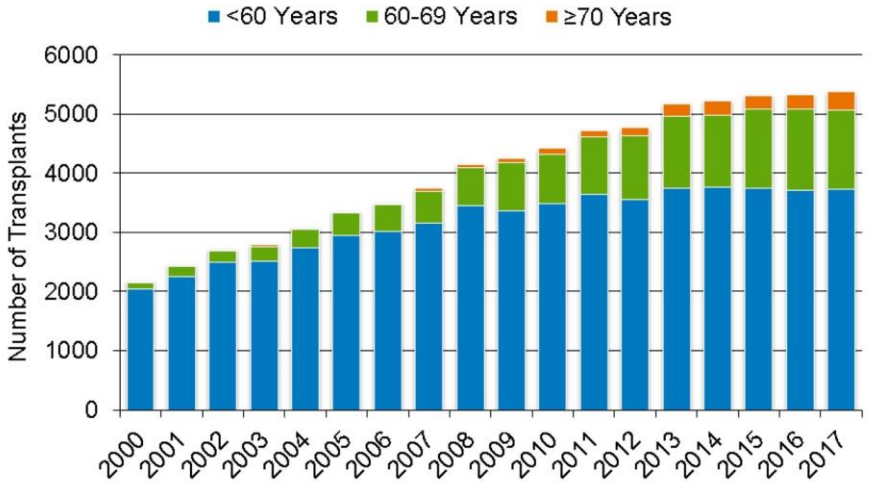
Trends in Allogeneic HCT for Blood Cancers by Age



D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2018. Available at https://www.cibmtr.org

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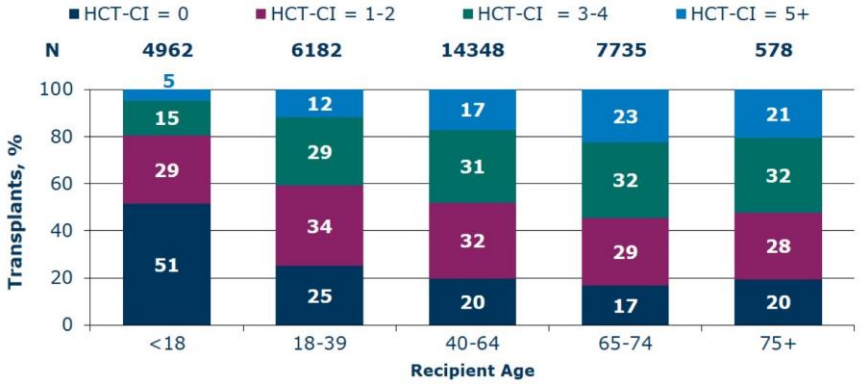
Comorbidities in Allogeneic HCT Recipients

HCT-CI Comorbidity	Score
Arrhythmia	1
Heart	1
Cerebrovascular disease	1
Diabetes	1
Hepatic disease (mild)	1
Infection	1
Inflammatory bowel disease	1
Obesity	1
Depression	1
Peptic ulcer	2
Pulmonary disease (moderate)	2
Renal failure (moderate/severe)	2
Rheumatologic disorder	2
Heart valve disease	3
Hepatic disease (moderate/severe)	3
Prior solid tumor	3
Pulmonary disease (severe)	3



Abbreviation: HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index.

Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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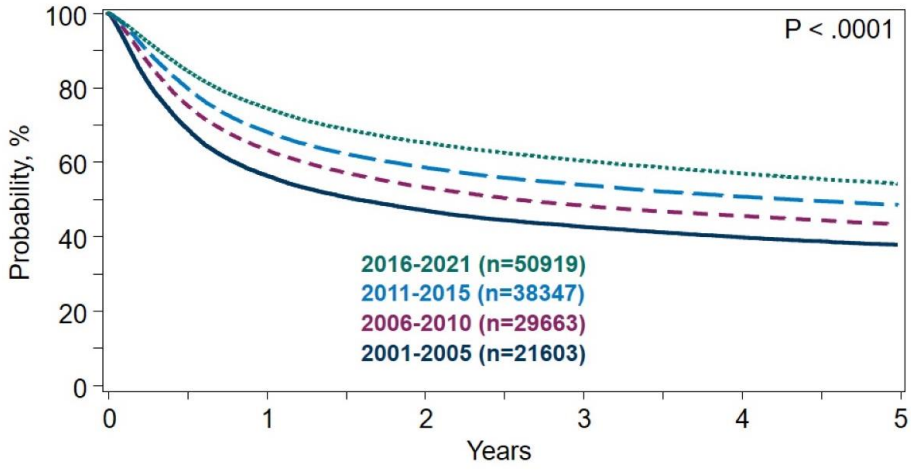
Improved Survival After Allogeneic HCT



Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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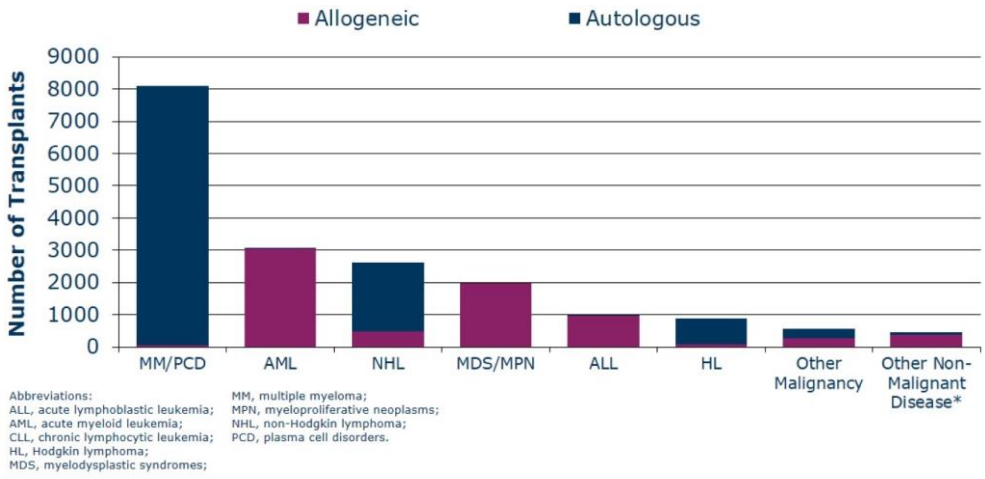
Indications for HCT in the US (2022)



Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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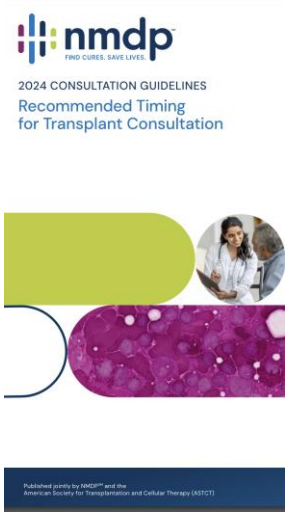
Indications for HCT in Blood Cancers


Biol Blood Marrow Transplant 26 (2020) 1247–1256
ELSEVIER
Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org
ASTCT
American Society for Transplantation and Cellular Therapy

Guideline

Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy

Abraham S. Kanate[1,*], Navneet S. Majhail[2], Bipin N. Savani[3], Christopher Bredeson[4], Richard E. Champlin[5], Stephen Crawford[6], Sergio A. Giralt[7], Charles F. LeMaistre[8], David I. Marks[9], James L. Omel[10], Paul J. Orchard[11], Jeanne Palmer[12], Wael Saber[13,14], Paul A. Veys[15], Paul A. Carpenter[16], Mehdi Hamadani[13,14]



Kanate AS et al. *Transplant Cell Therapy*. 2020;26:1247-1256.
https://bethematchclinical.org/medical-education-and-research/materials-catalog/hct-guidelines-for-consultation-timing/

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Common Indications for HCT in Blood Cancers

Autologous	Allogeneic

• **Myeloma**
  • Newly diagnosed
  • Relapsed
• **DLBCL and Hodgkin lymphoma**
  • Relapsed/refractory
• **Mantle cell lymphoma**
  • CR1
  • Relapsed
• **T-cell lymphoma**
  • CR1
  • Relapsed
• **Germ cell tumors**
  • Relapsed/refractory
	• **AML**
	  • CR1 – other than favorable risk
	  • >CR1
	• **ALL**
	  • Based on risk factors and initial treatment
	• **CML**
	  • Beyond chronic phase
	• **MDS**
	  • Intermediate/high risk
	• **MF**
	  • Intermediate/high risk
	• **Lymphoma and CLL**
	  • Relapsed

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; MDS, myelodysplastic syndrome; MF, myelofibrosis

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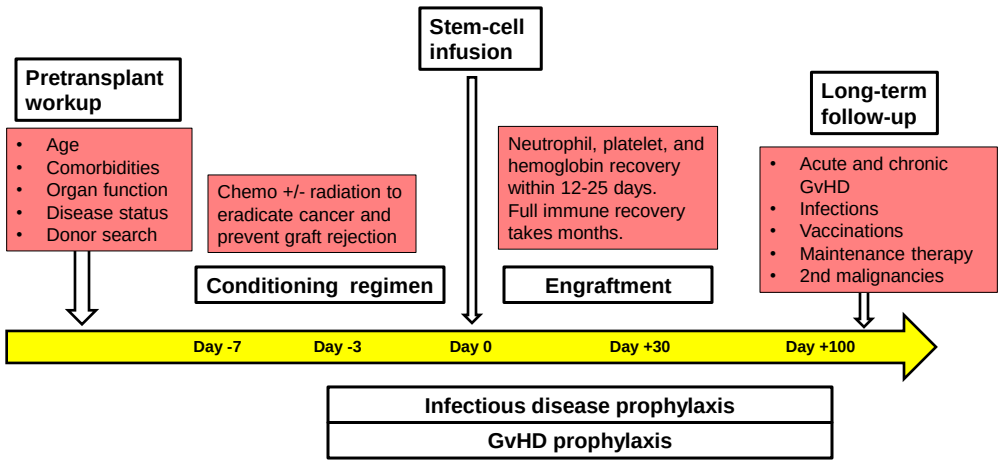
Overview of HCT



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Role of the HCT Pharmacist

- Medication management, including specialized knowledge of high-dose antineoplastics and antimicrobials
- Chemotherapy and medication counseling
- Symptom management
- Therapeutic drug monitoring – for example, tacrolimus (Prograf®), cyclosporine (Neoral®, Gengraf®, Sandimmune®), busulfan (Busulfex®), and antifungals
- Discharge planning and transitions of care
- Policy and guideline development
- Education of team members, trainees, patients, and caregivers
- Evidence-based program development and evaluation

Clemmons AB et al. *Biol Blood Marrow Transplant*. 2018;24:914-922.

