Indications for Hematopoietic Cell Transplant in Pediatric Acute Lymphoblastic Leukemia

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Childhood ALL: Achieving Cure for Many

Overall Survival in B-ALL

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

Hunger et al. SIOP, 2013.
Survival Improvements Over 20 Years: T-ALL vs B-ALL

<table>
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<th>5 yr OS% 1990-94</th>
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<tr>
<td>B-ALL</td>
<td>84.9 +/- 0.5% (n=5068)</td>
<td>92.2 +/- 0.5% (n=6078)</td>
</tr>
<tr>
<td>T-ALL</td>
<td>70.7 +/- 1.7% (n=748)</td>
<td>90.6 +/- 2.7% (n=449)</td>
</tr>
</tbody>
</table>

- 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

Hung et al. JCO. 2012; SIOP. 2013.

Limited Ability to Cure ALL After Medullary Relapse

IMR = isolated medullary relapse

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?

Assessing the Components of Cure for ALL

Adapted from Bill Carroll.
AALL0232 NCI HR: EFS and OS by Day 29 MRD

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
Somatic Blast Alterations Are Prognostically Important

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
Poor Outcome of Ph-Like ALL With CRLF2-R

Outcome of AYA B-ALL

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

5 yr EFS - Young Adult ALL
- BCR-ABL1: 23.2%
- BCR-ABL1-like: 16.1%
- MLL-rearranged: 43.2%
- Other: 57.9%
How Will We Identify Patients at High-Risk for Relapse and Treat Them?

“NCI HR, Ph-like, MRD+,CRLF2-JAK2+”

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
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

Hematopoietic Cell Transplant Process in Pediatric Acute Lymphoblastic Leukemia

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Director, Next Steps Survivorship Program
Children’s Wisconsin
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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.

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
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 (e.g., NK cells, B-cells, T-cells, neutrophils)
- Results in “graft-vs-leukemia”

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 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.
Sibling vs Unrelated Donor

Survival after HLA-Matched Sibling Donor HCT for ALL, Age <18 Years, 2006-2016

- Early (n=593)
- Intermediate (n=805)
- Advanced (n=98)

Survival after Unrelated Donor HCT for ALL, Age <18 years, 2006-2016

- Early (n=1,086)
- Intermediate (n=1,574)
- Advanced (n=165)

Haploidentical HCT Recipients in the US, by Graft Type

- Bone Marrow
- Peripheral Blood

Number of Transplants

- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
The HCT Vicious Circle

Donor

T-Cells recognizing histoincompatibility (donor-recipient cell differences)

Recipient

GVHD

Rejection

Donor Selection/HSC Source/HSC manipulation

Conditioning Regimen/Immune Suppression
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.
When Is the Right Time to Start the Conditioning?

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...
Outcomes Improved if MRD Negative State Can be Achieved

No relapses if MRD negative pre-HCT

Survival improved if MRD negative pre-HCT

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

![Multiple Sources]

- Bone Marrow
- Peripheral Blood
- Umbilical Cord Blood

*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.
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
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).
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)

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
The HCT Process (in 6 Steps)

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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)
Revaccination

Risk Factors for Early and Late Complications

Pre-HCT comorbidities

Primary therapy (chemotherapy/RT)

Post-HCT exposures: (infections, medications)

DIAGNOSIS

Conditioning regimen

GVHD

Pre-HCT

HCT

Post-HCT

Genetic factors

Age & Gender

Lifestyle factors

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.

Example: Cardiovascular Health

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


Importance of Continued “Survivorship” Care

- Survivors
- cGVHD
- Communication and Coordination of Care
- Caregivers
- Older Adult Survivors
- Childhood and AYA Survivors
- Surveillance for new cancers
- Long term and late effects
- Health Promotion and Disease Prevention
- Psychosocial Care and QOL

Immunotherapy as an Alternative or in Addition to HCT

- Targeted monoclonal antibodies (rituximab)
- Bispecific T-cell engagers (blinatumomab, inotuzumab)
- Chimeric antigen receptor T-cell therapy (CART)
Immunotherapy as an Alternative or in Addition to HCT

Harnessing the power of our own immune system to fight leukemia cells

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

Creating Autologous T-Cells to Target Leukemia

Infusion: Of CAR T-cells into patient

Leukapheresis: Collect T-cells

Growth: Of T-cells expressing the chimeric receptor

Viral Transduction: Chimeric receptor into T-cells

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 achieve complete remission
- Only 7 of these patients ultimately relapsed
- 6-month EFS = 67%, OS = 78%


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

Summary

Questions
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.

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
We have one goal: A world without blood cancers.

THANK YOU