1

Indications for Hematopoietic Cell Transplant in Pediatric Acute Lymphoblastic Leukemia

Michael J. Burke, MD
Associate Professor
Medical College of Wisconsin
Director, Pediatric Leukemia & Lymphoma Program
Children's Hospital of Wisconsin
Milwaukee, WI

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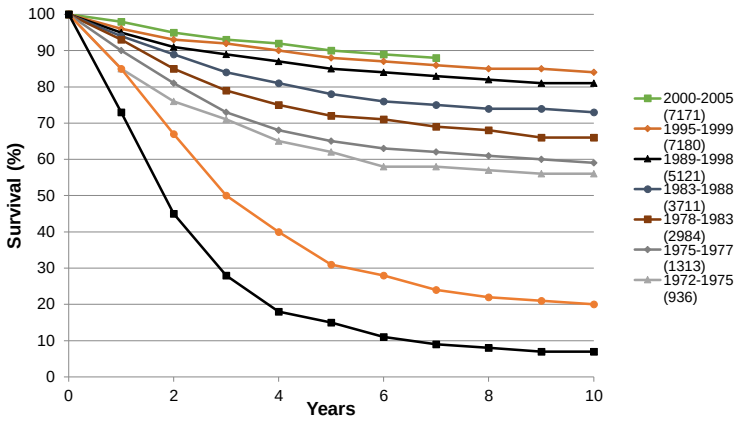
Childhood ALL: Achieving Cure for Many



Adamson. *Hunger*. 2015.

3

Overall Survival in B-ALL

Patient Group	5 yr OS% 2000-05	5 yr OS% 2006-09	P Value
B-ALL	91.1 +/- 0.4% (n=6617)	92.2 +/- 0.5% (n=6078)	0.057
NCI HR B-ALL	84.5 +/- 0.9% (n=1911)	85.0 +/- 1.2% (n=1946)	0.968
NCI SR B-ALL	95.2 +/- 0.3% (n=4546)	96.1 +/- 0.4% (n=4087)	0.037

Hunger et al. *SIOP*. 2013.

4

Survival Improvements Over 20 Years: T-ALL vs B-ALL

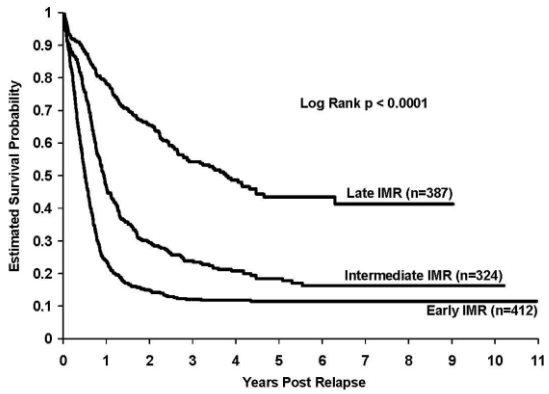
Patient Group	5 yr OS% 1990-94	5 yr OS% 2006-09
B-ALL	84.9 +/- 0.5 (n=5068)	92.2 +/- 0.5% (n=6078)
T-ALL	70.7 +/- 1.7% (n=748)	90.6 +/- 2.7% (n=449)

- OS difference for T-ALL vs B-ALL was 14.2% in 1990-94 and 1.6% in 2006-09
- Improved survival for T-ALL likely helps to explain the improved survival for African Americans over past 20 years

Hunger et al. *JCO*. 2012; *SIOP*. 2013.

5

Limited Ability to Cure ALL After Medullary Relapse



IMR = isolated medullary relapse

Nguyen. *Leukemia*. 2008.

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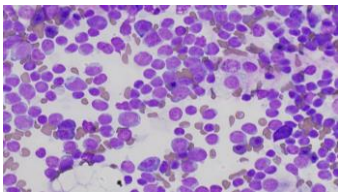
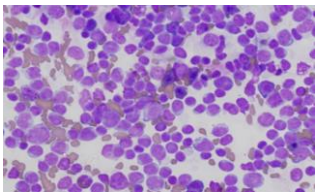
Our Mission



Who will be cured?



Who will have treatment failure?

What 21st century methodologies can we use to identify patients at high risk of treatment failure or increased morbidity?

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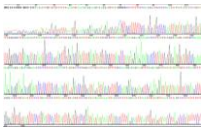
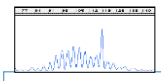
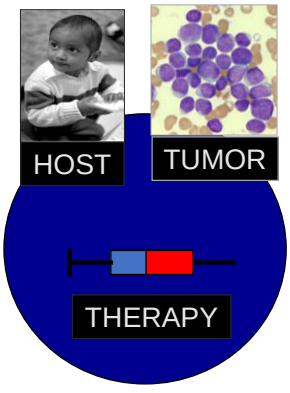
Assessing the Components of Cure for ALL

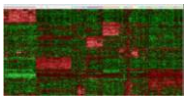


Somatic sequence variations

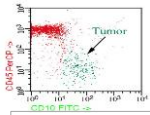


Genetic Polymorphisms Drug Metabolism





Gene Expression Profiling



Minimal Residual Disease

Adapted from Bill Carroll.

