Acute Lymphoblastic Leukemia in Pediatric & AYA Patients: Treatment Options including BMT, Care & Support

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Jointly Sponsored Program

- The National Marrow Donor Program/Be The Match
- The Leukemia & Lymphoma Society
Learning Objectives

At the conclusion of this webinar, attendees will be able to:

• Describe the latest treatments for acute lymphoblastic leukemia (ALL) for pediatric, adolescent and young adult (AYA) patients including current and emerging therapies.

• Explain the impact of timely blood and marrow transplantation (BMT) consultation.

• List the psychosocial impact of diagnosis, treatment trajectory, and strategies to support patients and families.

• Identify educational programs and resources to support patients and caregivers.

Continuing Education

• **Nurses** – The National Marrow Donor Program is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation (COA).
  – Up to 1.25 contact hours may be claimed for this educational activity.

• **Social Workers** – The Leukemia & Lymphoma Society, provider #1105 is approved as a provider for social work continuing education by the Association of Social Work Boards [www.aswb.org](http://www.aswb.org). Approved Continuing Education Program (ACE). Approval Period: 12/2014 - 12/2017. LLS maintains responsibility for the program. Social workers should contact their regulatory board to determine course approval.
  – Social workers will receive 1.25 CE clinical clock hours.
  – LLS is recognized by the New York State Education Department's State Board for Social Work as an approved provider of continuing education for licensed social workers #0117. LLS maintains responsibility for the program. Social workers will receive 1.25 clinical CE contact hours for this activity.
Continuing Education cont.

- **Medical Technologists** – The NMDP is approved as a provider of continuing education in the clinical laboratory sciences through the ASCLS PACE Program. ASCLS PACE® 1861 International Drive, Suite 200, McLean, VA 22102.
  - Up to 1.0 contact hours may be claimed for program #115-007-16.

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- For technical support during the webinar, please email: nmdpeducation@nmdp.org.

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- Attendees will receive an email following the webinar with a link to the evaluation. All attendees completing the online program evaluation will receive a statement of continuing education.
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If you have multiple attendees on one phone line/viewing on one computer, please type the number of additional attendees in the ‘Chat’ window.
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If you have a question, please type your question in the ‘Chat’ window.
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ALL in AYA Patients
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Hematology/Oncology
What/who are AYA in oncology?

- People with cancer aged 15-39
- A distinct subgroup of oncology patients with unique challenges, both medical and psychosocial
- An underserved population

Incidence of cancer in AYA

- Cancer is 2.7 times more likely to develop in people between the ages of 15-30 than in the first 15 years of life
- In 2011, approximately 69,000 15-39 year olds were diagnosed with cancer
- The incidence of cancer in this age group has increased steadily over the past 25 years
- Cancer is most common cause of non-accidental death in this age group
Cancer Types in AYA

Leukemia in AYA

• ALL is the most common cancer in people from birth to age 21

• ALL is one of the leading causes of cancer related mortality in AYA

• There has been a continual increase in the incidence of ALL in AYA since 1975
  – Unclear whether that is due to improved reporting vs. truly increased incidence

• Age is one of the most important prognostic factors for outcome in ALL, and survival begins to decrease dramatically at age 15

• Unfavorable genetic abnormalities are more common in AYA

Source: SEER
Mortality/Survival
• 25 years ago diagnosis of cancer at this age carried a more favorable prognosis relative to other ages

• Since that time, there has been a relative lack of improvement in survival among adolescents and young adults

Survival

Source: SEER 13 Areas, 1992-2010
Why is survival different?

• Delay in diagnosis?
• Less access to treatment?
• Treatment adherence?
• Different cancer biology?
• Different metabolism of chemotherapy?
• Decreased enrollment on clinical trials?

How should we treat AYA with leukemia?

• AYA fare better when treated on pediatric protocols
  – Adult protocols
    • EFS 38% at 6 years
  – Pediatric protocols
    • EFS 64% at 6 years (vs. >75% for ages 0-10 on same protocols)
    • OS still < 45%

**Pediatric regimen in adult setting**

- These data prompted a prospective study to evaluate the feasibility of using a pediatric regimen for AYA in the adult oncology setting.

