Childhood Acute Lymphoblastic Leukemia

Karen Marcus MD
Leukemia: Definition

• Clonal malignancy (cancer) of blood precursor cells
• Leukemia cell: blast
• Acute leukemia: >25% malignant blast cells in bone marrow
  — Usually “packed”: > 80-90% blasts
Normal Hematopoiesis

stem cell

lymphoid

B

B-cell

T

T-cell

E

RBC

eosinophil

M

platelet

neutrophil

GM

monocyte

Eo
Childhood Cancer in U.S.

- Leukemia: 32%
- CNS: 20%
- Other: 11%
- Lymphoma: 11%
- Neuroblastoma: 8%
- Kidney: 6%
- Bone: 5%
- Sarcoma: 7%

SEER Data, 1975-95
Childhood Leukemia in U.S. (Age < 20 years)

- AML: 19%
- ALL: 74%
- CML: 3%
- Other: 4%

SEER data, 1975-95
Leukemia: Epidemiology

- ~3250 new cases in US/year
  - ~2500 new cases of ALL/year
- Annual incidence 39.5/million (age <20 yrs)
Leukemia: Age-Specific Incidence

![Graph showing age-specific incidence of leukemia for ALL and AML.](graph.png)
Childhood ALL: Etiology

• No known cause for vast majority of cases

• Down Syndrome
  – ~10-20 x increased risk of developing childhood leukemia
    • 50-75% of leukemia cases are ALL
  – Cumulative incidence of leukemia
    • ~2% by age 5 years
    • ~3% by age 30 years
  – Almost always have B-ALL (not T-ALL)
  – Higher risk of treatment-related complications (infections, mucositis)
  – Overall ALL outcome similar to non-Down Syndrome patients
Signs and Symptoms

• Replaced Marrow
  – Anemia: Pallor, decreased energy
  – Thrombocytopenia: petechiae, bruising, bleeding (rare)
  – Neutropenia: severe infection
  – Bone pain: limp, back pain
Signs and Symptoms

• Extramedullary Disease
  – Organomegaly: hepatosplenomegaly
  – Lymphadenopathy
  – CNS disease: h/a, meningismus, cranial nerve palsies
  – Skin: Leukemia cutis (AML, infants)
  – Testicular masses (ALL)
  – Ocular: retina, cornea

• Fever

• Exceedingly rare to pick up leukemia as incidental finding on routine CBC in asymptomatic patient
# CBC at Presentation

<table>
<thead>
<tr>
<th>Leukocyte count (/mm³)</th>
<th>%</th>
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<tbody>
<tr>
<td>&lt; 10,000</td>
<td>53</td>
</tr>
<tr>
<td>10-49,000</td>
<td>30</td>
</tr>
<tr>
<td>&gt;50,000</td>
<td>17</td>
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<tr>
<th>Hemoglobin (g/dL)</th>
<th>%</th>
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<tr>
<td>&lt;11.0</td>
<td>88</td>
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<table>
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<tr>
<th>Platelets (/mm³)</th>
<th>%</th>
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<tbody>
<tr>
<td>&lt;20,000</td>
<td>28</td>
</tr>
<tr>
<td>20,000-99,000</td>
<td>47</td>
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<tr>
<td>&gt;100,000</td>
<td>25</td>
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Differential Diagnosis

• Rheumatologic: JRA
• Infections: EBV
• Non-malignant Heme: aplastic anemia, ITP, leukemoid reaction
• Other malignancies: Neuroblastoma, Lymphoma
Leukemia: Initial Management

• Stabilize Patient
• Assess for Leukemia-related “emergencies”
Leukemia: Initial Management

1. **Assess for Possible Infection**

If febrile:

- Blood culture, regardless of age
- Begin broad spectrum antibiotics, regardless of ANC
  - Cefepime (with 48-hour vanco rule-out)
Leukemia: Initial Management

