Welcome & Introductions

Adult Acute Lymphoblastic Leukemia (ALL): Update on Diagnosis and Treatment

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Presentation Objectives

- Describe how ALL is diagnosed
- Delineate the role of cytogenetics in treatment planning
- Review the current treatment options for newly diagnosed and relapsed/refractory patients
- Discuss the role of clinical trials in the advancement of ALL treatment
- Review the types of side effects and their management
- Assess the importance of open communication with your healthcare team
Figure 2-2  Bone marrow showing predominantly small lymphocytes with high nuclear-cytoplasmic ratio and indistinct small nucleoli. L1 (×1000).
Chest mass in a patient with ALL
Acute Lymphoblastic Leukemia - Epidemiology

- 6,000 cases per year diagnosed in USA
- Two thirds occur in children
- Represents 75% of all cases of acute leukemia in children and 10-20% of all cases of acute leukemia in adults
- In children the peak incidence occurs at age 4 and in adults at >age 65

World Health Organization
CLASSIFICATION OF LYMPHOID NEOPLASMS

- PRECURSOR LYMPHOID NEOPLASMS
  - B lymphoblastic leukemia with
    - NOS
    - t(9;22)(q34;q11.2); BCR/ABL1
    - t(v;11q23); MLL rearranged
    - t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
    - hyperdiploidy
    - hypodiploidy
    - t(5;14)(q31;q32); IL-3-IGH
    - t(1;19)(q23;p13.3); E2A/PBX1 (TCF3-PBX1)
PHILADELPHIA CHROMOSOME
t(9;22)(q34;q11)

WHO CLASSIFICATION OF LYMPHOID NEOPLASMS

• PRECURSOR LYMPHOID NEOPLASMS
  • T lymphoblastic leukemia/lymphoma
    - Pro T sCD3-, cyCD3+, CD7+
    - Pre T CD7+, CD2+, CD5+
    - Cortical T CD1a+
    - Mature T CD1a-
  • Burkitt-cell leukemia (now classified with Burkitt lymphoma as a mature B cell neoplasm)
ADVERSE PROGNOSTIC FACTORS FOR ADULT ALL

- Age > 35 years
- WBC > 30K/μL (B cell); 100K/μL (T cell)
- Cytogenetics t(9;22), t(4:11), +8, -7, complex, hypodiploid/near triploid
- Time to CR > 4 weeks
- Minimal residual disease: > 10(-3) to 10(-4) after induction, > 10(-4) or increasing after consolidation

### CHEMOTHERAPY OF CHILDHOOD ALL: HISTORICAL PERSPECTIVE

<table>
<thead>
<tr>
<th>SINGLE AGENTS</th>
<th>FREQUENCY OF CR(%)</th>
</tr>
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<tbody>
<tr>
<td>Prednisone</td>
<td>57</td>
</tr>
<tr>
<td>Vincristine</td>
<td>55</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>21</td>
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</tbody>
</table>

### COMBINATION AGENTS

<table>
<thead>
<tr>
<th>AGENTS</th>
<th>FREQUENCY OF CR(%)</th>
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</thead>
<tbody>
<tr>
<td>Pred+VCR</td>
<td>85</td>
</tr>
<tr>
<td>Pred+6-MP</td>
<td>81</td>
</tr>
<tr>
<td>Pred+VCR+6-MP+MTX</td>
<td>94</td>
</tr>
</tbody>
</table>

CR=Complete Remission, Pred=Prednisone, VCR=Vincristine, MTX=Methotrexate, 6-MP=6 Mercaptopurine

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### CHEMOTHERAPY OF CHILDHOOD ALL: HISTORICAL PERSPECTIVE

- Total therapy: 4 Phases (Pinkel, JAMA, 1971)
  - Induction of complete remission with Pred+VCR
  - High doses of antimetabolites IV qd for one week
  - Cerebrospinal irradiation
  - Prolonged maintenance therapy with combination of agents over 2 to 3 years
Improvements in Outcome of Pediatric ALL in 2255 Pts. At St. Jude's 1962–2005

Kaplan-Meier Analyses of Event-free Survival (Panel A) and Overall Survival (Panel B) in 2628 Children with Newly Diagnosed ALL.