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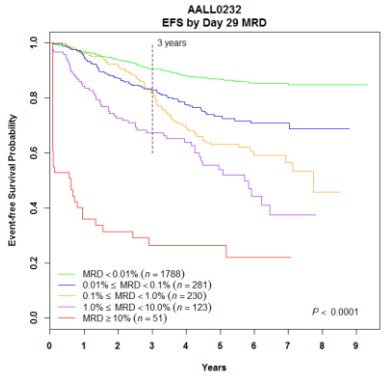
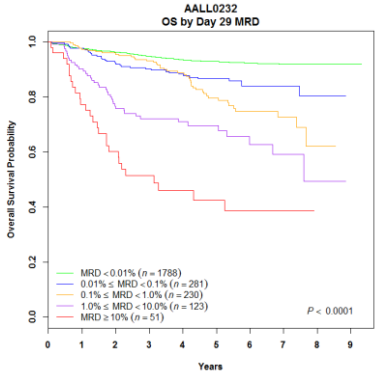
AALL0232 NCI HR: EFS and OS by Day 29 MRD





Borowitz et al. 2015.

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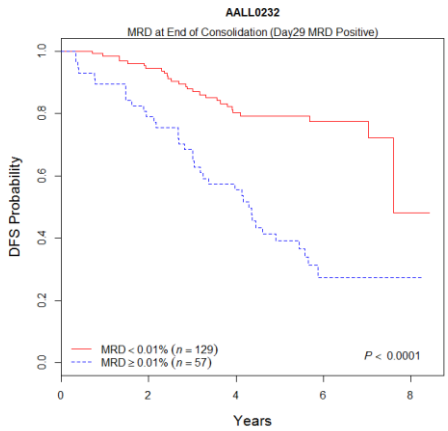
End Consolidation MRD Clarifies Outcome of Day 29 MRD ≥0.1%



- First COG data clearly showing that EOC MRD predicts outcome in B-ALL patients
- Shows that BMT decisions should not be made based on end of induction MRD
- What to do with EOC MRD+ patients will be a significant discussion point for design of 2018 B-ALL trial

Borowitz et al. 2015.

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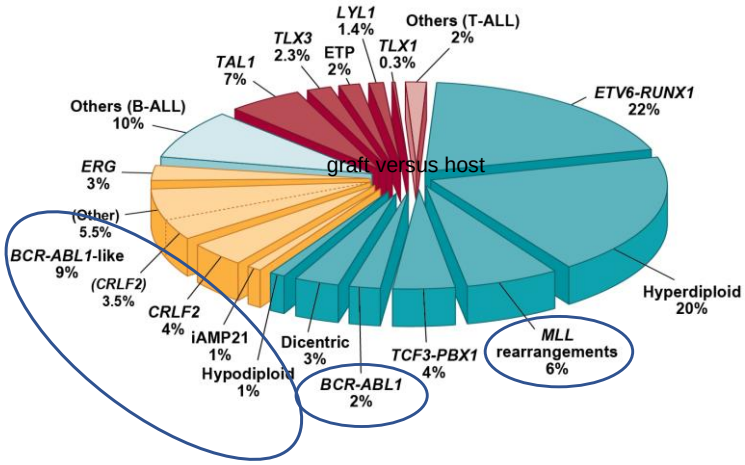
Somatic Blast Alterations Are Prognostically Important



Courtesy of Pui CH.

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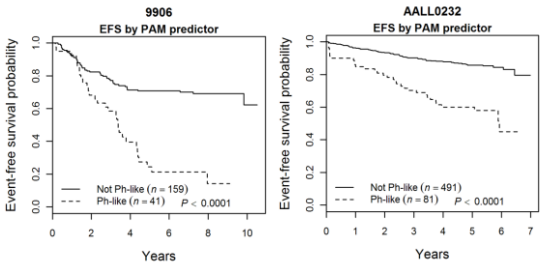
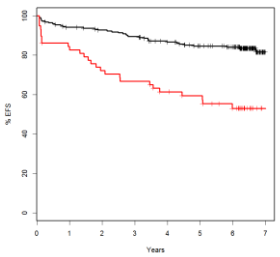
Outcome of Ph-Like ALL

- AALL0232 HR-ALL trial Ph-like ALL pts are more than 3x likely to die than other HR ALL pts
  - 5-yr EFS: 59% v 85%; OR=3.46; p<0.001
- Ph-like ALL may be rapidly identified by LDA card





Multivariable analysis shows Ph-like GEP is independently predictive of poor outcome

Loh. *Blood*. 2013.

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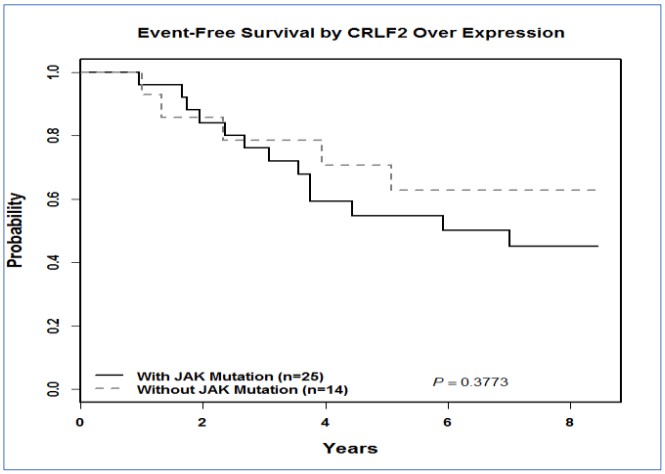
Poor Outcome of Ph-Like ALL With *CRLF2*-R



AALL0232 analyses; unpublished.