2. Assess for Need for Transfusions
   – Transfuse PRBC’s, platelets (leukodepleted, CMV-negative, irradiated)
Leukemia: Initial Management

3. Assess for signs/sx of Hyperleukocytosis:
   • WBC >100,000/mm³
   • Signs/Symptoms of sludging in CNS, Lung
   • IV fluid, anti-leukemic therapy
   • Pheresis (AML more often than ALL)
4. Assess for possible DIC:
   - Risk for life-threatening bleeding
   - AML > ALL
     - For ALL patients: T-ALL > B-ALL
   - Check PT/PTT/fibrinogen in all patients
   - Transfuse FFP, cryoprecipitate as needed
Leukemia: Initial Management

5. **Assess and Treat Acute Tumor Lysis Syndrome**
   - High uric acid, high potassium, high phosphate (low calcium)
   - Can result in renal failure (uric acid precipitates)
   - Should check electrolyes, BUN/Cr, uric acid in all patients
     - G6PD in case rasuburicase needs to be used
   - Prevention/treatment:
     - IV hydration (no K in IVF)
       - Bicarbonate no longer routinely used
     - Allopurinol (Rasburicase)
Leukemia: Initial Management

4. Assess for Anterior mediastinal mass:
   - T-cell ALL (almost exclusively)
   - Range of symptoms may be present
   - Obtain CXR in all patients at initial diagnosis
   - Consider CXR in new asthmatic prior to treating with steroids
Summary of Initial Management

- CBC with differential
- DIC screen
- Clot to blood bank
- “Tumor Lysis Labs”: Lytes, BUN/Cr, Ca, Mg, Phos, Uric Acid
  - G6PD (in case rasburicase is needed)
- Chest x-ray
Diagnostic Evaluation

- Bone Marrow Aspirate/Biopsy
  - Morphology
  - Flow cytometry
  - Cytogenetics: Karyotype, FISH, PCR

- Spinal Fluid (with IT therapy—after diagnosis is made)
**ALL: Immunophenotype**

- **B-ALL:** 85% of patients
- **T-ALL:** 15% of cases
  - Higher median age at diagnosis (adolescents)
  - Higher presenting leukocyte counts
  - Anterior mediastinal mass
  - Male predominance
Childhood ALL: Treatment and Outcome
Childhood ALL: Dramatic Improvement in EFS

Probability of Event-free Survival (%)

Years after Diagnosis

- 1950s
  - Era 1 (n = 91): 8 ± 3%
- 1960s
  - Era 2 (n = 825): 33 ± 2%
- 1970s
  - Era 3 (n = 429): 51 ± 2%
- 1980s
  - Era 4 (n = 356): 71 ± 2%

P < 0.001
Childhood ALL Outcome: 2014

CR rate: >95%

4 yr EFS: 86% [95% CI 82-88%]

4-yr OS: 92% [95% CI, 89-94%]

Median f/u: 4.5 years
Why Improvement in Outcome?

• **Not** a result of new drugs
  – Most of the agents used today were available in 1960s-1970s

• Better supportive care
  – Transfusions
  – Antibiotics
  – Acute tumor lysis syndrome

• Recognition of CNS as sanctuary site

• Risk-adapted therapy
Risk-Adapted Therapy

• **Intensity of therapy** stratified based on patient’s risk of relapse

• Patients assigned to “risk group” based on presenting features that have been previously correlated with outcome
  – “High risk” features: more intensive therapy
  – “Low risk” features: less intensive therapy

• **Goal of Risk-Adapted Therapy**: Treat away the higher risk of relapse
Risk-Adapted Therapy

• Prognostic Factors used to risk-classify patients with ALL
  – Age
  – Presenting WBC
  – Immunophenotype: B-ALL vs. T-cell
  – Presence/Absence CNS Leukemia
  – Leukemia Cytogenetics
  – Early Response to Initial Chemotherapy
ALL: Prognostic Factors