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AUTOLOGOUS STEM CELL TRANSPLANT

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Patient Case – John, 70 YO Male With Myeloma

- Past medical history of hypertension and diabetes
- Presented with anemia, lytic lesions, and renal failure
- Workup revealed 20% lambda-restricted plasma cells in bone marrow
- No high-risk cytogenetics
- Received Dara-RVD x 4 cycles, achieving VGPR
- Residual renal injury with serum creatinine 1.8 mg/dL
- ECOG performance status 1
- Referred for transplant evaluation

RVD: lenalidomide (Revlimid®), bortezomib (Velcade®), and dexamethasone (Decadron®)
ECOG, Eastern Cooperative Oncology Group; VGPR: very good partial response;

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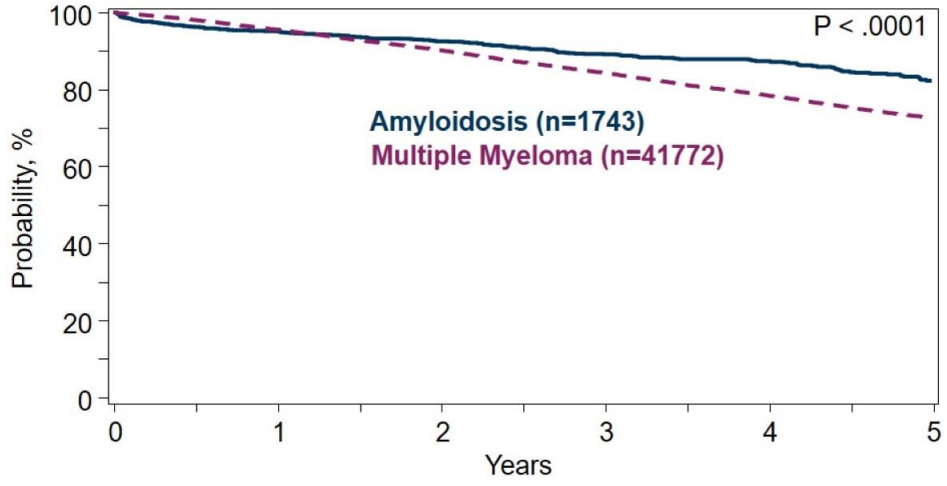
Survival After Autologous HCT for Myeloma (2016-2021)



Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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Pre-Transplant Evaluation

- Past medical history
- Cardiac assessment (TTE)
- Pulmonary assessment (PFTs)
- Renal and liver function (labs)
- Infectious disease markers – rarely a contraindication to transplant. Active infections should be treated to resolution.
- Psychosocial evaluation – identify potential barriers for compliance and adequate caregiver support
- Disease status assessment
- Fertility counseling and preservation whenever relevant and possible

PFT, pulmonary function tests; TTE, Transthoracic echocardiogram

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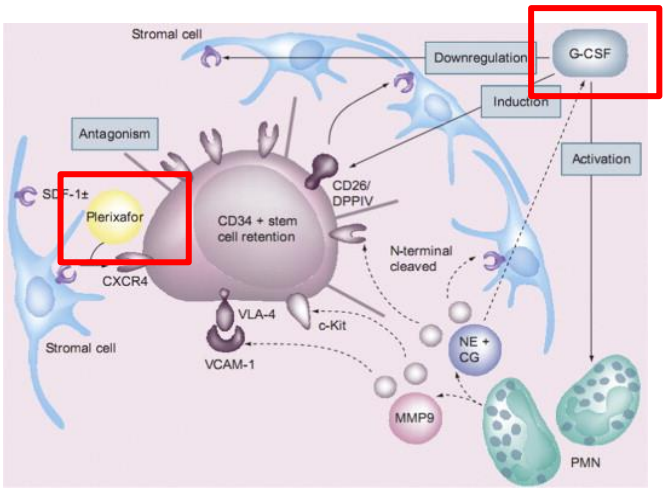
Methods for Stem Cell Mobilization

- Peripheral blood is the most common source of stem cells for autologous HCT
- Stem cells "mobilized" out of the bone marrow niche and into the peripheral blood using
  - Colony stimulating factors
    - High-dose granulocyte colony-stimulating factor (G-CSF) 10 mcg/kg/day
    - Plerixafor (Mozobil®) or motixafortide (Aphexda®) (CXCR4 antagonist) + G-CSF
  - +/- non-transplant doses of chemotherapy prior to G-CSF
    - Typically, a salvage chemotherapy regimen OR single-agent cyclophosphamide (Cytoxan®, Neosar®)



Fruehauf S et al. *Biol Blood Marrow Transplant*. 2010;16:1629-1648.

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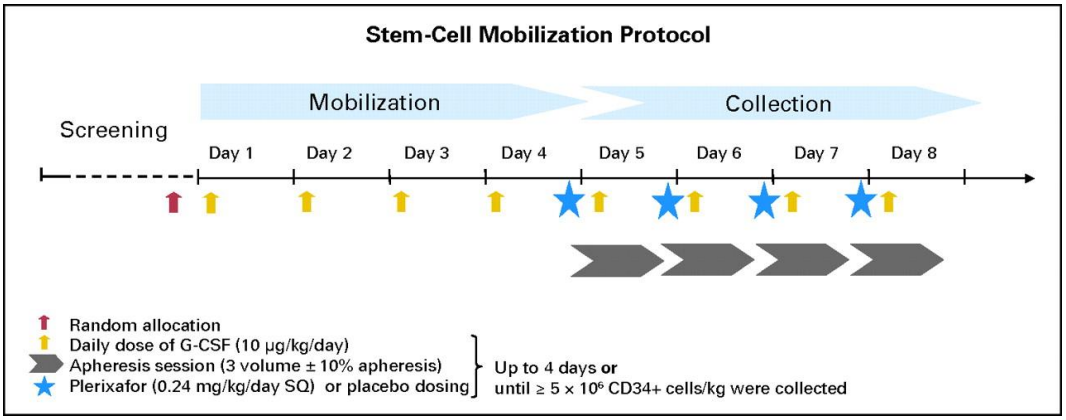
Stem-Cell Mobilization



Mozobil® is the brand name for plerixafor.
DiPersio JF et al. *J Clin Oncol*. 2009;27:4767-4773.

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Stem-Cell Mobilization

- Mobilization failure rates with current strategies are < 10%
- Factors which can negatively influence a patient's ability to mobilize
  - Bone marrow involvement with tumor
  - Fibrotic bone marrow
  - History of pelvic or abdominal irradiation
  - Bone marrow hypocellularity
  - Non-Hodgkin Lymphoma (vs. myeloma)
  - Prior exposure to chemotherapy
    - E.G. Alkylating agents, nitrosoureas, and lenalidomide
  - Older age (> 60-70 years) and low baseline platelet count (< 150 x 10^9/L)
  - Infection, iron overload, diabetes

Giralt S et al. *Biol Blood Marrow Transplant*. 2014; 20(3):295-308.
Gertz MA. *Br J Haematol*. 2010;150(6):647-662.
Kurnaz F. *Transfus Apher Sci*. 2015;53(1):3-7.

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Autologous Transplant Generally Uses Chemotherapy Conditioning

- Melphalan (Alkeran®, Evomela®) (multiple myeloma)
  - Melphalan (Alkeran®, Evomela®) 200 mg/m^2 (single or split dose)
  - Dose reductions (usually melphalan [Alkeran®, Evomela®] 140 mg/m^2) based on risk factors

- BEAM (lymphoma)
  - Carmustine (BiCNU®) 300 mg/m^2 IV x1 (day – 6)
  - Etoposide (VePesid®, Toposar®, Etopophos®) (VP-16) 100 mg/m^2 IV BID x 4 days (day –5 to day –2)
  - Cytarabine (Cytosar-U®) (Ara-C) 200 mg/m^2 IV BID x 4 days (day –5 to day –2)
  - Melphalan (Alkeran®, Evomela®)) 140 mg/m^2 IV x 1 (day –1)

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Day 0: Procedure for Transplant

- Day of infusion of stem cells referred to as “day 0”
- Pre-medications: acetaminophen, diphenhydramine
- Cells infused via central line and infusion time determined by volume
- Well tolerated
- Possible DMSO toxicity during infusion with cryopreserved cells
  - Nausea
  - Garlic-like odor from recipient
  - Bradycardia
  - Rare anaphylaxis

DMSO, Dimethyl sulfoxide

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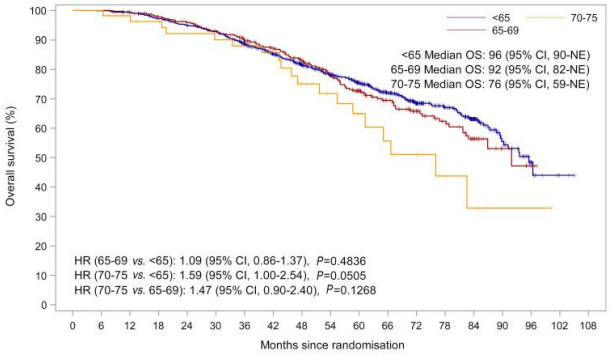
Major Complications of Autologous HCT

- Mortality is low
- Chemotherapy-related side effects
- Infections
- Engraftment syndrome
- Immune reconstitution



Pawlyn C, et al . Autologous stem cell transplantation is safe and effective for fit older myeloma patients: exploratory results from the Myeloma XI trial. Haematologica. 2022 Jan 1;107(1):231-242.

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Chemotherapy Side Effects

Chemotherapy Agent	Dose Limiting Toxicities	Acute Toxicities
Carmustine (BiCNU®)	Hepatic, Pulmonary	Headaches, nausea/vomiting, seizures
Cytarabine (Ara-C®)	Neurologic	Mucositis, conjunctivitis, pulmonary edema
Etoposide(VePesid®, Toposar®, Etopophos®)	Gastrointestinal	Hypotension, acidosis, mucositis, skin rash
Melphalan (Alkeran®, Evomela®)	Gastrointestinal	Nausea/vomiting, mucositis, pulmonary toxicity

Cancer Chemotherapy & Biotherapy: Principles & Practices, 4th Edition.

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Supportive Care: Mucositis

- Prevention
  - Cryotherapy for melphalan (Alkeran®, Evomela®)
    - Before, during, and after infusion → shown to decrease severity of mouth sores
    - Vasoconstriction→ decreased blood flow to oral mucosa
  - Oral hygiene
    - Sodium bicarbonate rinses, Biotene®, and/or Magic Mouthwash
- Management
  - Pain control requiring opioids like morphine or hydromorphone – some requiring PCA
  - Sucralfate suspension, acid-reducing agents (proton pump inhibitor, H2-antagonist)

PCA: Patient Controlled Analgesia

Lilleby K, et al. *Bone Marrow Transplant*. 2006;37:1031–1035.

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Supportive Care: Nausea and Vomiting

- Most conditioning regimens are considered **moderate or high emetic risk** and may be dose-related
- Prevention is KEY
- Common agents for prophylaxis in varying combinations
  - 5-HT3 antagonist – i.e. ondansetron (Zofran®), palonosetron (Aloxi®)
  - Corticosteroids – i.e. dexamethasone (Decadron®)
  - NK-1 receptor antagonist – i.e. fosaprepitant/aprepitant (Emend for Injection®)
- Agents for breakthrough and delayed nausea/vomiting
  - Ondansetron (Zofran®)
  - Prochlorperazine (Compazine®) or metoclopramide (Metozolv ODT®, Reglan®)
  - Lorazepam (Ativan®)
  - Scopolamine patch (Transderm Scop®)
  - Olanzapine (Zyprexa®)
  - Dronabinol (Marinol®)

NCCN.Antiemesis.V1.2019.

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Supportive Care: Diarrhea

- Potential causes of diarrhea
  - Infection (e.g., *Clostridium difficile*)
  - Chemotherapy
  - Antimicrobials
- Manage any infectious causes as appropriate
- Medications for non-infectious diarrhea
  - Loperamide (Imodium®)
  - Diphenoxylate/atropine (Lomotil®)
  - Opium tincture
  - Octreotide (Sandostatin®)

Richardson G, et al. *J Oncol Pharm Practice*. 2007;13:181–198.
Benson A.B, et al. *J Clin Oncol*. 2004;22:2918-2926.
Zidan J, et al. *Annals of Oncology*. 2001;12:227-229.