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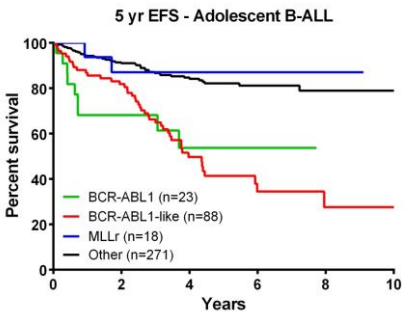
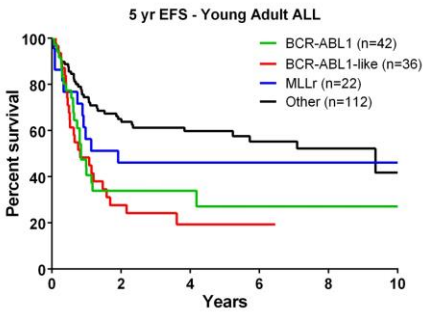
Outcome of AYA B-ALL





5 yr EFS
BCR-ABL1: 53.7%
BCR-ABL1-like: 40.0%
MLL-rearranged: 86.2%
Other: 82.0%

5 yr EFS
BCR-ABL1: 23.2%
BCR-ABL1-like: 16.1%
MLL-rearranged: 43.2%
Other: 57.9%

Roberts. *NEJM*. 2014.

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How Will We Identify Patients at High-Risk for Relapse and Treat Them?

"NCI HR, Ph-like, MRD+,CRLF2-JAK2+"

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What Is the Indication for Hematopoietic Cell Transplant (HCT) in ALL?

- Generally accepted that predicted event-free survival (EFS) <60% should warrant BMT in first remission (before relapse occurs)
- But the caveat exists that BMT outcomes should be considerably better than chemotherapy alone
  - Example of patients with HR BALL who are end of induction (EOI)
    MRD-positive AND end of consolidation (EOC) MRD-positive
    - Chemotherapy outcomes predict EFS <40% compared to >80% with BMT
- Using combination of underlying biology and treatment response (EOI MRD, EOC MRD) to best determine role for chemo versus BMT in first remission

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What Is the Indication for BMT in ALL?

- Any first relapse within 3 years from the diagnosis of ALL is an indication for BMT
- Any first relapse after 3 years from diagnosis of ALL where the MRD is >0.1% after re-induction chemotherapy is an indication for BMT
- Any relapse of TALL, Philadelphia chromosome–positive ALL or infant ALL is an indication for BMT

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Hematopoietic Cell Transplant Process in Pediatric Acute Lymphoblastic Leukemia

Rachel Phelan, MD, MPH
Assistant Professor
Medical College of Wisconsin
Director, Next Steps Survivorship Program
Children's Wisconsin
Milwaukee, WI

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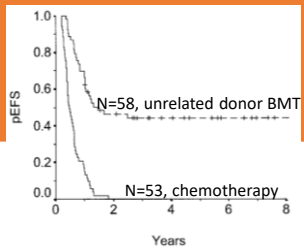
Why Do We Perform HCT in These Patients?

- High-risk patients:
  - very early BM or combined relapse
  - early BM relapse
- Chemotherapy alone resulted in subsequent relapse or death in all patients
- HCT improved outcomes with EFS of almost 50%

As previously mentioned, studies have shown improved outcomes over chemotherapy alone for high-risk patients



Borgmann A et al. *Blood*. 2003.

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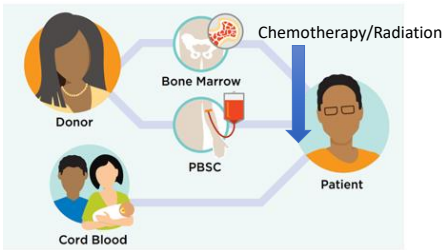
How Does HCT Work to Treat ALL?



Incorporates different treatment modalities:

Different types and doses of chemotherapy agents	Radiation	New immune system to fend off cancerous cells

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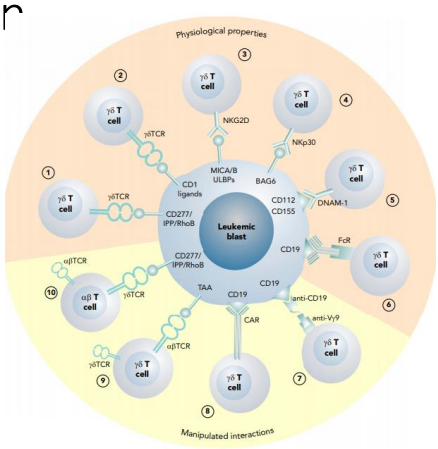
Our Immune System:
The Body's Protection

- Fends off infection (bacterial, viral, fungal)
- Also fights off mutated/cancerous cells
- Consists of multiple types of cells (eg, NK cells, B-cells, T-cells, neutrophils)
- Results in "graft-vs-leukemia"



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The HCT Process (in 6 Steps)

(1) Find a donor → (2) Conditioning

(3) Stem cell infusion → (4) Neutropenic phase

(5) Engraftment phase → (6) Post-engraftment period

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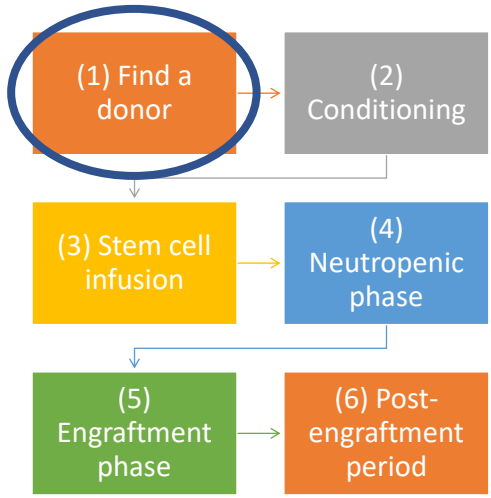
The HCT Process (in 6 Steps)



