Acute lymphoblastic leukemia
Approaches to risk stratification

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WHO WILL BE CURED?
Why is it important to cure ALL the first time around?

Survival after relapse stratified by time to relapse in 1961 pts who relapsed on legacy CCG trials during 1988-2002


Current strategies for curing ALL

- Risk groups at diagnosis determine intensity of therapy.
  - Identify patients destined to relapse in order to intensify therapy.
  - Identify patients who will do well with less intensive therapy to spare acute toxicities and late effects.
Why is it important not to overtreat ALL?

- Acute side effects (infections, thrombosis, etc.) are a substantial burden of therapy
- Survivors experience substantial late effects
  - 62.3% have at least one chronic condition
  - 27% have a grade 3 or 4 condition

Oeffinger K, NEJM 2006 (15): 1572

Why is it important not to overtreat ALL?

Table 1. Relative Risk of Selected Score Grade 3 or 4 Adverse Events in All Sites Compared With Siblings

<table>
<thead>
<tr>
<th>Condition</th>
<th>Children (N = 4130)</th>
<th>Siblings (N = 3057)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia refractory disease</td>
<td>0.63</td>
<td>0.61</td>
<td>1.07 (0.77–1.48)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.19</td>
<td>0.15</td>
<td>1.17 (0.68–1.99)</td>
</tr>
<tr>
<td>Severe nonhematologic infections</td>
<td>2.66</td>
<td>0.15</td>
<td>1.46 (0.77–2.80)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>0.65</td>
<td>0.15</td>
<td>1.65 (0.96–2.84)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.11</td>
<td>0.15</td>
<td>18.4 (6.3–55.9)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>1.56</td>
<td>0.15</td>
<td>1.06 (0.61–1.89)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>0.52</td>
<td>0.15</td>
<td>1.12 (0.61–2.13)</td>
</tr>
<tr>
<td>Hearing loss (not correctable by aid)</td>
<td>2.96</td>
<td>0.14</td>
<td>6.93 (2.3–18.6)</td>
</tr>
<tr>
<td>Legally blind in lens of surgery</td>
<td>3.21</td>
<td>0.16</td>
<td>5.85 (2.5–13.8)</td>
</tr>
<tr>
<td>Hearing (not correctable by aid)</td>
<td>2.79</td>
<td>0.16</td>
<td>1.57 (0.7–3.5)</td>
</tr>
</tbody>
</table>

Oeffinger et al 2006

ALL – “Core Biology”
Assessment of the Components of Cure

Real-Time Reference Laboratory System for Risk-Based Classification

- Minimal Residual Disease
- Host
- Tumor
- THERAPY
- Proteomics
- Genetic Polymorphisms
- Drug Metabolism
- Expression Arrays

Courtesy of Bill Carroll
Clinical markers for risk stratification

- NCI/Rome risk criteria
  - Age at diagnosis
  - Presenting WBC
- B precursor vs. T-cell disease
- Prognostic genetic factors
  - TT (Trisomy 4, 10, 17)
  - TEL/AML1, t(12;21)
  - BCR/ABL, t(9;22)
  - MLL/AF4, t(4;11)
  - Hypodiploidy (<44 chromosomes)
- Response to induction therapy

Classification of ALL-AALL03B1

- NCI Risk Group
- Chromosome Number
  - Trisomy 4, 10, 17
  - Hypodiploidy
- Translocations
  - TEL/AML1
  - BCR/ABL
  - MLL rearranged
- Early Treatment Response

Genotype Correlates with Outcome: Children’s Oncology Group

- TEL-AML (n = 176)
- Trisomies 4, 10, 17 (n = 746)
- t(1;19) (n = 139)
- t(4;11) (n = 44)
- t(9;22) (n = 132)

