Moving the Needle Towards Curing Childhood ALL

Mignon Loh, MD
Benioff Chair of Children’s Health
Deborah and Arthur Ablin Professor of Pediatric Molecular Oncology
Benioff Children’s Hospital
University of California, San Francisco
Improved Survival in Childhood ALL-COG Trials 1968-2009 (n=39,697)

Hunger SP, Mullighan CG. *N Engl J Med* 2015;373:1541-1552
What Has Been Responsible for Improvements in Outcome Over Past 5 Decades?

• Recognized that the CNS was a sanctuary site requiring focused therapy (intrathecal versus radiation therapy)
• Augmented chemotherapies-dose, schedule, combinations
• Recognized risk groups of patients who had high relapse rates needed more therapy
  • Older patients (> 10 years) needed more intensive therapies
  • Patients with higher white blood cell counts (> 50,000/uL) at diagnosis
  • Patients who were slow to respond to induction
• Identified genetic subgroups with prognostic significance
Augmented Therapy Improves Outcome for NCI HR-ALL

CCG 1961

Seibel et al. Blood 2008; 111: 2548

COG AALL0232

Larsen et al. J Clin Oncol 2016; 34: 2380
Tyrosine Kinase Inhibitors + Chemotherapy Improves Outcome for Ph+ ALL

7-yr DFS 71.7% vs. 21.4% for historical controls treated without TKIs

Have we reached the ceiling of cytotoxic therapies for ALL?
Intensifying Therapies Further Will Not Improve Outcomes-AALL0331-NCI SR

No benefit to intensified Consolidation for SR-Avg

SR-Fav: 5 yr CCR 94.4% (SE 1.0%)
SR-Fav + Int. PEG: 5 yr CCR 96.0% (SE 1.6%)

No benefit to intensified PEG-Asparaginase for SR-Fav
Intensifying Conventional Therapies are Excessively Toxic for NCI HR Patients

AALL08P1

- It is not safe nor feasible to deliver 8 bi-weekly PEG Asparaginase from Consolidation to Maintenance in less than 49 weeks in NCI HR patients

AALL1131

- It is not safe to add Clofarabine to Intensive consolidation therapy for NCI HR patients.
  - 12 Grade 4 or 5 infections (23%) versus 1 Grade 4 infection (2.0%) in Control Arm

Salzer, Burke, Cancer 2018; 124:1150
But...Therapies are Still Failing Our Patients

Borowitz et al, Blood, 2015; 126: 964
So…..what are the next questions?

- Targeted therapies for genomic subsets
- Epigenetic therapies
- Proteosome inhibitors
- Immunotherapy
  - Introduce agents/strategies based on established risks with potential benefits
- Maximize use of host polymorphisms to adequately dose drugs
- Maximize adherence interventions to ensure patients are taking their medicine
<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease</th>
<th>Primary Objective</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AALL1231</td>
<td>Newly Diagnosed T-ALL</td>
<td>Randomized trial of bortezomib on AALL0434 backbone</td>
<td>Suspended</td>
</tr>
<tr>
<td>AALL1631</td>
<td>Newly Diagnosed Ph + ALL</td>
<td>Randomized trial of imatinib in AALL0232 backbone vs EsPhALL for good responders</td>
<td>Open</td>
</tr>
<tr>
<td>AALL1521</td>
<td>Newly Diagnosed Ph-like ALL with JAK-STAT pathway alterations</td>
<td>To test if the addition of ruxolitinib to AALL1131 chemotherapy improves outcomes</td>
<td>Open</td>
</tr>
<tr>
<td>AALL15P1</td>
<td>Newly Diagnosed Infants with KMT2A-rearranged ALL</td>
<td>To test safety of adding azacitidine to Interfant backbone</td>
<td>Suspended</td>
</tr>
<tr>
<td>AALL1331</td>
<td>Relapsed ALL-BM, CNS, Testicular, any time</td>
<td>Randomized trial of blinatumomab vs cassettes of intensive chemotherapy</td>
<td>Open</td>
</tr>
<tr>
<td>AALL1621</td>
<td>Relapsed ALL-BM</td>
<td>To test safety and efficacy of inotuzumab in relapsed ALL</td>
<td>Open</td>
</tr>
</tbody>
</table>
Diagnostic Algorithm for Targeted Therapies for Current Clinical Trials