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Step 1: Find a Donor

-HLA (human leukocyte antigen—a protein on cell surfaces) typing is performed to ensure the genetics of the donor and recipient immune system cells are similar

Close "matches" decreases risk of graft vs host disease (GVHD)

-Matched sibling has been traditionally preferred

~25% chance each sibling will be a match

-National registries (NMDP) to find matched unrelated donors has increased the pool of donor options

> 20 million volunteer donors

-Use of umbilical cord blood

-Partially matched related donors

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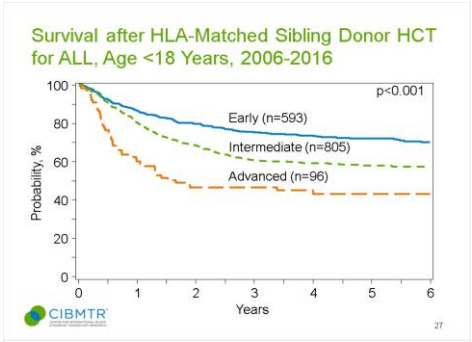
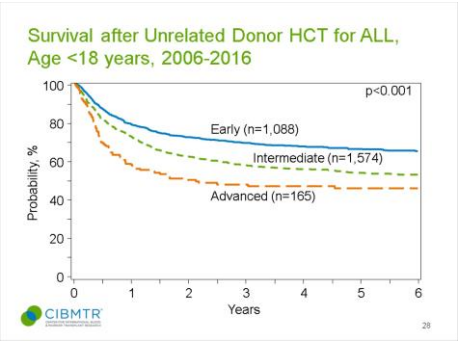
Sibling vs Unrelated Donor





D'Souza A, Fretham C. CIBMTR Summary Slides. 2018.

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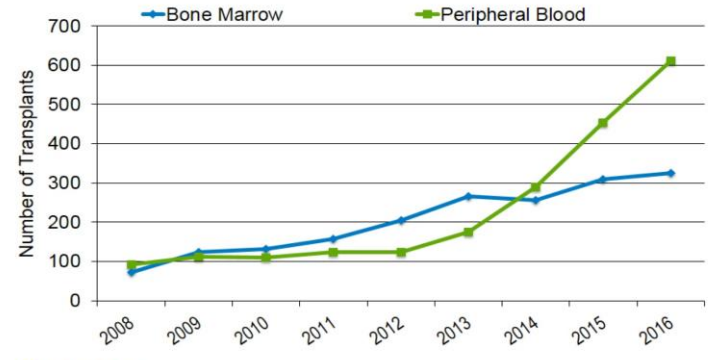
Haploidentical HCT Recipients in the US, by Graft Type



D'Souza A, Fretham C. CIBMTR Summary Slides. 2018.

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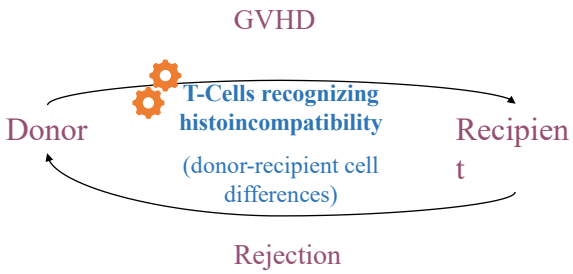
The HCT Vicious Circle



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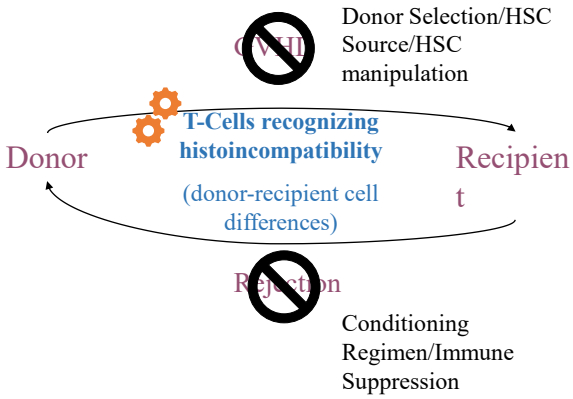
The HCT Vicious Circle



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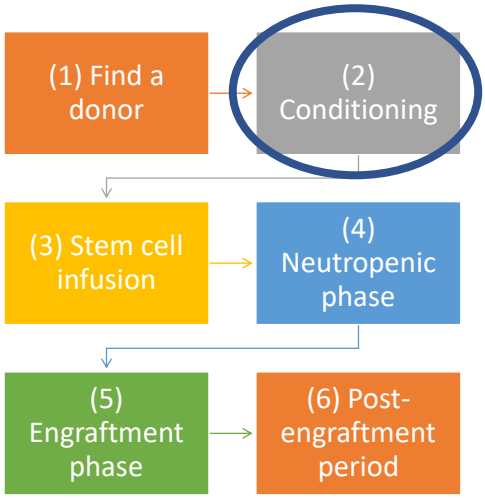
The HCT Process (in 6 steps)



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Step 2: Conditioning

- Consists of the chemotherapy and/or radiation given prior to infusion of the new stem cells (generally given over ~1 week)
  - Eliminates any residual cancer cells
  - Immunosuppresses the donor cells
  - Makes space for the new cells to come in

Common side effects: nausea/vomiting, hair loss, mucositis, decreased appetite, etc.