B-precursor ALL
Ploidy is associated with outcome

<table>
<thead>
<tr>
<th></th>
<th>4 Yr EFS (%)</th>
<th>SE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypodiploid</td>
<td>47.6</td>
<td>9.6</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>29.1</td>
<td>4.1</td>
</tr>
<tr>
<td>All Others</td>
<td>77.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- All Others (n=6590)
- <45 x-somes or DI <0.81 (n=82)
- t(9;22) (n=132)

**AALL03B1**

- **Eligibility**
  - Age < 30 years
  - >25% lymphoblasts in marrow
  - Immunophenotype consistent with ALL
  - Previously untreated
- **Accrual is 2000 patients/year**
  - 213 COG institutions enroll on AALL03B1
  - 64% of B-precursor patients are NCI SR (Age < 10 years and WBC < 50K)

**COG ALL Classification Study: AALL03B1**

<table>
<thead>
<tr>
<th>Local Institution</th>
<th>Suspended ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunophenotype</td>
</tr>
<tr>
<td></td>
<td>Cytogenetics</td>
</tr>
<tr>
<td></td>
<td>FISH for transp.</td>
</tr>
<tr>
<td></td>
<td>FISH for BCR-ABL, MLL-AF4, TCL-AMKL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference Laboratories</th>
<th>Local ALL</th>
<th>Standard Risk B-precursor ALL</th>
<th>High Risk B-precursor ALL</th>
<th>T-cell ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

- Amplified sample submitted to Reference Lab for:
  - Immunophenotype
  - DNA Index
  - Host polymorphism (optional)
  - Cell Banking (optional)
Risk stratification-end induction

- End induction: Refinement of initial risk group assignment

- Infant ALL AALL0931
- Standard Risk B-precursor AALL0321
- T-cell ALL AALL0434
- High Risk B-precursor AALL0232

- Standard Risk-Low
- Standard Risk-Avg
- Standard Risk-High
- Very High Risk
- High Risk

Response variables used for risk stratification

- Rapid Early Response (RER) defined by:
  - M1 marrow by day 8/15 AND
  - End induction (day 29) MRD <0.1% determined by flow cytometry

- Extended induction delivered to patients with >1% MRD or M2 marrow on day 29
  - Follow-up MRD and marrow assessment on day 43

Residual Disease Monitoring at End Induction: Flow Cytometry

- MRD Sensitivity 1/1000 - 1/10,000
- 24 hr turn around
- 28.6% of patients positive; Median .069%

Courtesy of Michael Borowitz, MD
AALL03B1-genetic subtypes, all B-precursor patients

<table>
<thead>
<tr>
<th>Genetic subtype</th>
<th>Number (n=6725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEL/AML or TT</td>
<td>42%</td>
</tr>
<tr>
<td>BCR/ABL</td>
<td>2.5%</td>
</tr>
<tr>
<td>MLL rearrangement</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

AALL03B1 data-response

<table>
<thead>
<tr>
<th>Patients [5996]</th>
<th>AALL0331 (SR)</th>
<th>AALL0332 (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>85.4%</td>
<td>72%</td>
</tr>
<tr>
<td>SR</td>
<td>11.6%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Percentages do not add up to 100 because some patients have not yet reached day 29 for this analysis.

Distribution of VHR patients

Number
Can we improve upon current risk stratification?

What is improved risk stratification?
   A. Improve EFS  
   B. Decrease morbidity

### Key prognostic variables
From POG 9900 series

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Day 29 MRD &gt; 0.01%</td>
<td>4.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NCI risk group</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trisomies 4 and 10</td>
<td>0.6</td>
<td>0.0005</td>
</tr>
<tr>
<td>Day 8 PB MRD &gt; 0.01%</td>
<td>1.5</td>
<td>0.018</td>
</tr>
<tr>
<td>TEL-AML1</td>
<td>0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Day 8 M1 bone marrow</td>
<td>1.0</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Borowitz et al., Blood 2008
End Induction BM MRD is Highly Prognostic: COG P9900

<table>
<thead>
<tr>
<th>Event-free survival probability</th>
<th>Years</th>
</tr>
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<tr>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>0.4</td>
<td>0.0</td>
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</table>

51% of events are in the MRD negative group

Planned MRD threshold for 2nd generation COG ALL trials

MRD threshold for AALL03B1

Day 8 PB MRD is Highly Prognostic: COG P9900

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</tr>
<tr>
<td>0.4</td>
<td>0.0</td>
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Only 16% of events occur in the MRD negative group

What additional measurements could we use to identify patients at high risk of relapse...or increased morbidity?