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Infection Prevention

Pathogen Type	Recommended Prophylaxis	Duration of Prophylaxis
Bacterial	Levofloxacin (Levaquin®) 500 mg daily Ciprofloxacin (Cipro®, Cipro XR®) 500 mg Q12H	Until resolution of neutropenia (i.e. ANC > 500)
Fungal	Fluconazole (Diflucan®) 400 mg daily	Until resolution of neutropenia (i.e. ANC > 500)
Viral	Acyclovir (Zovirax®) 400-800 mg Q12H (oral) Acyclovir (Zovirax®) 250 mg/m^2/dose Q12H (IV) Valacyclovir (Valtrex®) 500 mg Q12H	At least 12 months post-transplant
Hepatitis B*	Entecavir (Baraclude®) 0.5 mg daily Lamivudine (Epivir®) 100 mg daily	At least 6 months post-transplant
Pneumocystis jiroveci (PCP)/Toxoplasmosis*	TMP/SMX DS 1 tablet TIW Atovaquone 1 (Mepron®) 500 mg daily Dapsone (Aczone®)100mg daily Pentamidine (Pentam®) 4 mg/kg Q28 days	At least 6 months post-transplant

*In select patients
ANC: absolute neutrophil count; TMP/SMX: trimethoprim-sulfamethoxazole; TIW: three times a week; DS: double strength

Practice varies by institution
Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

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Infection Prevention

- Other Infectious Considerations:
  - **Tuberculosis**: consider prophylaxis with isoniazid in patients at increased risk of reactivation
  - **Strongyloides**: empiric treatment if pre-transplant screening is positive for *Strongyloides stercoralis* or unexplained eosinophilia with recent travel
    - Ivermectin 200 mcg/kg x 2 days (repeat two weeks later)

- Infection Control:
  - Protective isolation and room ventilation (≥ 12 air exchanges per hour, HEPA filters, positive air pressure
  - Chlorhexidine bathing
  - Hand hygiene, intravascular catheter care, food safety, avoid plants and flowers

Practice varies by institution

Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

39

Engraftment Syndrome

- Reported incidence varies depended on criteria used (more stringent ~10%, wider criteria ~70%)
  - Amyloidosis incidence ~25%
- Clinical syndrome occurring during neutrophil recovery with manifestations reminiscent of capillary leak syndrome
- Definition: Must meet all three major criteria OR two major criteria and one or more minor criteria within 96 hours of engraftment below:

Major Criteria	Minor Criteria
• Temperature of ≥ 38.3˚ C with no identifiable infectious etiology • Erythrodermatous rash involving more than 25% of body surface area; not attributable to a medication • Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia	• Hepatic dysfunction (total bilirubin ≥ 2 mg/dL or transaminase levels ≥ 2 x ULN) • Renal insufficiency (serum creatinine ≥ 2x baseline) • Weight gain (≥ 2.5% of baseline body weight) • Transient encephalopathy unexplainable by other causes

Spitzer TR. *Bone Marrow Transplant*. 2001;27(9):893–898.
Carreras E, et al. *Bone Marrow Transplant*. 2010;45(9):1417–1422.
Maiolino A, et al. *Bone Marrow Transplant*. 2003;31(5):393–397.

40

Engraftment Syndrome Management

- Prophylaxis: prednisone 0.5 mg/kg starting day +7
- Mild engraftment syndrome – not usually treated
  - Transient low-grade fevers
  - Limited rash
- Treatment of progressive or symptomatic engraftment syndrome, particularly with pulmonary involvement
  - Methylprednisolone (Solu-Medrol®) 1-2 mg/kg IV x 3 days
  - Rapid steroid taper thereafter
- Highly steroid-responsive

Spitzer TR. *Bone Marrow Transplant*. 2015;50:469-475.

41

ALLOGENEIC STEM CELL TRANSPLANT

42

Patient Case – Doris, 25 YO Female With AML

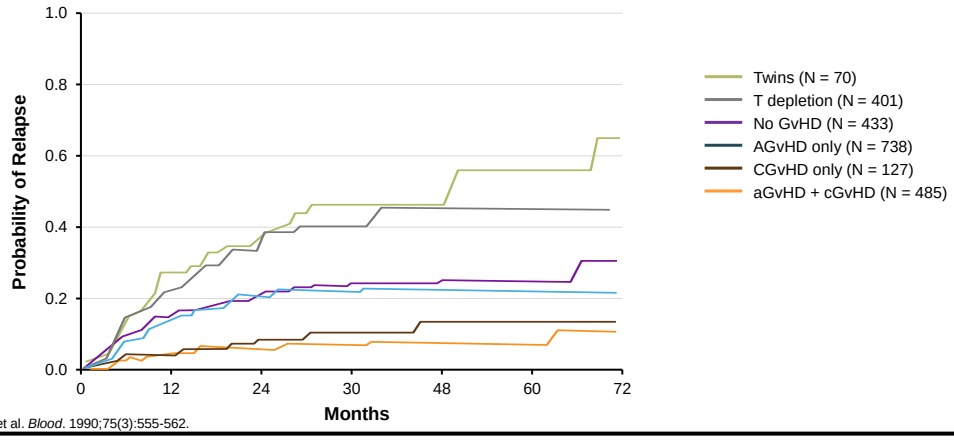
- No significant past medical history
- Presented with anemia, thrombocytopenia, and hyperleukocytosis requiring urgent leukapheresis
- Workup revealed non-M3 AML, normal cytogenetics, Flt3-ITD abnormality
- Underwent induction with 3+7+midostaurin (Rydapt®) and achieved CR
- Has 2 brothers who are not HLA identical
- Referred for transplant evaluation

Flt3 ITD, internal tandem duplication; CR, Complete response; HLA, human leukocyte antigen

43

Evidence of Graft-vs-Tumor Effect in Allogeneic HCT

Probability of Relapse After HLA-Identical Sibling Transplants for Leukemia

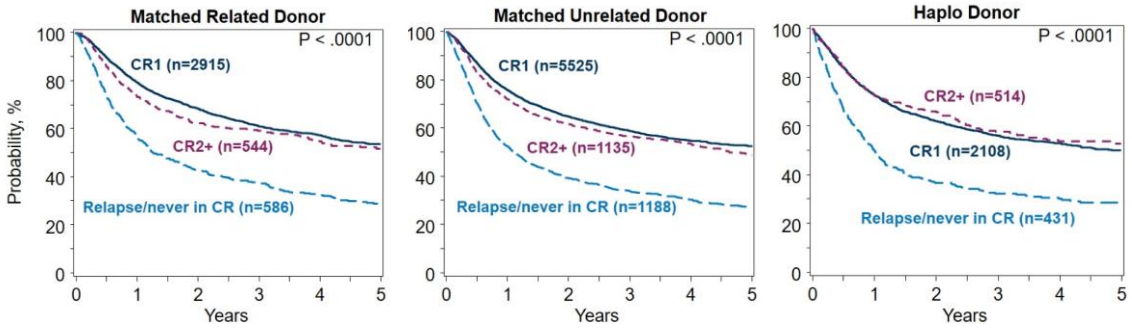


Horowitz MM et al. *Blood*. 1990;75(3):555-562.

44

Importance of Early Transplant and Donor Selection in AML

Survival after Allogeneic HCT for AML, 2016-2021



Early = CR1
Intermediate = CR2 or later
Advanced = Refractory

Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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Indications for Transplant in AML in Adults

Indication and Disease Status	Allogeneic HCT
Acute myeloid leukemia	
CR1, low risk	N
CR1, intermediate risk	S
CR1, high risk	S
CR2	S
CR3+	S
Not in remission	S

S – Standard of Care
N – Not Generally Recommended

European LeukemiaNet Recommendations

- Should be considered when the relapse probability without the procedure is predicted to be >35% to 40%.
- Generally not recommended in favorable risk AML in CR1 unless MRD+.
- Recommended for patients with adverse-risk AML and the majority of those with intermediate-risk AML.
- Allogeneic HCT is the only curative approach for primary refractory disease.

Kanate AS et al. *Transplant Cell Therapy*. 2020;26:1247-1256.
Döhner H et al. *Blood.* 2022;140(12):1345-1377.

46

Pre-Transplant Evaluation

- Past medical history
- Cardiac assessment (TTE)
- Pulmonary assessment (PFTs)
- Renal and liver function (labs)
- Infectious disease markers – rarely a contraindication to transplant. Active infections should be treated and resolved
- Psychosocial evaluation – **Compliance and stable long-term caregiver support critical for success of allogeneic HCT**
- Disease status assessment
- Fertility counseling and preservation whenever relevant and possible

PFT, Pulmonary Function Test; TTE, Transthoracic Echocardiogram

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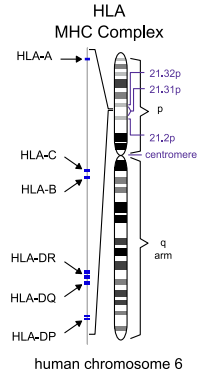
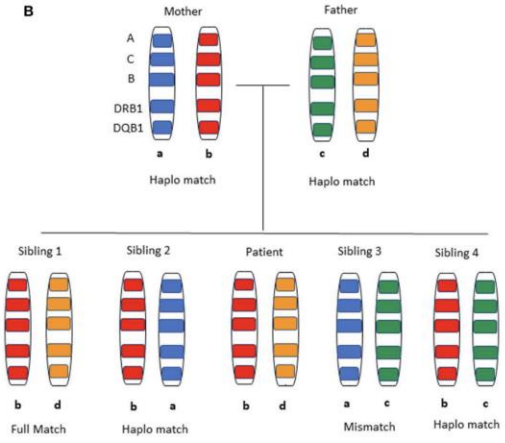
Donor Selection Is Based on HLA Matching



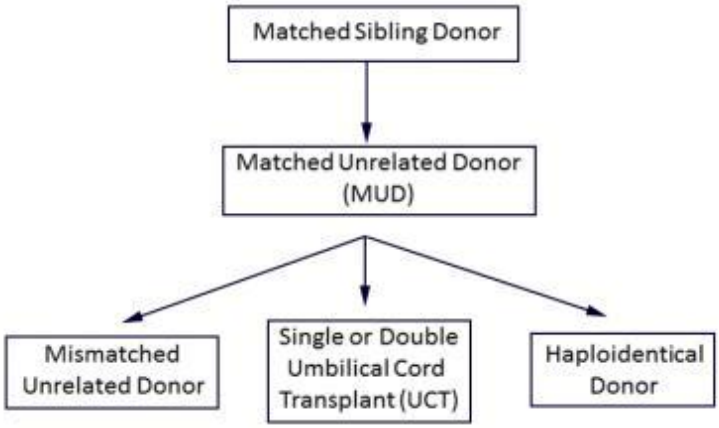
HLA = Human Leukocyte Antigen
MHC – Major Histocompatibility Complex



https://en.wikipedia.org/wiki/Human_leukocyte_antigen
Baumeister SHC et al. Front Immunol 2020. 11:191

48

Donor Selection Algorithm for Allogeneic HCT



Additional Factors
Age
Comorbidities
Sex/Parity
CMV serostatus
ABO status

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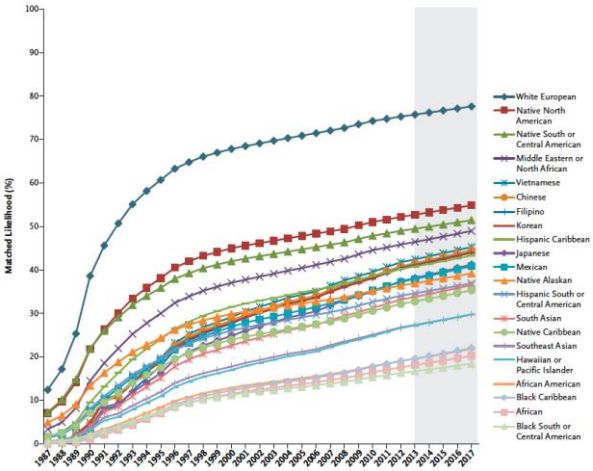
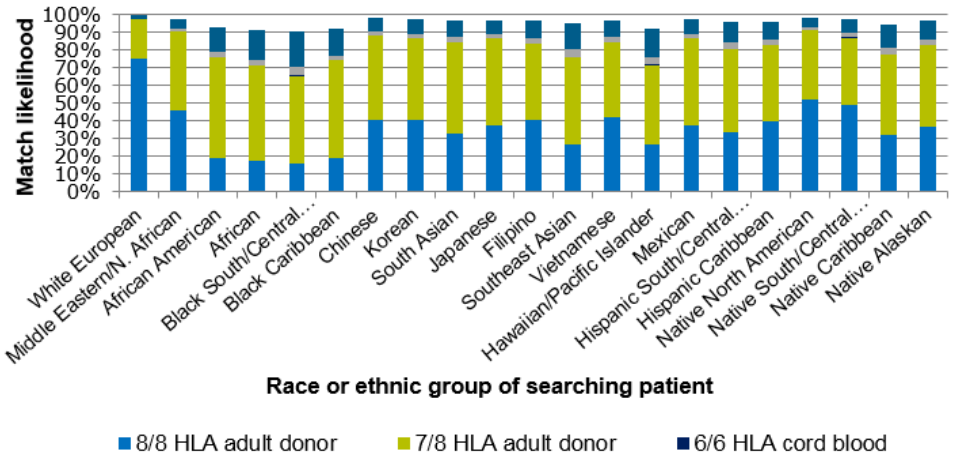
Unrelated Donor Availability for Allogeneic HCT



Gragert L et al. *N Engl J Med*. 2014;371(4):339-348.