Pui and Evans, NEJM 354:166, 2006
## THERAPY OF ADULT ALL

- Built on pediatric experience
- Followed outline of 4 phases of “total therapy”
- Incorporated new drugs as they became available, e.g., daunorubicin (1967), cytarabine (1968), asparaginase (1970)
- Intensified consolidation therapy with alternating cycles of non-cross-resistant drugs

## CONTEMPORARY ADULT ALL TREATMENT REGIMENS

- 1-2 months of induction with Daunorubicin, Prednisone (Pred), Vincristine (VCR), Asparaginase, Cyclophosphamide, Cytarabine, Methotrexate (MTX)
- Treat brain and spinal cord with MTX, Radiation
- Intensification/Consolidation with same agents as bullet #1
- Prolonged maintenance with 6-mercaptopurine, MTX, VCR, PRED
USA CCG-CALGB Comparison

Overall Survival

Estimated EFS probability

Years followed

7-year EFS
67% (CI 58-75%) 46% (CI 36-56%) 1.9 (CI 1.32-2.7)

P=0.0002

At risk
197 151 131 98 57 19 2
124 84 63 48 37 30 8

CALGB

Years followed

Overall Survival

At risk

Specified Cumulative Postremission Doses

<table>
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<tr>
<th>Dose</th>
<th>CCG (2 trials)</th>
<th>CALGB</th>
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<tbody>
<tr>
<td>VCR (mg/m²)</td>
<td>22/45</td>
<td>14</td>
</tr>
<tr>
<td>Cytarabine (mg/m²)</td>
<td>1,800/2,400</td>
<td>1,200</td>
</tr>
<tr>
<td>DXM (mg/m²)</td>
<td>210/420</td>
<td>140</td>
</tr>
<tr>
<td>ASP (U/m²)</td>
<td>90,000/318,000</td>
<td>48,000</td>
</tr>
<tr>
<td>Doxorubicin (mg/m²)</td>
<td>75/150</td>
<td>90</td>
</tr>
<tr>
<td>CPM (mg/m²)</td>
<td>3,000/4,000</td>
<td>3,000</td>
</tr>
<tr>
<td>MTX (IV or oral) (mg/m²)</td>
<td>90/1,000</td>
<td>100</td>
</tr>
<tr>
<td>Intrathecal MTX/cranial RT</td>
<td>132</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>mg/1,800 cGy</td>
<td>mg/2,400 cGy</td>
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Pediatric Approach to Adult ALL
Results of GRAALL-2003 in 212 Pt, Ages 15-60, Compared to 712 Pt on LALA-94

Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia: Early Results of US Intergroup Trial C10403
Abstract #796


On Behalf of the Alliance for Clinical Trials, the Eastern Cooperative Oncology Group and the Southwest Oncology Group
US Intergroup study for AYAs 16-39 years old: C-10403

Accrual completed on 9/15/12 (n = 300)

T-ALL patients receive prophylactic RT after DI
Maintenance therapy continues for 2 (F) – 3 (M) years

Overall Survival

Outcomes similar between ages 16-20, 21-29, 30-39
Abstract #319 Superiority of Pediatric Chemotherapy (Chemo) over Allogeneic Hematopoietic Cell Transplantation (HCT) for Philadelphia Chromosome Negative Adult ALL in First Complete Remission: A Combined Analysis of Dana-Farber ALL Consortium and CIBMTR Cohorts

Matthew D. Seftel, MD MPH FRCPC for the CIBMTR

Kaplan Meier Estimate of Overall Survival

- Chemo (N=107)
- HCT (N=422)

HR = 2.59 (1.86 - 4.34); P = 0.0001

73% 45%

Kaplan Meier Estimate of Disease Free Survival

- Chemo (N=107)
- HCT (N=422)

HR = 3.11 (2.00 - 4.66); P = 0.0001

71% 40%

CIF of Treatment Related Mortality

- Chemo (N=107)
- HCT (N=422)

HR = 7.48 (3.28 - 17.65); P = 0.0001

33% 4%

CIF of Relapse

- Chemo (N=107)
- HCT (N=422)

HR = 1.74 (1.07 - 2.82); P = 0.0252

25% 23%

*Left-Truncated at time of HCT for HCT patients*
Treatment of Relapsed or Refractory ALL

• Different chemotherapy drugs and schedules

• Blood or Marrow Transplant

• Monoclonal Antibody Therapy

Mechanisms of action of monoclonal antibody conjugates
(A) Naked (unconjugated) antibodies
(B) Bi-specific T-cell-engaging antibody.
(C) Antibodies linked to toxins.
(D) Antibodies linked to drugs.
(E) Chimeric antigen receptor T cells.