- C10403 used in the US adult cooperative groups
  - Standard arm of COG AALL0232

- Low treatment related mortality (3%)
  - Asparaginase well tolerated

- 2 year EFS 66%
- 2 year OS 78%


**What is AALL0232?**

- Children’s Oncology Group protocol for high risk ALL

- Standard 4 drug induction

- Increased CNS directed therapy

- Compared the use of dexamethasone and prednisone in induction

- Compared two interim maintenance and two delayed intensifications versus one of each
AALL0232 outcomes

- Incidence of osteonecrosis higher in older patients using dexamethasone

- High dose methotrexate significantly increased 5 year event free survival when compared with escalating dose methotrexate in interim maintenance

- Two delayed intensification courses incurred increased toxicity without better efficacy

- Thus, AYA on this protocol (and the adult protocol) receive prednisone and high dose methotrexate

Current Open COG ALL Phase III studies

- AALL1131
  - High risk B-ALL
  - Looks at Cyclophosphamide/Etoposide alone and in combination with Clofarabine
  - Clofarabine arm recently closed due to toxicity

- AALL1231
  - T-ALL using Bortezomib on BFM backbone

- AALL1331
  - Relapsed B-ALL
  - Blinatumomab
AALL1131

- Classifies all patients \( \geq 13 \) as very high risk
- Goal: to improve disease free survival with increased therapy post induction using etoposide and cytoxan
- Since 4 year disease-free survival \(<80\%\), accepted more toxic strategies
- One arm randomized to include clofarabine, closed due to unacceptable toxicity
- Transplant recommended post consolidation if hypodiploid or induction failure

AALL1231

- T-ALL adding Bortezomib
- Primary goal to prevent relapse due to dismal salvage rate.
- Aims:
  - decrease relapse rate
  - omit cranial radiation when possible
  - identify patients who are chemotherapy refractory and need novel agents or transplant
Bortezomib

- Proteasome inhibitor
- In vitro, found to have single agent activity against T-ALL
- In vivo in NOD-SCID mice with T-ALL had 100% response rate
- Shown to overcome chemotherapy resistance to anthracyclines, alkylators, and corticosteroids in other malignancies
- Acceptable toxicity profile in early phase trials
- Safely added to intensive ALL re-induction backbone, with early evidence supporting its use in T-ALL

AALL1331

- Relapsed B-ALL
- Aim: To compare overall survival of patients with the addition of Blinatumomab to a backbone of chemotherapy.
Blinatumomab

- Antibody that targets CD19 antigen and redirects CD3+ T cells for selective lysis of tumor cells
- Effective and well tolerated in Phase I/II studies

Other clinical trials

- 400 clinical trials listed for ALL on clinicaltrials.gov
- Most Phase I or Phase I/II looking at toxicity of newer agents in combination with chemotherapy for relapsed/refractory patients
- New agents in several different classes:
  - CAR T cells
  - Tyrosine kinase inhibitors (TKI)
  - HDAC inhibitors
  - JAK 1/2 inhibitors
  - Sirolimus
  - Monoclonal antibodies
Immunotherapy

- The future of cancer therapy
- Using the patient’s immune system to attack cancer cells
- Includes CAR T cells
- Hope for cancer targeted therapy with fewer long-term side effects

CAR T cells
CAR T cells

Next steps

• Working toward targeted therapy

• Beginning to do genome wide sequencing to look for actionable targets

• Ultimate goal to use therapy that targets only cancer cells in order to eliminate toxicities of chemotherapy
Outline

- Summarize the prevalence of ALL in children and AYA, including indications for BMT
- Highlight advances in transplant
- Discuss when to refer for transplant consultation
  - Evaluation: Assessing disease status; timing for transplant; donor selection; insurance matters; family support system/caregiver availability
- Outline donor options when a sibling match is not available
  - Review likelihood of finding an unrelated donor or cord blood unit
    - Donor recruitment initiatives through Be The Match
    - Review of survival data
Background

- Approximately 6,250 cases of acute lymphoblastic leukemia (ALL) are diagnosed annually in the United States
  - Both pediatric and adult patients
  - This represents about 23% of new acute leukemias and 0.4% of all new cancers
  - 5-year overall survival is 67.5% for all
    - Pediatrics is > 85%
- ALL is the most common indication for allogeneic hematopoietic cell transplantation (HCT) in patients <20 years with hematological malignancies