50

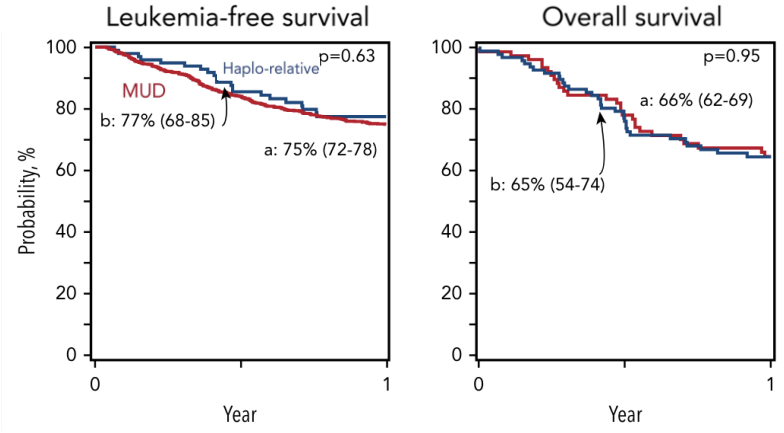
Likelihood of Finding Unrelated Donor or Cord Blood



Gragert L et al. *N Engl J Med*. 2014; 371(4):339-348.

51

Should HLA Matching Remain the Top Criterion?

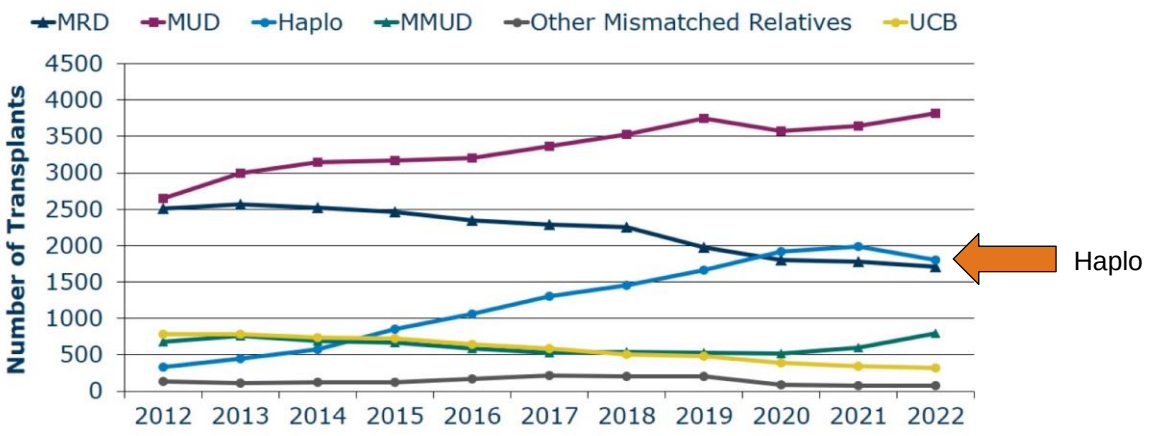


Retrospective data for myeloablative transplants for acute leukemia and MDS using PTCy prophylaxis

Gooptu L et al. *Blood*. 2021; 138(3):273-282.

52

Increase in Use of Haploidentical Donors



Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; Haplo, ≥2 HLA antigen mismatch; MMUD, mismatched unrelated donor ≤ 7/8 HLA allele match; UCB, umbilical cord blood

Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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Conditioning for Allogeneic HCT

Chemotherapy Agent	Dose Limiting Toxicities	Acute Toxicities
Busulfan (Busulfex®)	Hepatic, Gastrointestinal, Pulmonary	Seizures, nausea/vomiting, VOD/SOS
Cyclophosphamide (Cytoxan®, Neosar®)	Cardiac	Nausea/vomiting, hemorrhagic cystitis
Fludarabine (Fludara®)	Neurologic	Hemolytic anemia, CNS toxicity
Thiotepa (Tepadina®)	Neurologic	Nausea/vomiting, CNS toxicity, VOD/SOS
Total body irradiation (TBI)	Gastrointestinal, Hepatic, Pulmonary	Mucositis, enteritis, nausea/vomiting

VOD/SOS = veno-occlusive disease/sinusoidal obstructive syndrome

Cancer Chemotherapy & Biotherapy: Principles & Practices, 4th Edition.

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WHAT IF DORIS WAS A 67 YO WITH A CARDIAC EJECTION FRACTION OF 40%?

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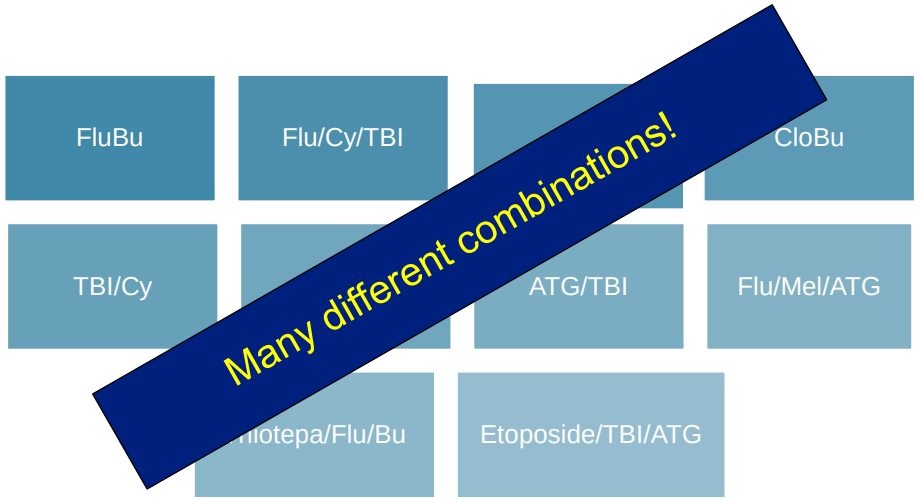
Conditioning Regimens Come in Different Flavors

Myeloablative Conditioning (MA)	Reduced Intensity Conditioning (RIC)	Non-Myeloablative Conditioning (NMA)
• Irreversible cytopenias • Stem cell support critical to prevent aplasia-related death	• Does not meet myeloablative or non-myeloablative definitions • Cytopenias vary in duration • Stem cell support should be given	• Minimal cytopenias, not requiring stem cell support • No direct impact on the tumor • Dependent on optimizing immunosuppression for engraftment and graft versus-tumor effect

Bacigalupo A, et al. *Biol Blood Marrow Transplant*. 2009;15(12):1628-33.
Deeg HJ, et al. *Blood*. 2010;116(23):4762-4770.

56

Conditioning Regimens



Flu – fludarabine (Fludara®); Bu – busulfan (Busulfex®); TBI – total body irradiation; ATG – anti-thymocyte globulin; Mel – melphalan (Alkeran®);
Clo – clofarabine (Clolar®); Cy –cyclophosphamide (Cytoxan®, Neosar®); etoposide (VePesid®, Toposar®, Etopophos®); thiotepa (Tepadina®)

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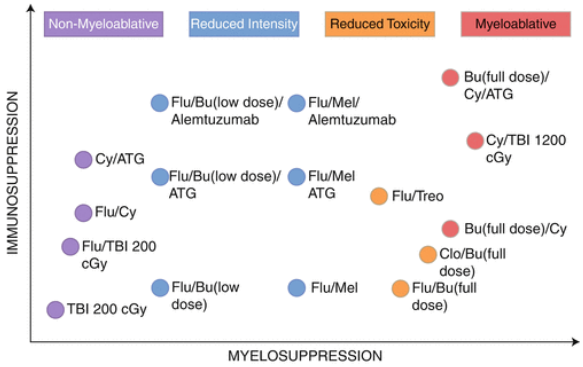
Conditioning Regimens - Association Between Intensity and Toxicity



Key:
Bu – busulfan (Busulfex®)
Cy – cyclophosphamide (Cytoxan®, Neosar®)
TBI – Total body irradiation
Flu – fludarabine (Fludara®)
ATG – Anti-thymocyte globulin
Mel – melphalan (Alkeran®, Evomela®)
Treo – treosulfan (Trecondyv®)

Deeg HJ, et al. *Blood*. 2010;116(23):4762-4770.

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Conditioning Chemotherapy Dose Adjustments Maximize Tolerability and Safety

- Certain conditioning chemotherapy requires adjustment for obesity (>120% of ideal body weight). Others require dose adjustments for renal function and other factors
- Examples of conditioning agents that require dose adjustments
  - Busulfan (Busulfex®)
  - Carmustine (BiCNU®)
  - Cyclophosphamide (Cytoxan®, Neosar®)
  - Etoposide (VePesid®, Toposar®, Etopophos®)
  - Melphalan (Alkeran®)
  - Thiotepa (Tepadina®)
- Busulfan level measurement and adjustment prevents severe adverse effects, like veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS)

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Day 0: Procedure for Transplant

- Allogeneic stem cell infusion is performed similarly to an autologous infusion with some important differences
- Allogeneic stem cell products are generally infused fresh, including unrelated donor stem cells that occasionally need to travel on transcontinental flights and be hand-delivered to the transplant center
- For ABO mismatched donor-recipient pairs, plasma reduction and/or RBC depletion are sometimes performed to minimize the risk for hemolytic reactions

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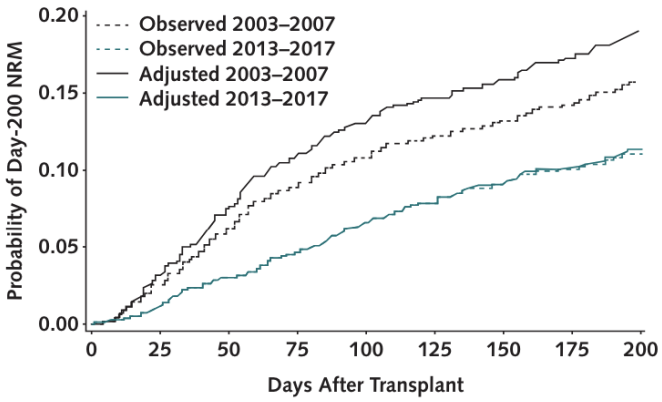
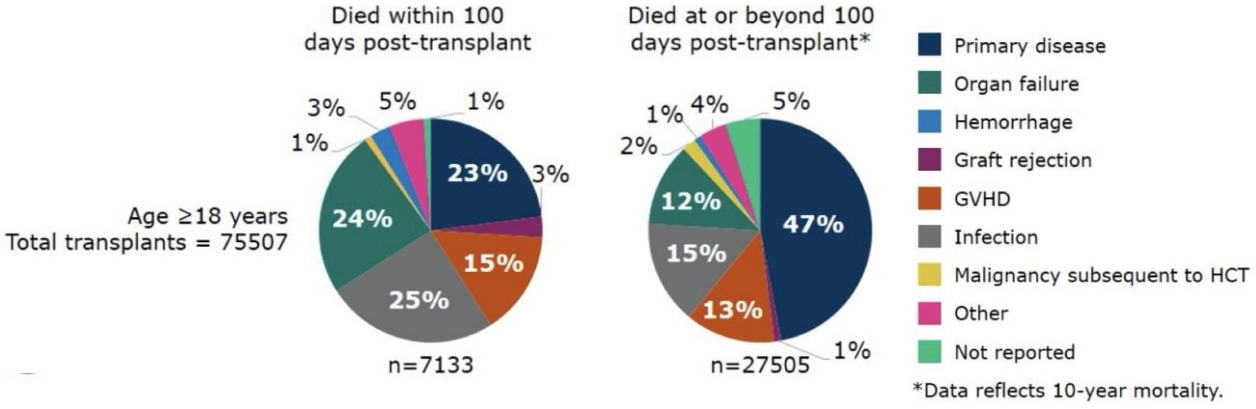
Complications of Allogeneic HCT



McDonald GB et al. *Annals Intern Med*. 2020;172:229-239.