Germline SNPs
What additional measurements could we use to identify patients at high risk of relapse?

- Genomic Blast alterations, e.g., Baro deletions or JAK lesions or High CRLF2?

Childhood Cancer TARGET* Initiative: High Risk ALL Pilot Project

- Therapeutically Applicable Research to Generate Effective Treatments
  - Discover candidate therapeutic targets by identifying genes that are consistently mutated in lymphoblasts from patients with HR-ALL
  - "Team science" approach to COG P9906 samples
    - COG: Stephen Hunger (Chair), William Carroll, Mini Devidas, Greg Reaman, Mignon Loh
    - Labs: Charles Mullighan, Jim Downing, Mary Relling, Cheryl Willman
    - NCI Office of Cancer Genomics: Daniela Gerhard
    - NCI Cancer Diagnosis Program: James Jacobson
    - NCI Cancer Therapy Evaluation Program: Malcolm Smith
    - NCI caBIG: Jinghui Zhang
High Risk Childhood ALL TARGET Initiative: COG P9906 Study Population

- Trial conducted by POG/COG from 3/00-4/03
- Identical ABFM therapy for all pts
- High risk pt population:
  - Higher WBC & older age
  - ~50% DFS on earlier trials
- No pts with Ph+, hypodiploid, or induction failure
- Few pts with "favorable" biological subtypes:
  - No trisomy 4/10 or TEL-AML1 unless CNS/testicular+
- 276 enrolled, 271 eligible

Lesions associated with poor outcome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Importance score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKZF1 (Ikaros)</td>
<td>-32.39</td>
</tr>
<tr>
<td>BTLA</td>
<td>-6.095</td>
</tr>
<tr>
<td>EBF1</td>
<td>-5.332</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Importance score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKZF1 (Ikaros)</td>
<td>-18.724</td>
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JAK mutations occur in 10% of high risk ALL patients

Mullighan et al., NEJM 2008

Mullighan et al., 2009

JAK mutations occur in 10% of high risk ALL patients
What additional measurements could we use to identify patients at high risk of relapse?

Gene Expression data on blasts to predict relapse

Willman et al., UNM

Disease-Free Survival: Clusters H6/R6 and H8/R8

Cohort (207)
H8 (37)
R8 (24)
H6 (20)
R6 (21)

H6, V6, R6, C6 Cluster Hazard Ratio: 0.35; P = 0.28
Older Children; P< 0.001
Low WBC; P=0.03

H8, V8, R8, C8 Cluster Hazard Ratio: 4.2; P < 0.001
Hispanic Race: P <0.002
Day 28 MRD (+): P < 0.0001

Can we use any/some/all of these approaches to further refine risk stratification in the future?

Germline SNPs
Genomic Blast alterations, e.g., (amers deletions?)
Gene Expression data on blasts to predict relapse

Harvey et al, Submitted
…and will there ever be a time when we can integrate these approaches?

Gene	
  
  Expression	on
t  
  blasts
to
t  
  predict
t  
  relapse

Germline SNPs

3 yr self reported
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

3 yr self report
white

male

Standard

Risk

Lacks

favorable
gene

risk

factors

Day 29 MRD neg.

Germline SNPs

3 yr self report
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

Germline SNPs

3 yr self report
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

Germline SNPs

3 yr self report
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

Germline SNPs

3 yr self report
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

GERMLINE SNPs

3 yr self report
white

standard

risk

favorable
gene

risk

factors

Day 29 MRD neg.