Age and Presenting WBC:
Recognized for decades as strong predictors of outcome

Favorable
- Age 1-10 years
- WBC < 50,000/mm³

Less Favorable
- Age < 12 months, or
  > 10 years
- WBC ≥ 50,000/mm³
Childhood ALL: Cytogenetics

• Multiple recurrent chromosomal abnormalities
  – **Ploidy**: Number of chromosomes
  – **Translocations**: Rearrangements of genes

![Pie chart showing frequencies of different cytogenetic abnormalities in ALL. The chart includes: Hyperdiploid (30%), Normal (10%), Random (11%), TEL/AML1 (25%), MLL (6%), TCR/X (7%), Ig/MYC (2%), E2A/PBX (5%), BCR/ABL (4%).]
Cytogenetic Abnormalities: Prognostic Significance

Favorable
- Hyperdiploidy – 51-65 chromosomes
- TEL/AML1 [(t12;21)]

~50% of patients

Unfavorable
- Hypodiploidy (<45)
- MLL translocations – chromosome 11
- Philadelphia chromosome [t(9;22)]

~10% of patients
“Favorable” Risk Group

- Age 1-10
- Lower WBC
- B-lineage
- Hyperdiploid > 50, or TEL/AML1
Early Response To Therapy

- Response after a few weeks of therapy strongly correlated with long-term outcome
- End of Induction Minimal Residual Disease (MRD)
What is MRD?

- At end of 1st month of treatment, >95% of children are in complete remission
  - Recovered blood counts
  - Marrow normal in appearance without visible blasts
- However, all patients have submicroscopic (“invisible”) disease
- MRD Assays: Quantification of very low levels of leukemia (1 in 1000-100,000 cells)
- Techniques:
  - Flow cytometry
  - PCR: leukemia-specific IgH and/or TCR gene rearrangements
Event-Free Survival Based on Day 30 MRD

Low MRD

High MRD

<table>
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<tr>
<th>MRD</th>
<th>N</th>
<th>5-yr RFS</th>
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<tr>
<td>&lt;0.001</td>
<td>269</td>
<td>89 ± 2%</td>
</tr>
<tr>
<td>&gt;0.001</td>
<td>39</td>
<td>33 ± 8%</td>
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p<0.001
Risk Group Stratification

- **Standard Risk:** All of the following
  - Age 1-10 years
  - WBC < 50,000/mm³
  - B-cell phenotype
  - No or very few leukemia cells in spinal fluid
  - No VHR features

- **High Risk:** Any of the following
  - Age > 10 years
  - WBC > 50,000/mm³
  - T-cell phenotype
  - Spinal fluid with ≥ 5 WBC/hpf and detectable lymphoblasts
  - And: No VHR features

**Very High Risk:** Any of the following
- High MRD at end of induction
- Adverse cytogenetics
  - MLL gene rearrangement
  - Hypodiploidy
## Risk Group Classification:

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<tr>
<th></th>
<th>Initial Risk Group</th>
<th>Final Risk Group</th>
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<tr>
<td></td>
<td>N=794</td>
<td>N=751</td>
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<tr>
<td><strong>SR</strong></td>
<td>462 (58%)</td>
<td>407 (54%)</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>332 (42%)</td>
<td>260 (35%)</td>
</tr>
<tr>
<td><strong>VHR</strong></td>
<td>0</td>
<td>66 (9%)</td>
</tr>
<tr>
<td><strong>Ph+</strong></td>
<td>0</td>
<td>18 (2%)</td>
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Childhood ALL: Treatment

• 2-3 years of chemotherapy
  – **Remission Induction**: 1 month
    • Multiagent, inpatient
    • Goal: Achieve CR (no visible leukemia)—96% of patients
  – **Intensification/Consolidation**: 6-9 months
    • Typically outpatient
    • Intensity of therapy varies by Risk Group
  – **Continuation/Maintenance**
    • Low-intensity, outpatient