61

Complications of Allogeneic HCT



Cusatis R, Litovich C, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Available at https://www.cibmtr.org

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Allogeneic HCT – Side Effects and Complications

Conditioning Toxicity	Immunologic	Other
• Infections: short term • Organ Failure (e.g., heart, lung) • VOD/SOS • Infertility • Neurocognitive	• Infections: short term and long term • Graft-versus-host disease (GvHD) • Graft failure	• Relapse • Psychological

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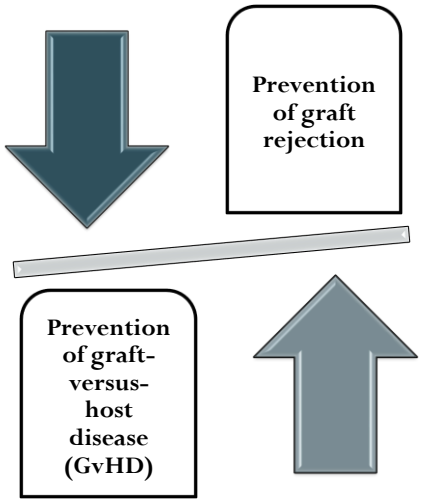
Role of Post-Transplant Immunosuppression

- Prevent graft rejection with conditioning regimen prior to stem-cell infusion, which helps eliminate host immune system and allow engraftment
- Prevent GvHD with long-term immunosuppression to suppress donor immune system to minimize recognition of host cells as foreign
- Most common regimens contain calcineurin inhibitors (i.e., tacrolimus [Prograf®] or cyclosporine [Neoral®, Gengraf®, Sandimmune®])



Copelan EA. *N Engl J Med.* 2006;354(17):1813-1826.

64

Graft-versus-Host Disease (GvHD)

- Immunocompetent donor lymphocytes recognize normal recipient tissues as foreign and react against them
- Severity can be mild to life-threatening
- May be associated with a beneficial “graft-vs-tumor” reaction (same lymphocytes react against residual cancer cells)
- Separating graft-versus-host from graft-versus-tumor responses has been the holy grail of allogeneic HCT research for decades
- GvHD occurs in 30-60% of allogeneic HCT recipients

Deol A et al. *Transplant Res Risk Manage*. 2011;3:31-44.

65

GvHD Prevention

- Better donor selection
- Optimization of conditioning regimen
- T-cell depletion from the graft
- Pharmacologic prophylaxis

66

GvHD Pharmacologic Prophylaxis

Prophylaxis Options	Agents
Calcineurin Inhibitors (CNI)	• Tacrolimus (Prograf®) • Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
Methotrexate (MTX) Otrexup™, Rasuvo®, Rheumatrex®, and Trexall™)	• Low-Dose Methotrexate • Mini-Methotrexate
mTOR Inhibitors	• Sirolimus (Rapamune®)
Anti-Metabolites	• Mycophenolate mofetil (Cellcept®) • Mycophenolate sodium (Myfortic®)
Anti T-Cell Agents	• Alemtuzumab (Campath®) • Rabbit Anti-Thymocyte Globulin (Thymoglobulin®) • Equine Anti-Thymocyte Globulin (ATGAM®)
Ex-Vivo T-Cell Depletion	• CliniMACS® – CD34+ cell selection
In-Vivo T-Cell Depletion	• Post-transplant high-dose cyclophosphamide
T-Cell Activation Modulator	• Abatacept (Orencia®)

Ferrara JL, et al. *Lancet*. 2009;373(9674):1550–1561.
Al-Homsi AS, et al. *Biol Blood Marrow Transplant*. 2015;21(4):604-11.
Mielcarek M, et al. *Blood*. 2016;127(11):1502-1508.

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GvHD Pharmacologic Prophylaxis

Immunosuppressant	Adverse Events	Therapeutic Drug Monitoring
Methotrexate (Otrexup™, Rasuvo®, Rheumatrex®, and Trexall™)	Mucositis, delayed engraftment, nephrotoxicity, hepatotoxicity	Not applicable
Tacrolimus (Prograf®)	Nephrotoxicity, hypertension, hyperglycemia, electrolyte abnormalities, TTP-HUS, neurologic toxicity	5–15 ng/mL
Cyclosporine (Neoral®, Gengraf®, Sandimmune®)		200–300 ng/mL
Mycophenolate mofetil (CellCept®)	Myelosuppression, gastrointestinal distress	Not applicable
Sirolimus (Rapamune®)	Cytopenias, hyperlipidemia, wound healing impairment, interstitial pneumonitis, rash, VOD, TTP-HUS	3–12 ng/mL
Cyclophosphamide (Procytox®)	Hemorrhagic cystitis, cardiotoxicity, hepatotoxicity, SIASH, nausea/vomiting	Not applicable
Abatacept (Orencia®)	Hypersensitivity reaction, hypertension, headache	Not applicable

VOD/SOS: veno-occlusive disease/sinusoidal obstructive syndrome
TTP-HUS: thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome
SIADH: syndrome of inappropriate antidiuretic hormone

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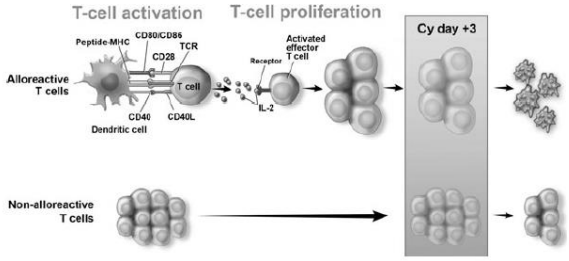
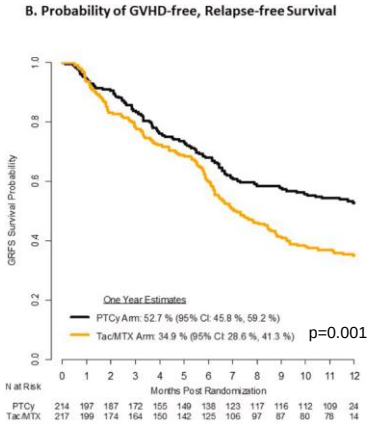
Post-Transplant Cyclophosphamide





Luznik L, et al. *Immunol Res* (2010) 47:65–77
Bolaños-Meade J, et al. N Engl J Med. 2023 Jun 22;388(25):2338-2348.

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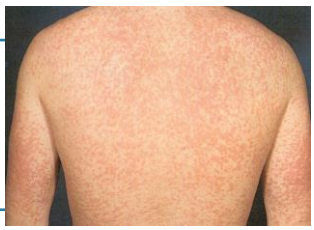
GvHD Classification

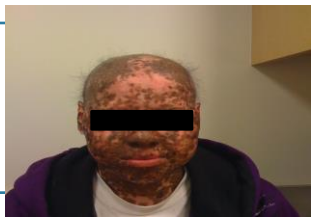
Acute GvHD

- Skin, liver, and gastrointestinal tract
- Classic definition: occurring within the first 100 days of stem cell transplant
- Late onset: occurring more than 100 days after stem cell transplant



Chronic GvHD

- Any tissue can be involved
- Classic presentation: Features of chronic GvHD only, no time limit
- Overlap syndrome: Features of both acute and chronic GvHD, no time limit



Mielcarek M, et al. *Blood*. 2016;127(11):1502-1508.

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Acute GvHD Grading

Table 1 Consensus grading of acute GVHD[74]

	Organ/Extent of Involvement		
	Skin	**Liver**	**Intestinal Tract**
Stage			
1	Rash on <25% of skin*	Bilirubin 2–3 mg/dL†	Diarrhea >500 mL/d‡ or persistent nausea§
2	Rash on 25–50% of skin	Bilirubin 3–6 mg/dL	Diarrhea >1,000 mL/d
3	Rash on >50% of skin	Bilirubin 6–15 mg/dL	Diarrhea >1,500 mL/d
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade			
0	None	None	None
I	Stage 1–2	None	None
II	Stage 3	or Stage 1	or Stage 1
III	—	Stage 2–3	or Stage 2–4
IV¶	Stage 4	or Stage 4	—

Przepiorka D et al. *Bone Marrow Transplant*. 1995;15(6):825-828.

71

Acute GvHD Initial Treatment

Grade I

- Re-initiate or optimize GvHD prophylaxis
- Topical steroids or topical immunosuppression

Grade II

- Systemic corticosteroids: prednisone 2 mg/kg/day
- Isolated GI GvHD: prednisone 1-2 mg/kg/day and non-systemic steroids (oral budesonide 3 mg Q8H)
- Re-initiate or optimize GvHD prophylaxis
- Topical agents for skin GvHD

Grade III-IV

- Systemic corticosteroids: prednisone 2 mg/kg/day
- Re-initiate or optimize GvHD prophylaxis
- Topical agents for skin GvHD
- Non-systemic steroids for GI GvHD

Dignan FL, et al. *British Journal of Haematology.* 2012;158:46-61.
Martin PJ, et al. *Biol Blood Marrow Transplant.* 2012;18(8):1150-1163.

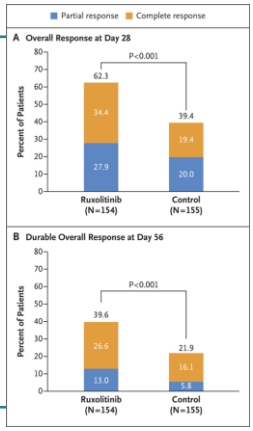
72

Steroid-Refractory Acute GvHD

Criteria: lack of improvement after 5 days or progression within 72 hours of 2 mg/kg of prednisone or equivalent steroid

Options:

- **JAK1/JAK2 inhibitor - Ruxolitinib (Jakafi®)**
- mTOR inhibitors - sirolimus (Rapamune®)
- Anti-metabolites - mycophenolate mofetil (CellCept®)
- Extracorporeal photopheresis (ECP)
- Anti-tumor necrosis factor alpha (TNFα) agents – infliximab (Remicade®), etanercept (Enbrel®)
- Interleukin-6 (IL-6) receptor antagonist – tocilizumab (Actemra®)
- Interleukin-2 (IL-2) receptor antibodies - basiliximab (Simulect®), denileukin diftitox (Ontak®)
- T-cell targeted agents - alemtuzumab (Lemtrada®), pentostatin (Nipent®), anti-thymocyte globulin
- Mesenchymal stem cells
- Clinical trials



JAK1/JAK2: Janus Associated Kinases 1 and 2

Dignan FL, et al. *British Journal of Haematology*. 2012;158:46-61.
Martin PJ, et al. *Biol Blood Marrow Transplant*. 2012;18(8):1150-1163.
Jagasia M, et al. *Biol Blood Marrow Transplant*. 2019;25(3):S52.
Zeiser R, et al. *N Engl J Med*. 2020; 382:1800-1810.