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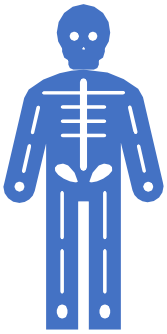
When Is the Right Time to Start the Conditioning?



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Pre-HCT Evaluations to Make Sure the Patient Can Tolerate HCT

- Cardiac Function
- Renal Function
- Lung Function
- Liver Function
- No active or uncontrolled infections
- **Disease status…**

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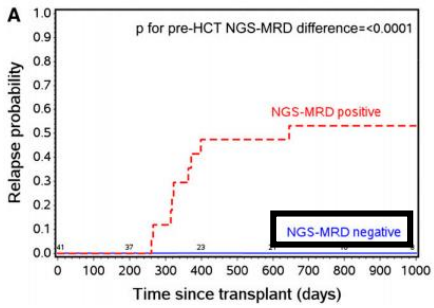
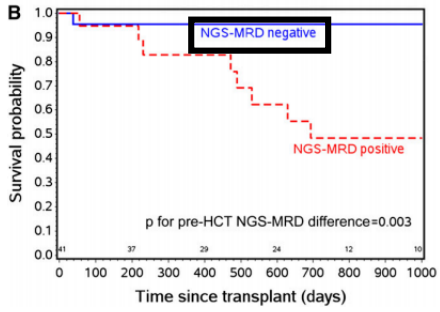
Outcomes Improved if MRD Negative State Can be Achieved



No relapses if MRD negative pre-HCT

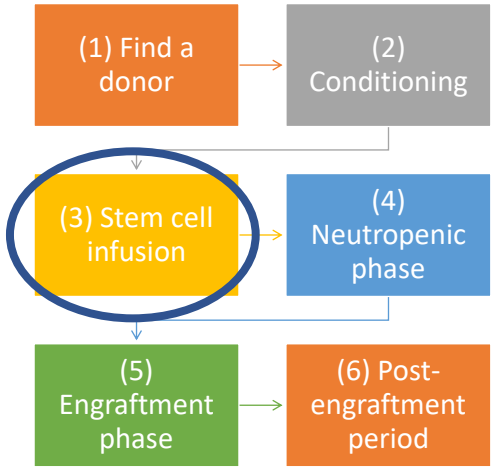


Survival improved if MRD negative pre-HCT

Pulsipher et al. *Blood*. 2015.

33

The HCT Process (in 6 steps)



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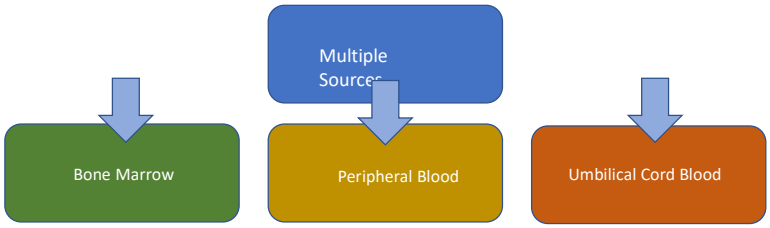
Step 3: Cell Infusion

- Given after conditioning is completed
- Via infusion through a central line



All cell sources with different risks and benefits

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More About Infusion

Anaphylaxis, volume overload, and transient GVHD are the major potential complications involved

Stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO) as a preservative and potentially can cause renal failure, in addition to the unpleasant smell and taste

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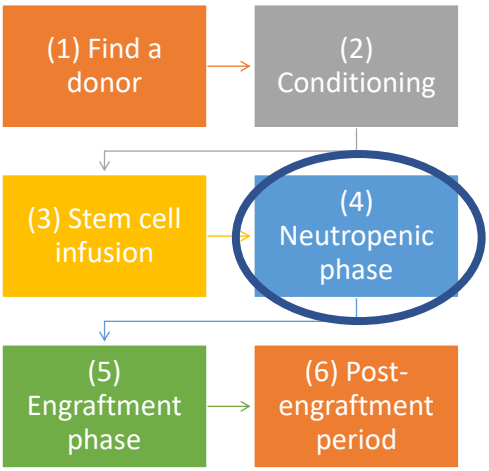
The HCT Process (in 6 Steps)



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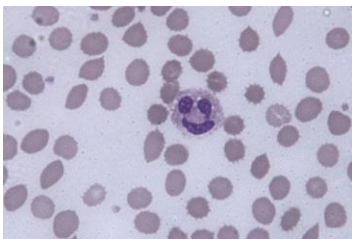
Step 4: Neutropenic Phase

- During this period (2-4 wk), the patient essentially has no effective immune system
- Healing is poor, and the patient is very susceptible to infection
- Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase



