Pediatric Acute Lymphoblastic Leukemia

Highlights of ASH 2015
Thai National Protocol Outcomes

1A Kaplan-Meier survival estimate

Number at risk

Time to relapsed (months)

78 64 40 24 10
• Outcome is very dependent on treatment
• Patient’s compliance
Treatment of ALL

- Induction: 1 month
- Intensification: 6-8 months
- Maintenance: 12-32 months
Treatment of ALL: risk stratification

Depends on

• Clinical features
• Age
• WBC
• Favorable vs Unfavorable
• Response to treatment
• MRD
Outstanding outcome for children with standard risk-low (SR-Low) acute lymphoblastic leukemia and no benefit to intensified peg-asparaginase (PEG-ASNase) therapy: results of Children’s Oncology Group Study AALL0331

Outstanding outcome for children with standard risk-low (SR-Low) acute lymphoblastic leukemia and no benefit to intensified peg-asparaginase (PEG-ASNase) therapy: results of Children’s Oncology Group Study AALL0331

• Given an expected EFS > 90%, this study sought to improve outcome in SR-Low without adding significant toxicity
AALL0331 Standard Risk B All Study

- Age 1-9 years, WBC < 50,000/ul
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3993 consented to post induction therapy
AALL0331 Standard Risk B All Study

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End induction risk assignment

- SR Low: 47%
- SR Average: 37%
- SR High: 16%

CNS 1
RER: M1 Day15 and MRD < 0.1% Day29
Favorable
Cytogenetics:
ETV6/RUNX1 or triple trisomy (4+10+17)
## AALL0331 SR-Low: Treatment

<table>
<thead>
<tr>
<th>Induction 5 weeks</th>
<th>Consolidation 4 weeks</th>
<th>Interim Maintenance 6 weeks</th>
<th>Delayed Intensification 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine D1,8,15,22</td>
<td>Vincristine D1</td>
<td>Vincristine D1, 11, 21, 31, 41</td>
<td>Dexamethasone D 1-7, 15-21</td>
</tr>
<tr>
<td>Dexamethasone x 28d</td>
<td>6 MP D1-28</td>
<td>MTX (IV) D1, 11, 21, 31, 41</td>
<td>Vincristine D1,8,15</td>
</tr>
<tr>
<td>Pegaspargase x 1 D4-6</td>
<td>IT MTX D1, 8, 15</td>
<td>IT MTX D31</td>
<td>Doxorubicin D1, 8, 15</td>
</tr>
<tr>
<td>IT Cyta D1, MTX D9,29</td>
<td>± pegaspargase D1,22</td>
<td>± pegaspargase D15,36</td>
<td>Pegaspargase x 1 D4-6</td>
</tr>
</tbody>
</table>

### Maintenance

- Vincristine monthly
- Dexamethasone monthly x 5d
- 6MP daily
- MTX (PO) daily
- IT MTX every 3 months
### AALL0331 SR-Low: Patient Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>1041</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>816</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td>ETV6/RUNX1</td>
<td>1150</td>
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<tr>
<td></td>
<td>Triple trisomy (4+10+17)</td>
<td>748</td>
</tr>
<tr>
<td><strong>MRD d29</strong></td>
<td>&lt;0.1%</td>
<td>1836</td>
</tr>
<tr>
<td></td>
<td>&lt;0.01%</td>
<td>1661</td>
</tr>
<tr>
<td></td>
<td>0.01-0.1%</td>
<td>175</td>
</tr>
<tr>
<td><strong>Regimens</strong></td>
<td>LRS standard</td>
<td>617</td>
</tr>
<tr>
<td></td>
<td>LRS-IV standard</td>
<td>312</td>
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<tr>
<td></td>
<td>LRA intensified</td>
<td>620</td>
</tr>
<tr>
<td></td>
<td>LRA-IV intensified</td>
<td>308</td>
</tr>
</tbody>
</table>

*LRS – Low Risk standard
*LRA – Low Risk ASnase
AALL0331 SR-Low: Efficacy

SR-Low 5y CCR: 95.2%
- Intensified: 96.0%
- Standard: 94.4%

SR-Low 5y OS: 98.8%
- Standard: 99.3%
- Intensified: 98.3%

P = 0.13
P = 0.05
Conclusion

• Using sentinel genetic lesions and MRD response about 35% of SR-ALL patients meet SR-Low criteria therapy and are certained to be cured with low-intensity regimen
T-Lymphoblastic Leukemia (T-ALL) Shows Excellent Outcome, Lack of Significance of the Early Thymic Precursor (ETP) Immunophenotype, and Validation of the Prognostic Value of end-Induction Minimal Residual Disease (MRD) in Children’s Oncology Group (COG) Study AALL 0434