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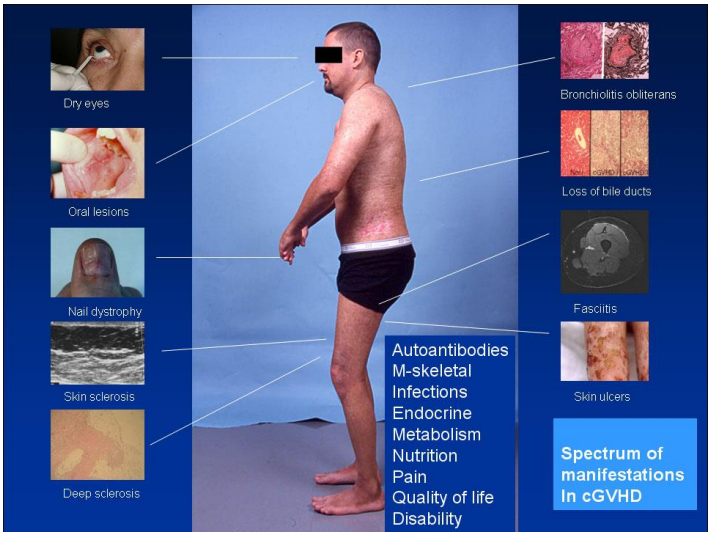
Chronic GvHD



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Chronic GvHD Treatment

Symptomatic Mild Chronic GvHD

- Organ-directed therapy:
  - Skin: topical steroids, sunscreen, moisturizer
  - Oral: dental hygiene, topical steroids (rinses)
  - Eye: ocular lubricants, steroid eye drops
  - Gastrointestinal: non-absorbable steroids

Moderate to Severe Chronic GvHD

- Prednisone 1 mg/kg/day +/- calcineurin inhibitor
- Slow taper over weeks to months

Steroid Refractory Chronic GvHD

- Ruxolitinib (Jakafi®)
- Belmosudil (Rezurock®)
- Ibrutinib (Imbruvica®)

Agents	Mechanism	Dosing	Side Effects
Ruxolitinib (Jakafi®)	JAK 1/2 inhibitor	10 mg twice daily	Myelosuppression Infections
Belmosudil (Rezurock®)	ROCK 1/2 inhibitor	200 mg once daily	Infections Edema Headache
Ibrutinib (Imbruvica®)	BTK inhibitor	420 mg once daily	Bleeding Infections Arrhythmias Hypertension

Zeiser R. *J Clin Oncol*. 2023 Apr 1;41(10):1820-1824. 2012;18(8):1150-1163.

75

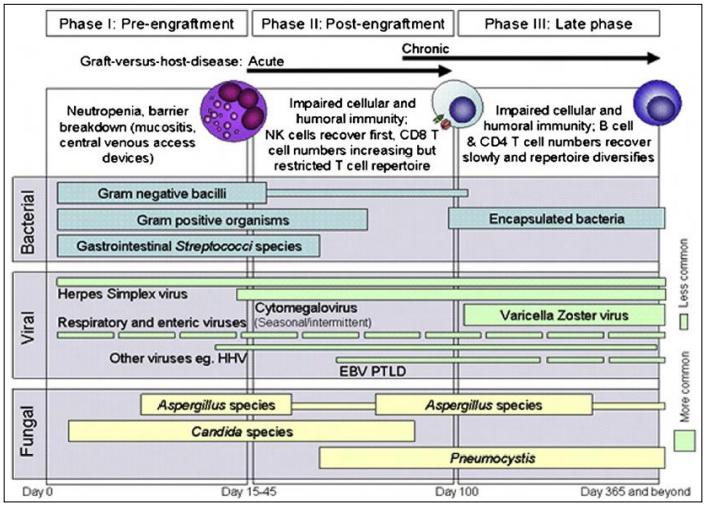
Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

- Incidence in myeloablative transplants varies between 3%-14% depending on conditioning regimen. Incidence is low after reduced-intensity conditioning
- The mortality of severe VOD can exceed 80%
- Clinically characterized by:
  - Jaundice
  - Tender hepatomegaly
  - Fluid accumulation → rapid weight gain/ascites
- Agents for prophylaxis: ursodiol
- Treatment: Supportive care, defibrotide

Cheuk D et al. *World J Transplant*. 2012;2(2):27-34.

76

Risk of Infections Post–Allogeneic HCT



Tomblyn M et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

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Infection Prevention

Pathogen Type	ation of Therapy
Bacterial	f neutropenia
Fungal	bered off immunosuppression
Viral	s post-transplant
Cytomegalovirus (CMV)	post-transplant
Hepatitis B (HBV)*	after discontinuation of ion
Pneumocystis jiroveci (PCP)/Toxoplasmosis	post-transplant, longer if still ession

Role of Intravenous Immunoglobulin (IVIG) Post Allogeneic HCT

- Some centers check total IgG levels in high-risk HCT recipients (e.g., those with unrelated marrow grafts)
- For patients with severe hypogammaglobulinemia (i.e., IgG < 400 mg/dL), IVIG prophylaxis may be considered
- The IVIG dose and frequency for a hypogammaglobulinemic HCT recipient should be individualized to maintain trough serum IgG concentrations > 400 mg/dL
- In the absence of severe hypogammaglobulinemia (which might be associated with bacteremia or recurrent sinopulmonary infections), routine monthly IVIG administration to HCT recipients >100 days after allogeneic or autologous HCT is not recommended

*In select patients

ANC: absolute neutrophil count; TMP/SMX: trimethoprim-sulfamethoxazole; TIW: three times a week; DS: double strength

Practice varies by institution

Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

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Infection Prevention

- Other Infectious Considerations:
  - **Tuberculosis**: consider prophylaxis with isoniazid in patients at increased risk of reactivation
  - **Strongyloides**: empiric treatment if pre-transplant screening is positive for *Strongyloides stercoralis* or unexplained eosinophilia with recent travel
    - Ivermectin 200 mcg/kg x 2 days (repeat two weeks later)
- Infection Control:
  - Protective isolation and room ventilation (≥ 12 air exchanges per hour, HEPA filters, positive air pressure
  - Chlorhexidine bathing
  - Hand hygiene, intravascular catheter care, food safety, avoid plants and flowers

Practice varies by institution
Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

79

Vaccinations After HCT

- Antibody titers against vaccine-preventable diseases decline after HCT, which may be associated with loss of functional immunity against pathogens
- Vaccinations with inactivated vaccines may be started as early as 6 months post-HCT (and earlier for COVID-19 and influenza)
- Live vaccines are contraindicated until at least 2 years after allogeneic transplant and 1 year off all immunosuppressive therapies
- HCT recipients' immunization status should be assessed, and their vaccinations updated as needed before travel
- Vaccination of family members and household contacts recommended to minimize exposure of vaccine-preventable diseases among HCT recipients
- Vaccination of donor has been shown to improve the post-transplant immunity of the patient in the case of tetanus toxoid, 7-valent PCV, and Hib conjugate vaccines.

HiB, Haemophilus influenzae type B; PCV, pneumococcal conjugate vaccine
Tomblyn M et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

80

Secondary Malignancies

- Definition: biologically distinct cancer developing after HCT
- Secondary malignancies are of two types:
  - Leukemia/MDS
  - Solid tumors
- Leukemias usually occur within the first few years, but solid tumors usually much later
- Standard screening for “screenable” tumors is usually started earlier
- Annual physicals and additional follow-up dependent on patient history
  - GI – endoscopies if persistent GERD or dysphagia, especially in those with immunosuppressive therapy > 24 months
  - Prior radiation or TBI, breast cancer screening starting at age 25 or 8 years after radiation (whichever comes first)
  - Annual skin exams, especially if TBI was used for conditioning

GERD, Gastroesophageal reflux disease; TBI, total body irradiation

Inamoto Y et al. *Bone Marrow Transplant*. 2015;50(8):1013-1023.

81

Summary

- Both autologous and allogeneic HCT are an essential part of the standard of care in a growing number of blood cancers
- Overall survival and treatment-related mortality have dramatically improved over the years
- Virtually all patients have a donor for an allogeneic transplant
- Timing of HCT is important to its success. Early referral is critical
- Close survivorship follow-up is important to manage long-term complications

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Hematopoietic Cell Transplantation as Treatment for Blood Cancers: The Team Approach

Tricia Skvarce, MSHS, PA-C
Supervisor Physician Assistant
Blood and Marrow Transplant
New York Presbyterian Hospital
Columbia University Irving Medical Center
New York, NY

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Role of the Inpatient BMT RN

- Direct, patient-centered care with a team-based approach
- Identify symptoms and abnormal vital signs
- Maintain clear and open lines of communication with the PA/MD, escalating concerning symptoms or vital signs
- Symptom management
- Develop patient rapport and ability to recognize subtle changes in patient's behavior or symptoms
- Provide patient education, including discharge education (medications, central line care, etc) as well as support to both patients and caregivers

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Role of the Inpatient BMT PA

- Possess broad training and knowledge in medicine, pharmacy, physiology, and pathology
- “First contact” or “point person” for our patients undergoing HSCT; on floor 24/7
- Recognize important lab trends and physical exam findings leading to broad differential diagnoses
- Actively contribute to the treatment plan by ordering diagnostic imaging/labs, interpreting results and offer treatment options for current symptoms
- Effectively communicate with entire care team, including nurses, attendings, consulting providers, and social work/care coordination
- Manage wide range of comorbidities and acute HSCT complications

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Role of the BMT PA (cont’d)

- Perform noninvasive procedures (bone marrow biopsies, lumbar punctures, arterial blood gases)
- Provide patient education and support, including discharge education on medications, dietary and lifestyle changes at home, and strict return instructions for concerning symptoms
- Participate in goals of care discussions with patients and family/caregivers, as well as provide end of life care

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Daily Assessment of HSCT Patients

Vital Signs

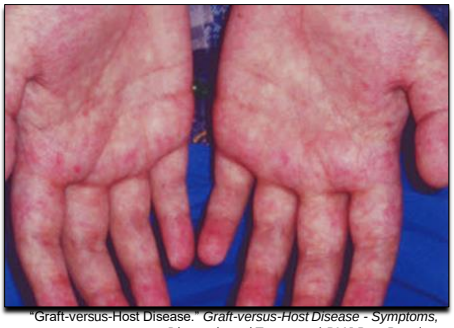
Temperature, BP, HR, RR, Oxygen status, Pain, Weights, Ins & Outs

Subjective complaints

Mouth pain, appetite, nausea, vomiting, bowel movements, headaches, visual changes, pain

Physical Exam Findings

Toxic appearance, level of alertness, mouth ulcerations/thrush, lung/heart auscultation, bowel sounds, abdominal tenderness, peripheral edema/volume status, rashes/petechiae, central line assessment



"Graft-versus-Host Disease." *Graft-versus-Host Disease - Symptoms, Diagnosis and Treatment | BMJ Best Practice*, bestpractice.bmj.com/topics/en-gb/946.