HR B-ALL

LDA

Induction

Ph+ → ABL TKI + chemotherapy

Ph-like → CRLF2+

CRLF2- → Archer fusionplex

Post-induction

Risk-adapted chemotherapy

+ ABL class kinase fusion

Post-induction

- RNA sequencing

INDuction

Ph-like → CRLF2+

CRLF2- → Archer fusionplex

Post-induction

Risk-adapted chemotherapy

+ ABL class kinase fusion

Post-induction

- RNA sequencing

Post-induction

Novel fusions/lesions

AALL1631
imatinib

AALL1131
dasatinib

AALL1521
ruxolitinib

AALL1521
ruxolitinib

adapted from Tasian, Loh, Hunger Blood 2017
## Promising New Immunotherapies for B-ALL

<table>
<thead>
<tr>
<th>Immune Therapy</th>
<th>Mechanism of Action</th>
<th>Patient Population Studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotuzumab</td>
<td>CD22-directed humanized moAB conjugated to calicheamicin</td>
<td>Adults with CD22+ R/R B-ALL</td>
<td>80.7% CR/CRi</td>
</tr>
</tbody>
</table>
| Blinatumomab   | Bispecific T cell receptor engager (BiTE) that redirects CD3+ T cells to CD19+ blasts | Adults with R/R Ph- B-ALL | 39% CR  
                             |                                                   | Children with R/R B-ALL | 39% CR |
| CAR T cells    | T cells transduced ex-vivo with chimeric anti-CD19 receptor | Children with CD19+ R/R B-ALL | 83% CR/CRi |

Future Distribution of Risk Groups for ALL-2019

VHR: AALL1721
CTL-019 in CR1—1.7%

PM: AALL1631,
AALL1131-Abl class
AALL1521—5.5%

HR: AALL1732
Randomized to
inotuzumab

SR-Avg: AALL1731
No randomized
intervention—1.8%

SR-Fav: AALL1731
Randomized to
blinatumomab
### Introduction of Molecularly or Immunologically Targeted Therapy

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Projected 5-yr DFS</th>
<th>Protocol</th>
<th>Therapeutic Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR-Favorable</td>
<td>&gt;95%</td>
<td>AALL1731</td>
<td>Standard therapy with 2 year duration</td>
</tr>
<tr>
<td>HR-Favorable</td>
<td>&gt;94%</td>
<td>AALL1732</td>
<td></td>
</tr>
<tr>
<td>SR-Avg &amp; High</td>
<td>~89%</td>
<td>AALL1731</td>
<td>Blinatumomab</td>
</tr>
<tr>
<td>High Risk</td>
<td>~80%</td>
<td>AALL1732</td>
<td>Inotuzumab</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>&lt;50%</td>
<td>AALL1721</td>
<td>CAR T-cell therapy in CR1</td>
</tr>
<tr>
<td>Ph+, Ph-like</td>
<td>60-85%</td>
<td>AALL1631, AALL1521, AALL1131</td>
<td>Molecularly targeted therapy</td>
</tr>
</tbody>
</table>

### Pie Chart

- **SR-Favorable**: 25%
- **HR-Favorable**: 33%
- **SR-Avg & High**: 33%
- **High Risk**: 25%
- **Very High Risk**: 33%
- **Ph+, Ph-like**: 33%

**B-ALL**
Summary

- We have reached the ceiling of conventional cytotoxic therapies for children and adolescents with ALL
  - No further benefit to intensifying conventional therapies
  - Excessive toxicity with intensifying conventional therapies
- Future trials will optimize addition of non-conventional therapies (TKI for genomic subsets and new immunotherapies) for patients
  - Will we eventually be able to substitute immunotherapy for cytotoxic chemotherapy blocks and limit common toxicities such as infections?
  - What other toxicities will we see emerge with immunotherapies?
  - What biomarkers predict response to immunotherapies?
  - Will the genetic fingerprint of relapse change with upfront immunotherapies?
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Patients with T and B-ALL have Witnessed Improvements in Survival

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>5 yr OS% 1990-94</th>
<th>5 yr OS% 2006-09</th>
<th>Reduction in death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL</td>
<td>84.9 +/- 0.5% (n=5068)</td>
<td>92.2 +/- 0.5% (n=6078)</td>
<td>48.3%</td>
</tr>
<tr>
<td>T-ALL</td>
<td>70.7 +/- 1.7% (n=748)</td>
<td>90.6 +/- 2.7% (n=449)</td>
<td>67.9%</td>
</tr>
</tbody>
</table>

90% 3-yr EFS for T-ALL in UKALL 2003 (Vora, ASH 2008), which uses the COG (Capizzi MTX + ASNase) augmented BFM backbone

Improved survival for T-ALL likely helps to explain the improved survival for African Americans over past 20 years

Hunger et al, *JCO 2012; SIOP 2013*