COG ALL – How do we improve outcome?

• Optimizing established therapies will not improve outcomes in the highest risk subsets; novel or targeted therapies are required. We will determine if:
  - Nelarabine improves EFS for patients with T-ALL (AALL0434)
  - Lestaurtinib (FLT3 inhibitor) improves EFS for infants with MLL-rearrangements (AALL0631)
  - Dasatinib in an intensive chemotherapy platform results in a > 60% EFS without SCT in Ph+ ALL subsets (AALL0622)
  - Clofarabine-based intensification improves EFS for B-precursor patients at highest risk for relapse

Overview-ALL0031

Frontline Induction/Consolidation (4 weeks)

Entry on AALL0031

Consolidation Block 1

Consolidation Block 2

HSCT

HLA-matched sibling/relative
1 Ag mismatched exclude HLA-DR

Reinduction 1 & 2
intensification 1 & 2
Maintenance 1 & 2
Integration of Imatinib with Intensive Chemotherapy in Ph+ ALL: COG AALL0031

Schultz KR et al, ASH Plenary Session Dec 2007

<table>
<thead>
<tr>
<th>Tx</th>
<th>Cons 1</th>
<th>Cons 2</th>
<th>Reind 1</th>
<th>Intens 1</th>
<th>Reind 2</th>
<th>Intens 2</th>
<th>Maint 1 - 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td></td>
<td></td>
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<tr>
<td>Cohort 2</td>
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<td>Cohort 3</td>
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<tr>
<td>Cohort 4</td>
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<tr>
<td>Cohort 5</td>
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</tbody>
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Continuous dosing of Imatinib

Yellow = Imatinib + chemotherapy
Blue = Chemotherapy alone

Chemotherapy Cohort 5 versus Related BMT or Unrelated BMT

- 3 Year EFS after 4 years of follow up
- Cohort 5 + imatinib 84±7%
- All BMT cohorts (1 - 5)
  - Related BMT 64±11%
  - Unrelated BMT 74±13%
- P = 0.75

COG AALL0622: Dasatinib in Ph+ ALL

- Dasatinib is a more effective TKI than imatinib
  - More potent and active against BCR-ABL mutants
  - Outstanding responses in adults with CML & Ph+ ALL refractory to or intolerant of imatinib
  - Led to FDA approval in 2006
- AALL0622 will augment AALL0031 therapy
  - Add dasatinib day 15-29 induction
  - Integrate dasatinib into AALL0031 chemo backbone
    - Cohort 1: 2 weeks dasatinib in every 3-4 week block
    - Cohort 2: continuous dasatinib
  - Good responders (day 29 MRD <1%) continue with chemo + intensified TKI (or matched sib transplant)
  - Poor responders get unrelated donor SCT
New Drugs

- No new drugs have been incorporated into standard of care front line ALL therapy since 1970s
  - New drugs needed for VHR groups such as poor early responders and relapsed pts
- Sometimes there is a clear molecular target and drug prioritization and testing is “easy”
  - BCR-ABL and TKI therapy
- More commonly there is no definite target, it is hard to pick the right drug to test, and we lack biological endpoints
  - Leading candidates ready now for testing are clofarabine and epratuzumab

ADVL1011

- Phase I trial of JAK inhibitor therapy for relapsed/refractory leukemia and MPN to open this spring
- Starting dose will be 100% of currently used adult dose
- Correlative biology trials will determine target inhibition, reduction of allele burden, etc.

Summary

- We've come a long, long way in curing ALL
- We've got a long, long way to go for patients who fail currently available therapy
Acknowledgements

• Steve Hunger
• Bill Carroll
• Elizabeth Raetz
• Jim Whitlock
• Naomi Winick
• Mini Devidas, Lead ALL Study Statistician
• The ALL Committee and Reference laboratories
• COG Investigators