BP, blood pressure; HR, heart rate; RR, respiratory rate

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Daily Assessment of HSCT Patients (cont'd)

- **Lab Trends**

  Count nadir, transfusion needs, creatinine trend, electrolyte derangements, LFT abnormalities, tacrolimus levels, coagulation factors

  ****imperative to look at lab trends over the last few days to weeks rather than one day's isolated values****

- **New/recent imaging studies**
- **Review active medication list**
- **Plan**

  Follow-up on existing consults and their recommendations, place new consults as needed, enter orders and make medication changes/adjustments, communicate the plan to RNs, patients and caregivers

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Summary of HSCT Complications by Organ System

HEME/ONC

Cytopenias, Bleeding

HEENT

Dry eyes, Visual changes, Mucositis, Mouth sores/ulcers, Thrush, Odynophagia, Dysphagia

ID

Neutropenic Fever/Sepsis, Viremias, PCP

CV

HTN, Arrhythmias, Hypotension, Heart Failure

PULM

Respiratory infections, Pleural effusions, Pulmonary edema, Engraftment syndrome

RENAL/GU

AKI (TMA, CNI-toxicity, ATN, pre-renal), Electrolyte imbalances, Hemorrhagic cystitis

GI/LIVER

Mucositis, CINV, poor appetite, diarrhea, VOD/SOS, GVHD

NEURO/PSYCH

AMS/Delirium, CNS/Neurotoxicities, Headaches, PRES

DERMATOLOGIC

Rashes, Petechiae, Engraftment Syndrome, Skin GVHD

"Early Complications of Hematopoietic Cell Transplantation." *UpToDate*,

89

GI Symptoms and Their Differential Diagnosis Related to BMT Timeline

Nausea/vomiting/anorexia

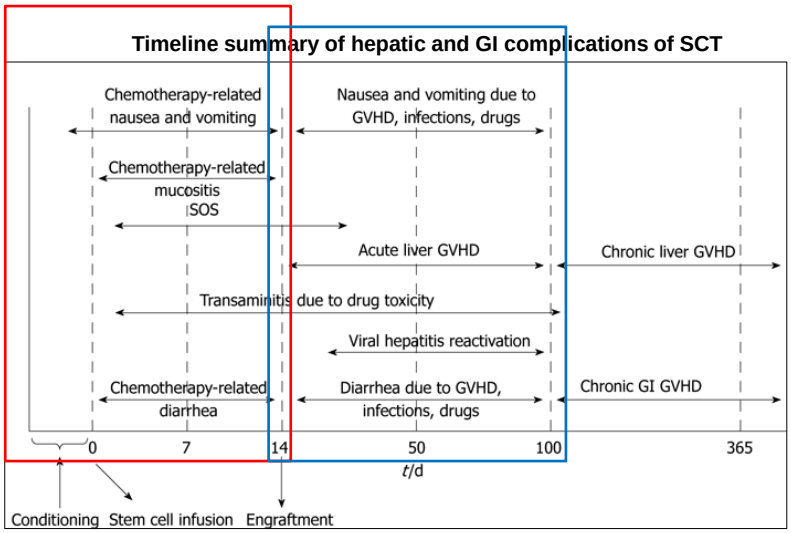
Chemo-induced, Mucositis, CMV gastritis, Acute GI GVHD

LFT abnormalities

Conditioning toxicity, VOD/SOS, Medication-induced, Liver GVHD, Viral hepatitis reactivation

Diarrhea

Chemo-induced, Engraftment Syndrome, typhlitis/colitis, C. diff, Enteric viruses, Acute GI GVHD, MMF, Adenovirus/CMV colitis



Tuncer HH et al. Gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *World J Gastroenterol.* 2012;18(16):1851-1860. doi:10.3748/wjg.v18.i16.1851.

90

Neutropenic Fever

Neutropenic fever/sepsis management is the *"bread and butter"* of heme/onc and HSCT

IDSA definition of neutropenic fever: a single oral T ≥38.3ºC or a T ≥38.0ºC sustained over 1-hour period in a patient with ANC <1500

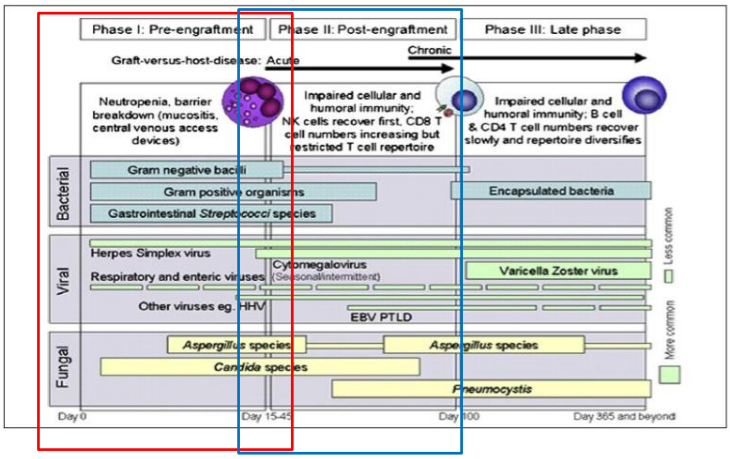
Prompt identification and intervention is required!

- Blood cultures, urinalysis/urine culture, lactate, respiratory pathogen PCR/respiratory culture, fungal markers, CXR
- Initiate empiric broad-spectrum antibiotics therapy within 1 hour
- Fluid resuscitation
- Supplemental oxygen
- Patient reassessment
- Identify possible sources

Freifeld, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the ISDA. *Clin Infect Dis*. 2011;52(4):e56.

91

Fever/Infection and Their Differential Diagnosis Related to BMT Timeline



Pre-engraftment

Gram negative bacteria, Gram positive bacteria (staph and strep), HSV, Respiratory viruses, Aspergillus, Candida

Post-engraftment

Gram negative bacteria, Gram positive bacteria (staph and strep), HSV, CMV, HHV6, Adeno, EBV, Respiratory viruses, Aspergillus, Candida, PCP

Tomblyn M et al. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.

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Post-transplant Cytoxan (PT-Cy)

- GVHD ppx administered on Days +3 and +4
- Adverse side effects: myelosuppression, nausea/vomiting, infections, cardiotoxicity, hemorrhagic cystitis, infertility, and secondary malignancies
- Administered with 24-hour Mesna infusion to reduce incidence of hemorrhagic cystitis
- Commonly see fevers early after stem cell infusion which resolves after PT-Cy ("Haplo storm")
  - Symptoms resemble Cytokine Release Syndrome (CRS): fever, hypoxia, hypotension, renal impairment, capillary leak syndrome
  - Must simultaneously rule out infection and initiate broad-spectrum antibiotics given anticipated neutropenia
- Associated with higher incidence rate of viral infections such as CMV, HHV6, adenovirus, and EBV; therefore, we routinely monitor viral PCRs at least weekly to capture any viral infections

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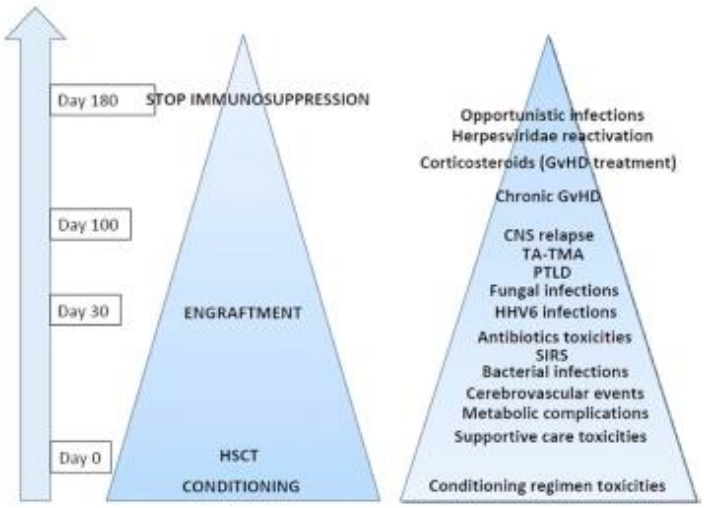
NEURO/PSYCH

- Headaches
- Tremors
- Mental status changes
- Delirium
- Seizures



Maffini E et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2017;23(3)388-397.

94

John, 70M w/ T2DM, HTN, and Multiple Myeloma in a VGPR

S/p melphalan 140 mg/m^2 (Alkeran®, Evomela®) and autologous stem cell transplant

Day +5

- Developed diarrhea and mild abdominal pain
  - C. diff and GI pathogen PCR both negative

Day +6 febrile to 38.4C, BP 105/68, HR 110, RR 18, O2 98% on RA

- Worsening abd pain and TTP in all 4 quadrants, +rebound tenderness
  - Pancultured, started on empiric abx (Zosyn® [piperacillin and tazobactam injection] + vancomycin [Vancocin®]) and received 1L fluid bolus
  - CT Abd/Pelvis w/ oral contrast (no IV due to renal impairment) showed circumferential wall thickening of the cecum and ascending colon, consistent with inflammatory colitis/typhlitis.
  - Made NPO
  - Blood and urine culture data negative

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John's BMT Course

- **Day +7** fever curve trending down, VS stable. Requires supportive care with pain medication. Intermittent blood and platelet transfusions.
- **Day +9** afebrile >48 hours, culture data remains negative. Pain improving, patient is hungry. Advanced diet to clears then transitional diet.
- **Day +11** day 1 of ANC >500. Tolerating diet, stool soft.
- **Day +16** ANC stable >1000 off GCSF. Plts stable >20k and not transfusion dependent. Discharged with cipro/flagyl to complete a 14 day course.

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Doris, 25F w/ FLT3+ AML s/p 7+3 and Midostaurin (Rydapt®) in a CR

- HSCT-CI score of 3 (Obesity, residual kidney insufficiency, anxiety)
- Conditioning regimen: Flu/Bu4
  - Busulfan (Busulfex®) IV q24h (days -6 through -3)
    - Target AUC = 5000 micromole*min/L
      - Dose 1 and 2: 259 mg
      - Dose 1 AUC = 3923 → increased to 401 mg for dose 3 and 4
  - Fludarabine (Fludara®) IV q24h (Day -6 through -3)
- Stem cell graft from 10/10 MUD, peripheral blood
  - CD34: 8.09 x10e6/kg, TNC: 11.23 x10e8/kg
- GVHD ppx: tacrolimus (Envarsus XR®, Protopic®, Astagraf XL®, Prograf®), MMF (Mycophenolate mofetil), and PT-Cy

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Doris' BMT Course

- Fluid Overload
  - Admission weight: 81kg
  - Day -1 patient was >2% (83kg); Day 0 patient was >5% (85 kg); Day +9 patient was >10% (90 kg)
- Infections: Staph epi bacteremia (day +6)
- Rapidly rising transaminitis and hyperbilirubinemia (started ~Day +7)
  - Initially attributed to toxicity from the conditioning regimen and antifungal ppx (posaconazole [Noxafil®])
    - Early peak: Tbili 5.6, Indirect bili 4.2 (day +9)
      - Fungal ppx changed to micafungin (Mycamine®)

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Doris' BMT Course Cont'd

- AKI (started ~Day+12)
  - Initially attributed to vancomycin (Vancocin®) and/or supratherapeutic tacrolimus (Envarsus XR®, Protopic®, Astagraf XL®, Prograf®)
    - Tacrolimus (Envarsus XR®, Protopic®, Astagraf XL®, Prograf®) and vancomycin (Vancocin®) doses adjusted,
      Cr stabilized then improved by Day +16

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Doris' BMT Course Cont'd

- Day +15 Abd U/S with dopplers: HSM, mod ascites, patent vasculature, normal flow
- Day +18 underwent transjugular liver biopsy with a portal pressure gradient of 17 mmHg, pathology c/w severe VOD/SOS
  - Started defibrotide (Defitelio®) on Day +18 and uptitrated ursodiol (Actigall®, Urso®, Urso Forte®, Urso DS®)
  - Aggressive diuresis with return to baseline wt
- Day +20 AST/ALT began to normalize, bilis plateaued at 18.
- Continued defibrotide (Defitelio®) therapy
  - Tbili steadily trended down
  - Discontinuation of defibrotide (Defitelio®) therapy on Day +50, bilis remained stable
- Discharge on Day +55