New ALL Cases by Age Group
Advances in BMT for ALL in Pediatrics

- Allogeneic transplant is recommended for pediatric ALL patients who experience primary induction failure, but subsequently achieve a first complete remission (CR1)
- Allogeneic transplant and intensive chemotherapy with imatinib have equivalent early outcomes for Ph+ ALL in CR1
- HLA-matched related and unrelated donors provide equivalent outcomes
- Myeloablative total body irradiation containing conditioning regimens are recommended


Advances in BMT for Adults with ALL

- Patients transplanted in earlier disease stage have better outcomes than patients with advanced disease
- Allogeneic transplant is superior to autologous transplantation or chemotherapy for patients with ALL in first complete remission (CR1).
  - The survival advantage is of greater statistical significance for patients with standard-risk ALL than for patients with high-risk ALL
- In the absence of an HLA-matched donor, consider cord blood transplant for adult ALL in CR1
- HLA-matched related and unrelated donor allogeneic transplant produces similar survival outcomes
# Acute Lymphoblastic Leukemia (ALL) - Pediatric
## Timing for Referral for BMT Consultation

- Infant at diagnosis
- High Risk CR1 including:
  - Philadelphia chromosome positive
  - WBC >100,000 at diagnosis
  - 11q23 rearrangement
- Primary induction failure
- Presence of minimal residual disease after initial or subsequent therapy
- First relapse
- CR2 and beyond, if not previously evaluated

Consultation should include:
- Performing high resolution HLA typing on patient and any potential full siblings to determine the possibility of a donor

NMDP/Be The Match/ASBMT REFERRAL GUIDELINES Recommended Timing for Transplant Consultation, 2016.

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# Timing of Referral for Pediatric Patients

- Upon diagnosis, if high-risk, consider a referral to a Transplant Center (TC) sooner.
  - This may only need to be for HLA typing of patient & full siblings (if applicable)
    - HLA typing may take up to 2 weeks to complete
    - Patients and chosen donor will need an initial and confirmatory HLA typing prior to transplant
      - TCs can vary on the type of samples required for HLA typing
    - Protocols may dictate that transplant be considered within the scope of therapy
## Education

- Referral early to a Transplant Center also allows for thorough education to occur
  - Transplant has the potential for many complications
  - Education is an important part of the process
    - By providing time, this gives the family a chance to digest the information and make informed health decisions
    - NMDP /Be The Match has many resources for families and patients

## Acute Lymphoblastic Leukemia (ALL) – Adult

**Timing for Referral for BMT Consultation**

- High resolution HLA typing is recommended at diagnosis for all adult patients
- Early after initial diagnosis, all ALL adult patients should have a BMT consult including:
  - CR1
  - Primary induction failure or relapse
  - Presence of minimal residual disease after initial or subsequent therapy
  - CR2 and beyond, if not previously evaluated

Updated treatment guidelines for clinicians

Free 2016 Clinical Guidelines include:

- HCT consultation timing for 15+ diseases
- Recommended post-transplant screening and preventive practices
- Clinical screening and diagnostic tools for chronic GVHD, with picture atlas
- Recommended vaccination schedule

Available in mobile app, print and online
BeTheMatchClinical.org/guidelines

At The Transplant Center (TC)

- Advantage for the referral to be made is earlier rather than later.
- TC will have a process for referrals
  - Check on insurance to insure that the center would be covered
  - Check to insure that HLA typing of patient and if applicable siblings, is covered
  - TC can begin preliminary search process work
Consult at UNC: One Perspective

- Referral form is completed by the referring physician/designee to the Pediatric BMT Program
  - Includes both internal and external referrals
  - Financial coordinator confirms that patient has insurance and that UNC is covered by the insurance plan
    - Restrictions for HLA typing (patient, siblings, cost constraints) is also clarified
    - This is not approval for transplant
  - MD is assigned at the weekly team meeting
- Decision is made whether to proceed with consult first or completion of HLA typing
  - Completion of HLA typing of patient and siblings helps to shape the donor discussion during the consult