• **CNS-directed therapy**
  • Intrathecal chemotherapy
  • Cranial radiation for subset (10-20%)

• **Stem cell transplant**: Only for relapsed/refractory disease
CNS-Directed Therapy

• Cranial irradiation + IT therapy had been standard for all children with ALL
• Intensification of systemic and intra-thecal chemotherapy effective for standard risk and most high risk patients
• Now protocol-specific use of cranial RT
• Dose for prophylactic RT: 12 Gy in 8 fractions
• Dose for CNS 3 disease: 18 Gy in 10 fx
Outcome by Risk Group

4-yr EFS
SR  94% [90-96%]
HR  87% [81-92%]
VHR 79% [64-88%]
Toxicities of Therapy

**Acute**
- Infections
- Asparaginase-related
  - Pancreatitis
  - Clots
- Fractures
- Seizures

**Long-term**
- Cardiac
- Neurocognitive
- Short stature/obesity
- Cataracts
- Bone (AVN)
- Second Malignancies
Primary Care for the Child with ALL

On Therapy

• Immediate evaluation for any fever
  – Blood culture, antibiotics
  – Admission to hospital if neutropenic or ill-appearing

• Bactrim for PCP prophylaxis (until 6 months off-therapy)

• No vaccines to patient, except annual flu shot (no intranasal!)
  – No restriction on vaccines to siblings (except no intranasal flu vaccine)
Primary Care for the Child with ALL

Off-Therapy

• Routine fever evaluation (once central line removed)
• May resume all vaccines after 6 months
  – No need to repeat vaccines given prior to diagnosis
• Consider possible late effects
  – Growth
  – School performance
  – Cataracts
  – Cardiac (LV dysfunction)
  – Second tumors (if radiation)
Future Directions

• Identify New Prognostic Factors
  – Identification of biologically distinctive subsets
    • eg, Ph-like ALL (~15% of patients)

• Develop New Therapies
  – Targeted Therapy (based on underlying genetics)
    – Immunotherapy

• Minimize Toxicity
Targeted Therapy: TKI

- Ph+ ALL: ~5% of childhood ALL
  - More common in adolescents/adults
- t(9;22) forms bcr-abl fusion kinase
- TKI: tyrosine kinase inhibitor
  - Targets bcr-abl kinase
  - Prolonged responses in CML
  - Transient responses in relapsed, Ph+ ALL (weeks-months)
TKI + Chemo Improves Cure Rates for Childhood Ph+ ALL
Toxin-Conjugated Monoclonal Antibodies

- Leukemia-specific antibody linked to toxin
- “Targeted” cell kill:
  - Antibody binds to leukemia
  - Toxin internalized into cell
  - Most normal cells are spared
- Several trials open of B-cell ALL-specific antibodies linked to
  - Pseudomonal exotoxin
  - Calicheamicin
  - Monomethyl auristatin (anti-mitotic agent)
CAR T-cells

1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer

- T-cells harvested from patient
- Harvested cells transfected with genes that allow the T-cells to become specific for tumor (e.g., targeting CD19 in B-ALL)
- Transfected cells infused back to patient
- Trials underway in B-ALL (adult and pediatric)
Childhood ALL: Summary

• Most common cancer in children
• >80% event-free survival with 2-3 years of chemotherapy (primarily outpatient)
  – Stem cell transplant only after relapse
  – Overall, 90% are long-term survivors
• Risk-adapted therapy: Intensity of therapy based on risk of relapse
  – Presenting features: age, WBC count
  – Biologic features of leukemia: Chromosomal abnormalities
  – Early Response to therapy: MRD
• Current Treatment Protocols
  – Decrease toxicity, improve QOL
  – Develop new, more effective therapies
Acknowledgements to Dr Lewis Silverman, Director of Hematologic Malignancy Service, Dana-Farber/Boston Children’s Cancer and Blood Disorders Center