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EXPLORING HEMATOPOIETIC CELL TRANSPLANT THROUGH A PSYCHOSOCIAL LENS

Muyun Zhao, LMSW
Social Worker
BMT Program at New York Presbyterian Hospital
Columbia University Irving Medical Center
New York, NY

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Role of the HCT Social Worker

Inpatient	Outpatient
Work with the interdisciplinary team, conduct initial assessment and follow up	Conduct pre-transplant assessment and target psychosocial barriers that could potentially negatively impact transplant outcomes
Offer support during hospital stay	Offer support in the outpatient setting
Assist in advocating for patient	Assist in advocating for patient
Communicate to outpatient SW for continued follow up	Communicate with inpatient SW to establish a smooth transition
Make appropriate referrals for discharge	Assist with post-transplant needs in the community

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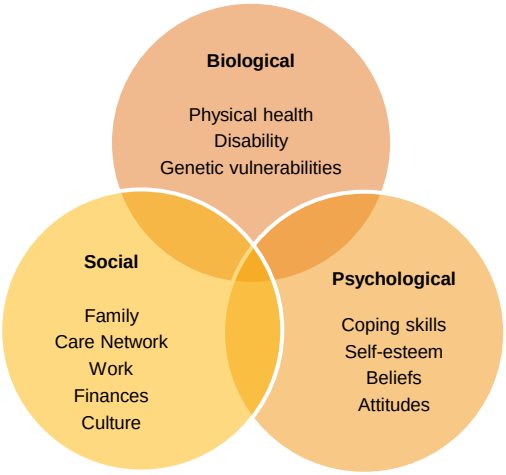
Psychosocial Assessment

Getting to know our patients and their unique needs



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Psychosocial Care Plan and Considerations for Transplant

- Housing
- Transportation
- Disability
- Finances
- Immigration status
- Substance use
- Family dynamics
- Any barriers to accessing care

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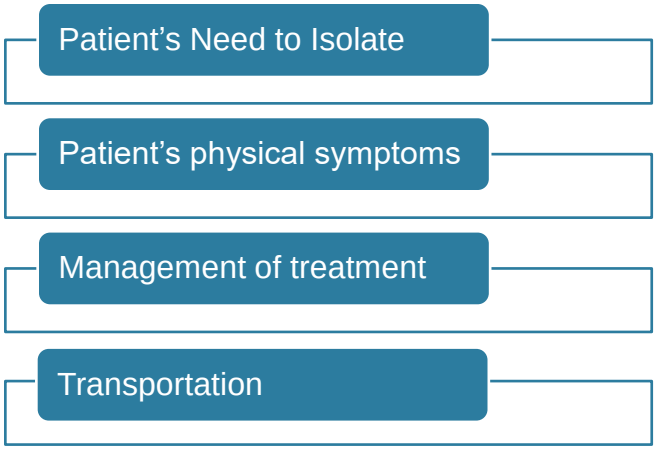
Role of the Care Partner



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Emotional Impact

Anxiety	Depression	Frustration
Fear	Grief	Happiness

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Patient Case– John, 70 YO Male with Myeloma

Identified Needs	Interventions
Retired with fixed income/Medicare only and many co-pays	Review available financial assistance programs, HIICAP, SSDI, DollarFor, EPIC or Extra Help Program
Resides 2hrs from transplant center and needs local post transplant housing	Utilize American Cancer Society's-Hope Lodge, Be The Match
Needs help within the community	Referral for community case management agencies, Senior Centers, visiting nurse

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Patient Case- Doris, 25 YO Femail with AML

Identified Needs	Interventions
Adjustment to illness	Ongoing social work support as well as linking to support resources
Care partner is in another country	Referral for legal support
Support for her child/parenting support	Connect her to Red Door Community and The Family Center

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Resources - All Free!

The Leukemia and Lymphoma Society

https://www.lls.org/

The Bone Marrow and Cancer Foundation

https://bonemarrow.org/

Be the Match

https://bethematch.org/

American Cancer Society

https://www.cancer.org/

The Family Center (NYC Specific)

https://www.thefamilycenter.org/

Red Door (Support Groups are NYS only but workshops under "for members" and then "calendars" are for everyone)

https://reddoorcommunity.org/family-support/

Look Good Feel Better

https://lookgoodfeelbetter.org/virtual-workshops/

Patient Advocate Foundation

https://www.patientadvocate.org/

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Resources - All Fee!

Health Insurance Information and Assistance Program

https://aging.ny.gov/health-insurance-information-counseling-and-assistance-program-hiicap

Elderly Pharmaceutical Insurance Coverage Program

https://health.ny.gov/health_care/epic/

HITE, resources for NY

https://hitesite.org/

Cancer Care

https://www.cancercare.org/

My Cancer Circle

https://mycancercircle.net/

Family Reach Foundation

https://familyreach.org/

The Icla Da Silva Foundation

https://icla.org/

Modest Needs

https://www.modestneeds.org/

Dollar For

https://dollarfor.org/

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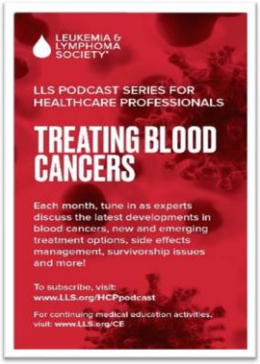
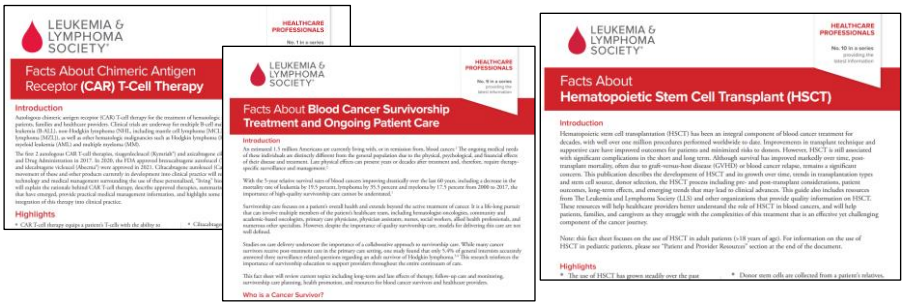
FREE LLS RESOURCES FOR HEALTHCARE PROVIDERS

- ❑ CME & CE courses: www.LLS.org/CE
- ❑ Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- ❑ Videos for HCPs: www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs: www.LLS.org/HCPpodcast





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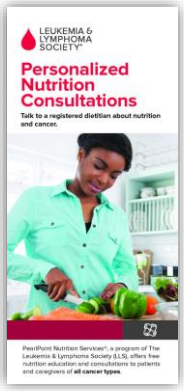
FREE LLS RESOURCES FOR PATIENTS

- ❑ **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - ➢ www.LLS.org/IRC
- ❑ **Nutrition Education Services Center** – one-on-one nutrition education with a registered dietician for patients/caregivers of all cancer types (NESC).
  - ➢ www.LLSNutrition.org
- ❑ **Clinical Trial Nurse Navigators** – RNs and NPs provide a personalized service for patients seeking treatment in a clinical trial, sift through the information and provide information to bring back to their HC team (CTSC).
  - ➢ www.LLS.org/CTSC
- ❑ **Reach out Monday–Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/IRC
  - Email: infocenter@LLS.org
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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HERE TO HELP: LLS COMMITMENT

LLS is committed to providing education and resources to help patients access clinical trials.

CLINICAL TRIAL SUPPORT CENTER

- A team of highly trained nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide education to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, individualized search to discuss with their HCP.
- Provide guidance and serve as advocates throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a personal connection and develop long term relationships to help better serve our patients.

LEUKEMIA & LYMPHOMA SOCIETY®

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FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

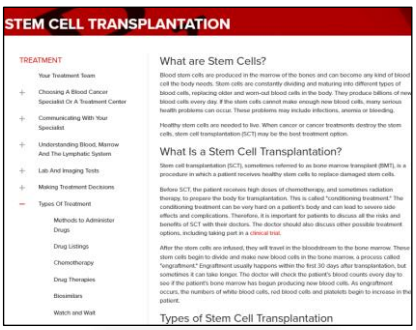
❑ **Webcasts, Videos, Podcasts, booklets**:

- ➢ www.LLS.org/Webcasts
- ➢ www.LLS.org/EducationVideos
- ➢ www.LLS.org/Podcast
- ➢ www.LLS.org/Booklets

❑ **Support Resources**

❑ Financial Assistance: www.LLS.org/Finances
- Urgent Need
- Patient Aid
- Travel Assistance

❑ Other Support: www.LLS.org/Support
- LLS Regions
- Online Weekly Chats Facilitated by Oncology SW
- LLS Community Social Media Platform
- First Connection Peer to Peer Program



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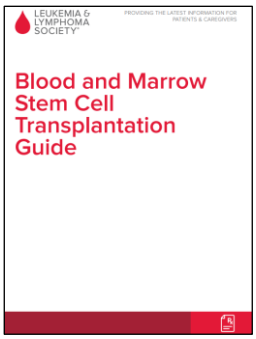
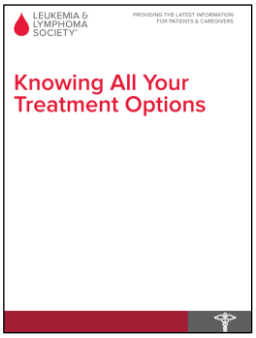
FREE LLS RESOURCES FOR YOUR PATIENTS





www.LLS.org/Treatment

BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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The ASTCT offers opportunities to connect with multidisciplinary colleagues, grow skills and expertise, and stay up to date on the latest research in Hematopoietic Cell Transplantation, Cellular Therapy and Gene Therapy, including Continuing Education.

LIVE AND VIRTUAL MEETINGS
Attend the premier event in the evolving field of hematopoietic cell transplantation and cellular therapy.

CLINICAL EDUCATION CONFERENCE
Discuss post-transplant challenges such as infections, GVHD, organ dysfunction and maintenance with APPS, nurses and fellows.

VIRTUAL FUNDAMENTALS OF HCT TRAINING COURSE
Gain a broad understanding of hematopoietic cell transplantation and cellular immunotherapy.

VIEW ALL MEETINGS

ASTCT®
American Society for Transplantation and Cellular Therapy

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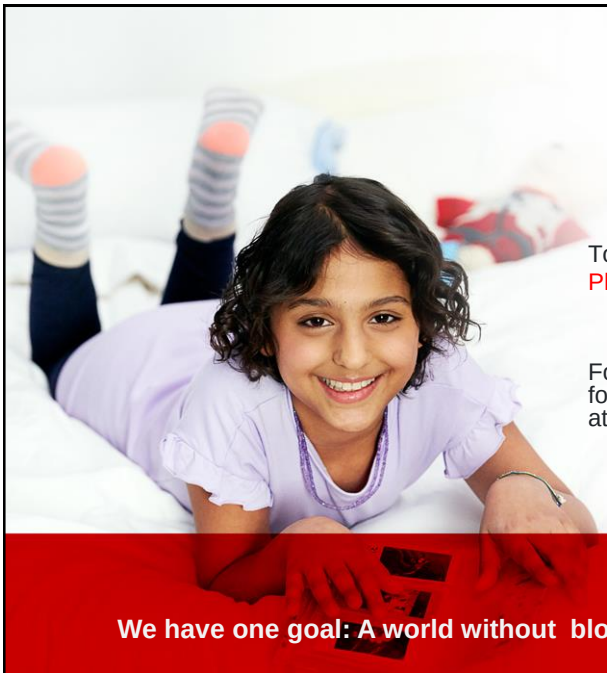

THANK YOU

To speak with an Information Specialist or to refer a patient:
Phone (800) 955-4572 Email: Infocenter@LLS.org

For questions about this program, concerns, or assistance for people with disabilities or grievances, please contact us at Profeducation@LLS.org

We have one goal: A world without blood cancers

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