Breakthrough therapy designation for Blinatumomab (5 mos ahead of schedule), REMS program

• Requires confirmatory randomized trial
• $89,000 for one month of Rx

E1910: Randomized Ph III Adult Frontline ALL

Study Design
• US Intergroup study
• 360 Patients
• US, Canada, Israel
• 1:1 Randomization
Inotuzumab ozogamicin

R/R ALL, Single agent activity - ORR 58%, Median survival of 6.3 mos

Advani et al. JCO 2010

Chimeric Antigen Receptor-Modified T Cells

CARs consist of:
- scFv
- hinge region
- transmembrane & signaling domain – usually CD3ζ or FcεRIγ, also CD28 and CD137 (41BB)

Chimeric Antigen Receptor-Modified T Cells

- T cells are collected from a patient
- Retrovirally transduced with CAR genes
- Expanded ex vivo
- Infused back to the patient

**Summary of Clinical Outcomes**

<table>
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<tr>
<th></th>
<th>Number of Patients, N=27</th>
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<tbody>
<tr>
<td>Overall CR Rate</td>
<td>24/27 (89%)</td>
</tr>
<tr>
<td>MRD Negative CR Rate</td>
<td>21/24 (88%)</td>
</tr>
<tr>
<td>Median Time to CR (range)</td>
<td>22.5 days (9 – 33)</td>
</tr>
</tbody>
</table>

- Median follow-up: 6 months
- 12 patients remain disease-free
  - 7 patients w/o subsequent HSCT
- 10 patients proceeded to allo HSCT
- 9 patients relapsed during follow-up
- T cells persisted 1 – 3 months post T cell infusion
Side Effects Management

- Nausea and vomiting – anti-emetics
- Fatigue – Exercise
- Anemia – Red Blood Cell Transfusions
- Low Platelets (Thrombocytopenia) – Platelet Transfusions
- Infections – Antibiotics
- Neuropathy – Anti-seizure medication, pain medication
- Complementary/Alternative Approaches

Early Survivorship Issues

- “Being cancer free does not mean being free of cancer”
  Lingering side effects
  Neuropathy
  Fatigue
  Cognitive dysfunction
  Joint issues
  Lymphedema
  Sexual dysfunction
Long-Term Medical Issues

- Secondary Malignancies
- Cardiovascular Disease
- Endocrine Issues
- Cognitive Dysfunction
- Fatigue
- Lymphedema
- Fertility

Open Communication with your healthcare team

- Make a list in advance of the things you want to discuss at your appointment.
- If you don’t understand something your doctor is saying, ask questions until you do understand.
- Take notes, or get a friend or family member to take notes for you.
- Being honest about symptoms can help doctors order the right tests and make the right diagnoses.
Open Communication with your healthcare team

• Ask your doctor to write down instructions for you.

• Ask your doctor for printed material about your condition or suggestions for where you can get more information.

• Don’t forget that other members of your health care team, such as nurses and pharmacists, can be good sources of information. Talk to them, too.

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Question and Answer Session

Dr. Litzow’s slides are available for download at www.LLS.org/programs
The Leukemia & Lymphoma Society (LLS) offers:

- **Live, online chats** that provide a friendly forum to share experiences with others. *Living with Acute Leukemia Chat* held on Thursday nights, 8:00-10:00 pm ET, *Caregiver Chat* held on Tuesday nights from 8:00-10:00 pm ET, *Young Adults Chat* held on Tuesday nights, from 8:30-10:30 pm ET.
  - WEBSITE: [www.LLS.org/chat](http://www.LLS.org/chat)

- **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  - WEBSITE: [www.LLS.org/whatask](http://www.LLS.org/whatask)

- Free education materials: [www.LLS.org/publications](http://www.LLS.org/publications)

- Past ALL education programs: [www.LLS.org/leukemiaeducation](http://www.LLS.org/leukemiaeducation)

- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - EMAIL: infocenter@LLS.org  
  - TOLL-FREE PHONE: (800) 955-4572