Consult at UNC: One Perspective

- Depending on timing of consult:
  - Prior to or at consult, patient is given educational materials such as NMDP resources: Basics of Transplant, Allogeneic Transplant, and the Super Sam Versus The Monsters video.
- Day of consult:
  - Meet with the Transplant MD for a thorough history, physical, possibly laboratory blood work and discussion regarding transplant
  - Meet with the Transplant Coordinator
    - Key contact person until patient is admitted for transplant
  - Meet with the BMT Social Worker
    - This portion of the consult should occur prior to insurance approval as a psychosocial assessment may be required
    - This visit may identify psychosocial risk factors or barriers such as availability of a caregiver, compliance history, and travel and lodging challenges
Day of Consult at UNC

• Transplant Discussion:
  – Purpose of transplant and why and when the patient may need this potential curative therapy
  – Donor choices: does the patient have a matched sibling, unrelated, cord blood unit, or needing to look for an alternative donor (haploidentical)
    • Discuss the various methods of stem cell collection and donor work-up
  – Pre-evaluation: What needs to be accomplished prior to admission
  – Central line requirements
  – Preparative regimen and potential side effects of medications

Day of Consult at UNC

• Transplant Discussion (con’t):
  – Risks:
    • Preparative regimen
    • Stem cell infusion
    • Post transplant acute
  – Supportive care provided
  – The transplant procedure itself
  – Expected length of hospital stay
  – Expected time to remain locally if outside 1 hour driving distance
  – Potential late effects and monitoring

- Transplant consult is not brief; this visit can take 90 – 120 minutes
- Important to pause and ask patient and family members if they have questions throughout visit
If No Match Sibling...

- About 70% of patients (7 out of 10) who need a transplant do not have a close match in their family.
- An unrelated donor/cord blood preliminary search should be initiated.
  - Even if not moving forward with transplant, the TC may decide to know what are the donor options.
    - Preliminary search does not cost the patient
      - Must be requested by a physician
      - This free search returns a snapshot of potential matching donors and cord blood units on the Be The Match Registry
  - Why is this search important?
    - Provides the patient’s transplant physician an idea of how challenging the search for a donor or cord blood unit may be

Likelihood of finding unrelated donor or cord blood

Range 98-99%: patients <20 years, when searching for adult donor, then cord blood

- Race or ethnic group of searching patient for hematopoietic cell transplantation
  - 8/8 HLA adult donor
  - 7/8 HLA adult donor
  - 6/6 HLA cord blood
  - 5/6 HLA cord blood
  - 4/6 HLA cord blood

## Donor Recruitment Initiatives

- While a close HLA match is still the most important factor for matching a donor and patient, research has also shown that younger donors provide better outcomes.
- Doctors request donors in the 18–44 age group more than 95% of the time.*
  - Recruitment of Younger Donors
    - 18 – 44 years of age
    - No fee to join
  - Adding more members who increase the ethnic diversity of the registry increases the variety of tissue types available.
  - Increasing Donor Commitment and Availability
    - Expansion of preliminary search donor contact processes
  - Recruitment of and access to cord blood units

*NMDP FY2015 Annual Numbers.

## Earlier transplant for patients has a significant impact on survival

- Data from the CIBMTR shows that those transplanted earlier have better outcomes than those transplanted later or with advanced disease.
It Takes a Team

- Taking a patient through BMT, regardless of age, takes a team.
- Prior to moving forward with BMT, patients and families may meet with other members of the team.
  - Advanced Practice Professionals (APPs)
  - Pharmacists
  - Nursing staff
  - School teacher
  - Social Worker, Psychologist
  - Child Life Specialist, Recreational Therapist
Transplant is Difficult…

- Both medically and psychosocially

- If red flags, such as barriers or significant challenges, arise during the BMT consult or psychosocial evaluation, consider developing specific expectations for the patient/family to meet in order to be able to move forward with transplant
  - Goal: Trying to avoid potential complications that can occur because of the concerns that have been identified.
  - Goal: We want our patients/families to succeed.

When Psychosocial Challenges Are Identified

- At UNC, BMT Complex Review Committee was developed
  - Multidisciplinary group, comprised of pediatric and adult MD, lead APP, lead transplant coordinator, social workers, lead pharmacist, clinical program director, inpatient and outpatient nursing leadership
  - Goal:
    - Discuss the concerns/challenges identified in the pre-transplant visits
    - Develop potential solutions for addressing concerns
      - Share this information and expectations with the patient/family prior to moving forward with BMT
Why Timing Is Important?