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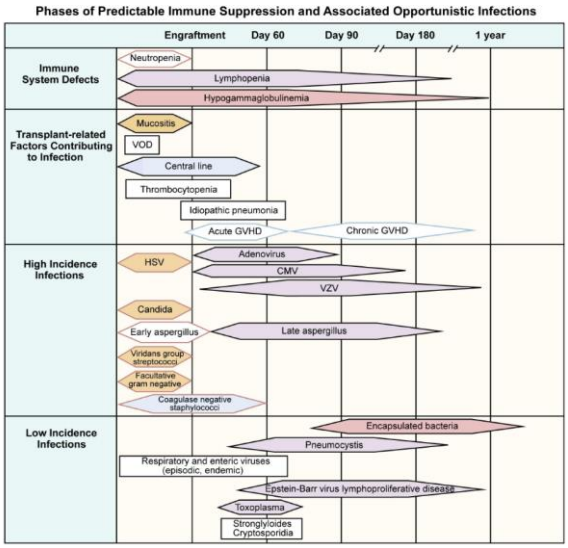

Phases of predictable immune suppression with their opportunistic infections among allogeneic hematopoietic stem cell transplantation recipients. Adapted from Burik and Freifeld. This figure was published in *Clinical Oncology*, 3rd edition, Abeloff et al., Chapter: Infection in the severely immunocompromised patient, Pages 941–956, Copyright Elsevier (2004).

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The HCT Process (in 6 Steps)

(1) Find a donor → (2) Conditioning

(3) Stem cell infusion → (4) Neutropenic phase

(5) Engraftment phase → (6) Post-engraftment period

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Step 5: Engraftment Phase

- During this period (several weeks), the healing process begins
  - Resolution of mucositis and other lesions acquired
  - Fever begins to subside and infections often begin to clear
  - The greatest challenges at this time are management of GVHD and prevention of viral infections (especially CMV)

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Potential Complications

- Infections
- Graft Rejection/Failure
- Liver Disease
- Lung Disease
- Renal Disease
- Heart Disease
- Graft vs Host Disease

Acute and Chronic Forms of all of the above are a risk that we discuss

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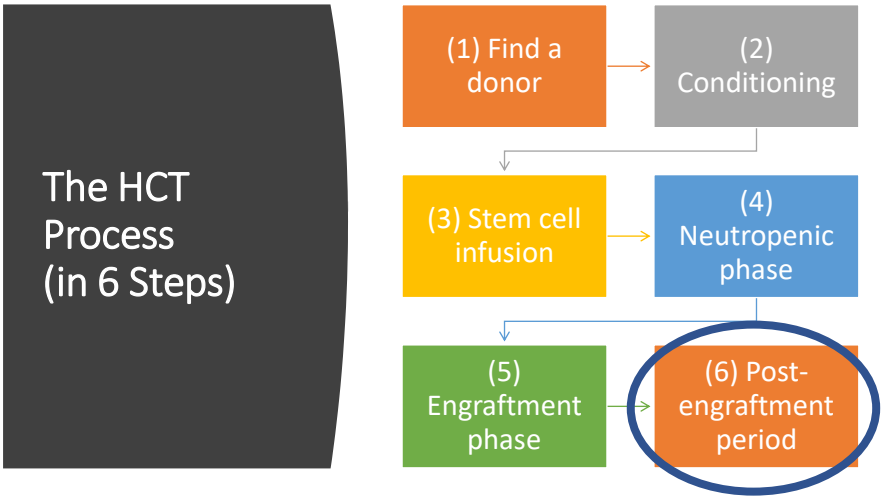

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Step 6: Post-Engraftment Phase

- This period lasts for months to years
- Hallmarks of this phase:
  - gradual development of tolerance
  - weaning off immunosuppression
  - management of chronic GVHD
  - documentation of immune reconstitution (new immune system beginning to function)

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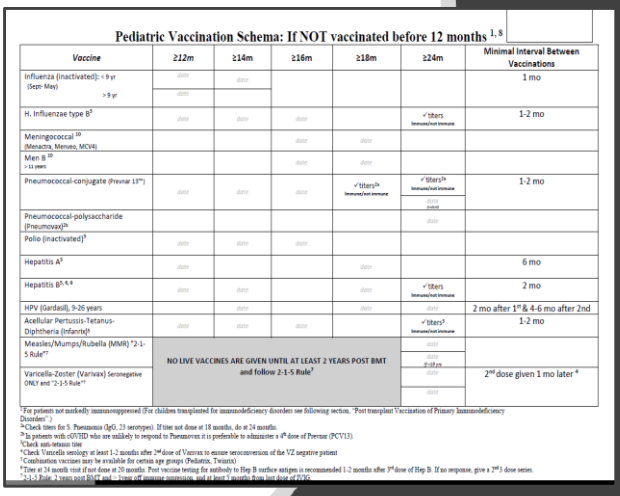

Pediatric Vaccination Schema: If NOT vaccinated before 12 months [1, 8]

Vaccine	≥12m	≥14m	≥16m	≥18m	≥24m	Minimal Interval Between Vaccinations
Influenza (inactivated): < 9 yr (Sept- May)	date	date				1 mo
> 9 yr	date					
H. Influenzae type B[5]	date	date	date		✓titers Immune/not immune	1-2 mo
Meningococcal[10] (Menactra, Menveo, MCV4)			date	date		
Men B[10] - 11 years			date	date		
Pneumococcal-conjugate (Prevnar 13™)	date	date	date	✓titers[2b] Immune/not immune	✓titers[2b] Immune/not immune	1-2 mo
					date 2nd dose	
Pneumococcal-polysaccharide (Pneumovax)[2b]					date	
Polio (inactivated)[3]	date	date	date			
Hepatitis A[9]	date			date		6 mo
Hepatitis B[6, 8, 9]	date	date		date	✓titers Immune/not immune	2 mo
HPV (Gardasil), 9-26 years		date		date	date	2 mo after 1st & 4-6 mo after 2nd
Acellular Pertussis-Tetanus-Diphtheria (Infanrix)[4]	date	date	date		✓titers[3] Immune/not immune	1-2 mo
Measles/Mumps/Rubella (MMR) *2-1-5 Rule*[7]	NO LIVE VACCINES ARE GIVEN UNTIL AT LEAST 2 YEARS POST BMT and follow 2-1-5 Rule[7]				date 2nd dose	
Varicella-Zoster (Varivax) Seronegative ONLY and *2-1-5 Rule*[7]					date	2nd dose given 1 mo later [4]
					date	