AALL0434: T ALL Study

Standard 4 drug induction

Post-induction: 2 x 2 randomization (results blinded)
   Capizzi MTX + Pegaspargase vs. High dose MTX randomization

Nelarabine randomization (Six 5-day courses for Intermediate and High risk)

Cranial irradiation: Int and high risk ( ~ 90% of total)
AALL0434: T ALL Study

- Enrolled 1895 patients between 1/07-7/14
- Age 1-30 years
- ETP status assessed at diagnosis
  - Not routinely reported to referring institutions
- MRD assessed by flow cytometry
  - Performed in single reference laboratory
  - Diagnosis and Day 29 bone marrow
## AALL0434 – Subtype and Outcomes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>Frequency</th>
<th>MRD D29 &lt;0.01%</th>
<th>Induction Failure</th>
<th>4year EFS (%± SE)</th>
<th>4year OS (%± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETP</td>
<td>130</td>
<td>11.3%</td>
<td>18.6%</td>
<td>7.8%</td>
<td>82.9±6.2</td>
<td>91.0±4.8</td>
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<tr>
<td>Near ETP</td>
<td>195</td>
<td>17.0%</td>
<td>35.2%</td>
<td>6.7%</td>
<td>84.7±6.2</td>
<td>92.6±4.4</td>
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<tr>
<td>Not ETP</td>
<td>819</td>
<td>71.6%</td>
<td>69.5%</td>
<td>1.1%</td>
<td>86.9±2.5</td>
<td>91.5±2.0</td>
</tr>
</tbody>
</table>

Induction failure defined as > 25% blasts by morphology in bone marrow at Day 29
Conclusions

• T-ALL treated with ALL0434 therapy has an excellent outcome

• No difference in outcome for ETP vs non-ETP
  – Day 29 MRD for ETP and Near ETP
  – Induction failure for ETP and Near ETP

• Utility of MRD risk stratification confirmed

• Treatment response more important than subtype
Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia: Early Results of US Intergroup Trial C10403

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

• To evaluate the feasibility and effectiveness (with EFS as a primary endpoint), of treating AYA ALL patients (ages 16-39 years) using the standard arm of the successful Children’s Oncology Group regimen (COG AALL 0232)
Survival Differences in Older Adolescents with ALL

Survival of Adolescents/Young Adults (AYA), Ages 16-20 years
C-10403: AYA ALL, 16-39 years old

<table>
<thead>
<tr>
<th>I</th>
<th>C</th>
<th>IM</th>
<th>DI</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td>DNR</td>
<td>Cyclo</td>
<td>MTX</td>
<td>DOX</td>
<td>DEX</td>
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<td>Dex</td>
<td>Peg-ASP</td>
<td>Dex</td>
<td>6MP</td>
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<tr>
<td>Peg-Asp</td>
<td>Peg-Asp</td>
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<td>Peg-Asp</td>
<td>6MP</td>
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<tr>
<td>IT-MTX</td>
<td>Ara-C</td>
<td>IT-MTX</td>
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<td>IT-MTX</td>
</tr>
<tr>
<td>IT-AraC</td>
<td>6MP</td>
<td>IT-MTX</td>
<td>6-TG</td>
<td>IT-MTX</td>
</tr>
</tbody>
</table>
C10403: AYA ALL

• Enrolled 296 eligible patients from 11/07-9/12
• Median age: 25 years
  – < 20 years: 25%
  – 20-29 years: 49%
  – 30-39 years: 27%
• 61% Male, 39% Female
C10403 Event Free Survival
C10403 Overall Survival

[Graph showing survival probability over months]
C10403: Conclusions

- Pediatric ALL regimen administered by adult hematologist/oncologist validated in large North American intergroup trial
- 2 year EFS of 66% and OS of 79% is a major improvement compared to 34% EFS in historical controls in CALGB
- Outcomes similar to other prospective international studies of pediatric regimen in AYAs
The only official
2015 Highlights of ASH®
in Asia
C10403: Conclusions

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Thank you!