- Transplant is like a dance – need to choreograph all the pieces…
  - The care of the patient
  - Identifying the donor
  - Clearance of the donor and patient
  - Timing of the patient’s admission with the collection of the donor’s stem cells
- The more time available, the smoother the process may be for the patient and family

References


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Senior Social Worker, Oncology
Ann & Robert H. Lurie
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No financial conflict of interests to disclose.

Psychosocial Impact of a Child’s Cancer Diagnosis: Trauma Informed Care
Learning Objective

• Describe the psychosocial impact of diagnosis and treatment, and strategies to support patients and families.

Anxiety State from New Diagnosis

• Difficulty processing and integrating information
• Short-term memory impairment
• Perceptual field narrows (tunnel vision)
• Distortion of time
• Negative thinking
• Physical symptoms (change of appetite, sleep, abdominal pain, etc.)
Response to Anxiety State

- Use empathy and acknowledge that diagnosis is a trauma
- Understand parents are not willfully ignoring your teaching
- Speak clearly and simply (use plain language) as medical terminology can be confusing or overwhelming
- Repeat information without judgment
- Remind parents of next step frequently
- Redirect tunnel vision in a neutral tone
- Give information in writing in their preferred language

Encourage Resilience

- Introduce families to the medical and psychosocial support team roles so they don’t feel alone
- Address concerns of guilt or blame that they did not notice something sooner
- Emphasize they can call with questions and they're not an inconvenience
- Communicate consistently & respectfully
- Encourage parent self-care
Social Work Support

- Supportive counseling
- Problem solving
- Resources – financial, transportation, local counseling options
- Work-related forms and letters
- Guidance in communicating with patient, siblings, family members, school and friends

Programs and resources to support patients and caregivers

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National Marrow Donor Program /Be The Match
Free LLS Resources for Your Patients

- Publications for your patients: [LLS.org/booklets](http://LLS.org/booklets)
- What to ask: Questions for patients to ask the healthcare team: [LLS.org/whattoask](http://LLS.org/whattoask)
- Education programs: Telephone and web education programs, and local education programs: [LLS.org/programs](http://LLS.org/programs)
- Other helpful organizations resource directory: Directory of national and international resources: [LLS.org/resourcedirectory](http://LLS.org/resourcedirectory)

Free LLS Resources for You & Your Patients

- Information and resources, contact an LLS Information Specialist
  **PHONE:** (800) 955-4572    **EMAIL:** infocenter@LLS.org

- Live, weekly online chats: forums facilitated by oncology SWs to share experiences and chat with others: [LLS.org/chat](http://LLS.org/chat)
- Financial support for patients: [LLS.org/finances](http://LLS.org/finances)
- Education videos for patients: [LLS.org/educationvideos](http://LLS.org/educationvideos)
  
  *Cancer Survivorship in Young Adults: ALL*

- Professional education programs: many offer CE & CME credit: [LLS.org/professionaled](http://LLS.org/professionaled)
- Staying Connected: Facilitating the Learning Experience During & After Cancer Treatment
Free support and resources for your patients

- Confidential one-on-one support and guidance
  - Experienced team of Patient Services Coordinators
  - Peer Connect program
  - Caregiver’s and Parent’s Companion Programs

- Free resources you can distribute to help patients learn about, prepare for and live healthy after transplant:
  - Basics of Transplant video series
  - Transplant Basics booklet
  - Transplant and ALL fact sheet

Order, view or download: BeTheMatchClinical.org/order

Updated treatment guidelines for clinicians

Free 2016 Clinical Guidelines include:

- HCT consultation timing for 15+ diseases
- Recommended post-transplant screening and preventive practices
- Clinical screening and diagnostic tools for chronic GVHD, with picture atlas
- Recommended vaccination schedule

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Questions & Answers with Experts

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Joni Lamb, LCSW

To ask a question, use the Q&A icon
or
General questions / technical support
Email: nmdpeducation@nmdp.org

Health Professional
Continuing Education Programs

• The Leukemia & Lymphoma Society
  Professional Education Program
  – LLS.org/professionaled

• National Marrow Donor Program /Be The Match
  – BeTheMatchClinical.org/Resources-and-Education/