*For patients not markedly immunosuppressed (For children transplanted for immunodeficiency disorders see following section, "Post transplant Vaccination of Primary Immunodeficiency Disorders".)
[2b] Check titers for S. Pneumonia (IgG, 23 serotypes). If titer not done at 18 months, do at 24 months.
[3] In patients with cGVHD who are unlikely to respond to Pneumovax it is preferable to administer a 4th dose of Prevnar (PCV13).
[4] Check anti-tetanus titer
[5] Check Varicella serology at least 1-2 months after 2nd dose of Varivax to ensure seroconversion of the VZ negative patient
[7] Combination vaccines may be available for certain age groups (Pediarix, Twinrix)
[8] Titer at 24 month visit if not done at 20 months. Post vaccine testing for antibody to Hep B surface antigen is recommended 1-2 months after 3rd dose of Hep B. If no response, give a 2nd 3 dose series.
[9] 2-1-5 Rule: 2 years post BMT and > 1year off immune suppression and at least 5 months from last dose of IVIG

Revaccination

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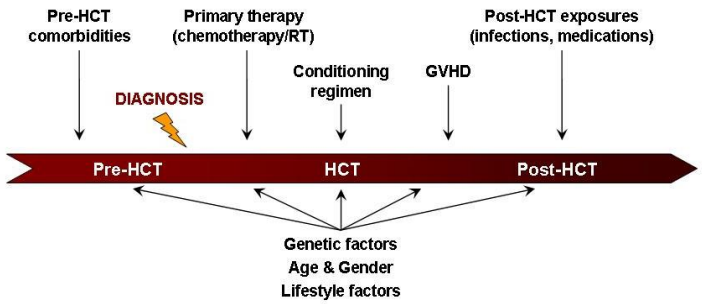
Risk Factors for Early and Late Complications



Majhail N, Rizzo J. *BBMT*. 2013.

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Reminder: Potential Complications

- Infections
- Graft Rejection/Failure
- Liver Disease
- Lung Disease
- Renal Disease
- Heart Disease
- Graft vs Host Disease

Acute and Chronic Forms of all of the above are a risk that we discuss

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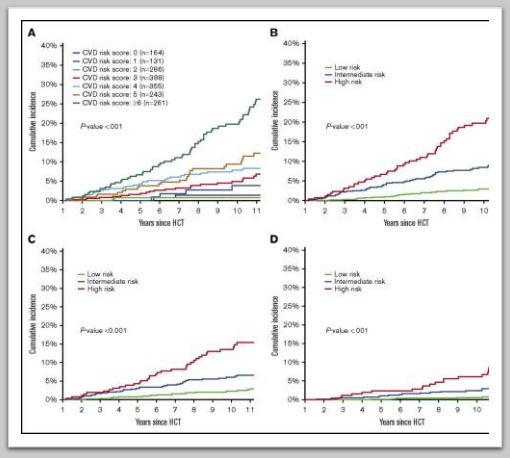

Example: Cardiovascular Health

Armenian SH et al. *Blood Adv*. 2018;2:1756-1764.

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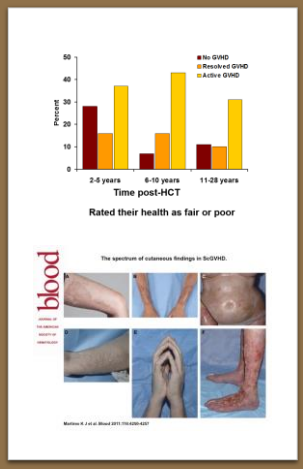

Example: Chronic GVHD

- Can involve any organ/body system:
  - Skin
  - Eye
  - Mouth
  - Pulmonary disease
  - Immunological dysfunction
  - Esophageal and vaginal strictures/fibrosis
  - Joint contractures
- The strongest association between reduced quality of life following HCT is the presence of chronic GVHD
- Increases the risk of squamous cell carcinoma following HCT

Fraser CJ et al. *Blood*. 2006.
Pidala et al. *Blood*. 2011.
Curtis et al. *Blood*. 2005.

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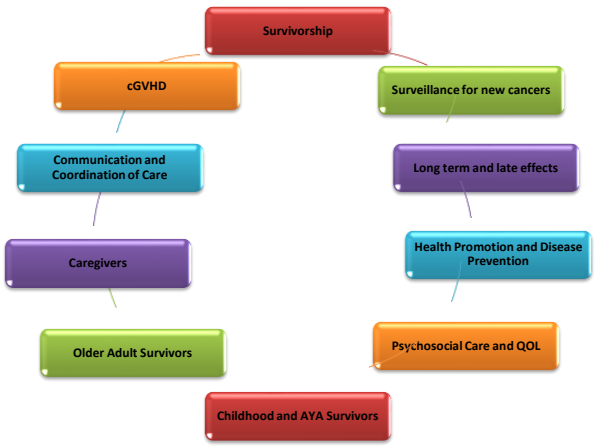
Importance of Continued "Survivorship" Care



Nekhlyudov et al. *Lancet Oncol*. 2017;23:1968-73.

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Novel Therapies

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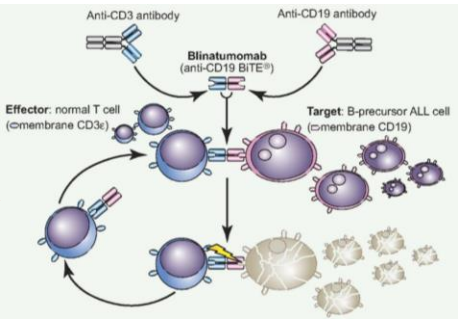
Immunotherapy as an Alternative or in Addition to HCT

<u>Harnessing the power of our own immune system to fight leukemia cells</u>

- Targeted monoclonal antibodies (rituximab)
- Bispecific T-cell engagers (blinatumomab, inotuzumab)
- Chimeric antigen receptor T-cell therapy (CART)



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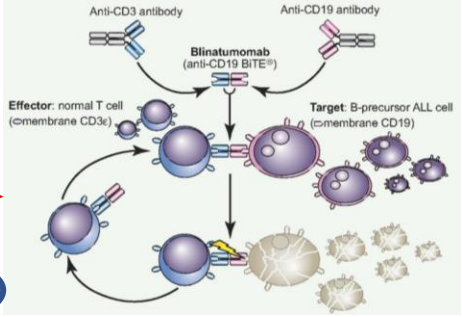

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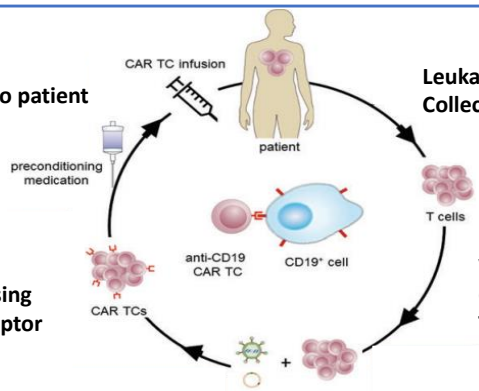
Creating Autologous T-Cells to Target Leukemia

Infusion:
Of CAR T-cells into patient

Growth:
Of T-cells expressing the chimeric receptor



Leukapheresis:
Collect T-cells

Viral Transduction:
Chimeric receptor into T-cells

Shubert et al. *Hum Gene Ther.* 2016; Frey NV, Porter DL. *Am J Hematol.* 2016.

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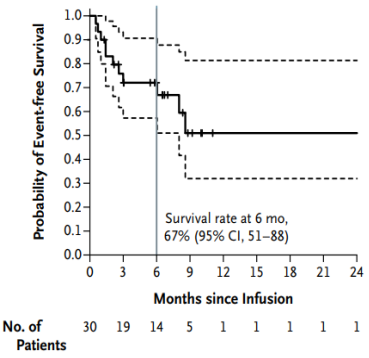
CART Therapy Leads to High Rates of CR

- N=30 children and adults with pre–B-ALL
- 80% of patients had detectable leukemia prior to infusion
- 90% were able to achieved complete remission
- Only 7 of these patients ultimately relapsed
- 6-month EFS = 67%, OS = 78%



Maude S et al. *New Eng J Med*. 2014.

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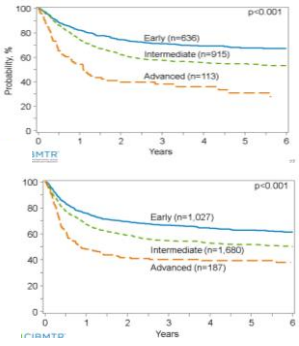
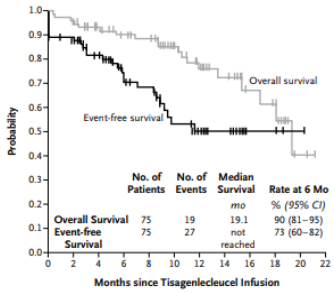
Not Enough Data at This Time to Say That CAR T-Cell Outcomes Are Better Than HCT



Early = ALL in 1st CR 1
Intermediate = ALL in ≥ 2nd CR
Advanced = Acute leukemia in relapse



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Summary

- Overall survival for childhood ALL has dramatically improved in the last 50 years
- Despite these improvements, some children have poor initial responses or eventually relapse
- HCT is an available treatment modality for high-risk or relapsed patients
  - Many improvements have been made in recent years
  - Requires long-term follow-up care
- Novel treatments have the potential to change the landscape of short-term and long-term outcomes

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Questions

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LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Free Nutrition Consults:** www.LLS.org/nutrition
- **Caregiver Support:** www.LLS.org/caregiver
- **Free Education Booklets:** www.LLS.org/booklets
- **Free Telephone/Web Programs:** www.LLS.org/programs
- **Live, weekly Online Chats:** www.LLS.org/chat
- **LLS Community:** www.LLS.org/community

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

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LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org
- **Education Videos**

  Free education videos about survivorship, treatment, disease updates, and other topics: www.LLS.org/educationvideos
- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection
- **What to Ask**

  Questions to ask the treatment team: www.LLS.org/whattoask
- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance, and more: www.LLS.org/support

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THANK YOU
We have one goal: A world without blood cancers
LEUKEMIA &
LYMPHOMA
SOCIETY

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