Therapy Optimization in Infant Acute Lymphoblastic Leukemia

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Infant Leukemia Committee, Japan Children’s Cancer Group (JCCG)
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I have no personal or financial interests to declare:

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Contents

• Infant ALL overview

• Treatment: the Japanese experience

• Development of novel therapeutic strategy
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Infant ALL

- ALL diagnosed at <1 year of age
- Approximately <5% of ALL in children
  - New cases per year: 30 in Japan, 90 in U.S.
- \textit{KMT2A/MLL} rearrangements (MLL-r) found in 70-80%
  - >70 diverse MLL fusion partners
  - \textit{MLL-AF4} is most common (50%), followed by \textit{MLL-ENL, MLL-AF9}
  - A most significant poor prognostic factor in infant ALL
- Infants with MLL-r ALL are likely to present with …
  - high leukocyte counts, hepatosplenomegaly, and overt CNS disease
  - leukemic blasts with CD10 negative pro-B cell phenotype, with frequent co-expression of myeloid antigens

\textbf{POOR PROGNOSIS} in infants with MLL-r ALL !!
- 30-40% EFS
- Young infant (<3 months old) have worst prognosis
Contents

• Infant ALL overview

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Japan Infant Leukemia Study Group  
MLL96 & MLL98 (1995-2001)

**Infants with ALL**

**MLL-r:**
- Induction (2 weeks)
  - 3 drug
  - CPA
  - Ara-C/VP-16
  - TIT

**MLL-g:**
- Induction (4 weeks)
  - 4 drug
  - CPA
  - Ara-C/VP-16
  - TIT

**Consolidation**
- HD-MTX
- PSL
- L-asn
- CPA
- TIT

**Intensification**
- VCR
- DNR
- Ara-C
- 6-MP
- TIT

**Re-induction**
- 4 drug
- CPA
- Ara-C/VP-16
- TIT

**Maintenance**
- 6-MP/MTX
- Ara-C/VP-16 pulse
- VCR/PSL pulse
- TIT

**Intensification courses**

**phase A**
- HD-MTX
- VCR/Dexa
- CPA
- TIT

**phase B**
- HD Ara-C
- MIT
- VP-16
- TIT

**phase C**

**Allo-HSCT**
Survival rates of MLL96 & MLL98 studies

frequent early events among MLL-r infants

MLL98: Excellent 3-year post-transplant EFS achieved, when HSCT performed in 1CR

HYPOTHESIS:
“Intensification of pre-HSCT chemotherapy & HSCT in early post-remission might prevent early relapse & translate into a better outcome.”

JPLSG MLL03 (2004-2009)

Induction
7-day PSL monotherapy
Dex/VCR/DXR/CPA/Ara-C/VP-16/TIT

1st Consolidation
MIT/HD Ara-C/VP-16/TIT

2nd Consolidation
VCR/HD-MTX/HD Ara-C/TIT

≤ 4 months

Allogeneic HSCT

- Conditioning regimen: **busulfan***/etoposide/cyclophosphamide
  (*Dose adjusted based on individual PK study result*)
- Donor: ≥ 4/6 HLA-matched unrelated cord blood, or
  ≥ 5/6 HLA-matched related bone marrow
- GVHD prophylaxis: cyclosporine or tacrolimus, & MTX

ASNase not included based on in vitro drug resistance assay data
(Pieters R. Leukemia 1998)

Koh K, Tomizawa D et al. Leukemia 2015
MLL96/98/03: Event-free survival
only MLL-r patients

Koh K, Tomizawa D et al. Leukemia 2015
BMT vs. Chemotherapy

COG1953 & POG9407: no difference in EFS

Remission BMT ON+OFF (n = 53)
Control chemotherapy (n = 47)

Log-rank $P = .60$
RHR for RBMT: Control = 1.15

Dreyer Z. J Clin Oncol 2011;29;214-222
BMT vs. Chemotherapy

**Interfant 99**: *BMT might benefit for HR MLL-r infants*

**Medium risk MLL-r infants**
- without HR features

**High risk MLL-r infants**
- Age < 6 mo
- WBC > 300K or PPR

Mann G. *Blood* 2010;116;2644-2650
Infants transplanted with BU-conditioning are high-risk of developing pulmonary hypertension ≤100 days post-transplant.

Table 1: Clinical and pathological characteristics of pulmonary hypertension (PH) developed within 100 days after hematopoietic stem cell transplantation (HSCT)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Dx</th>
<th>Preconditioner</th>
<th>Stem cell</th>
<th>HVOD</th>
<th>Onset of PH post-HSCT</th>
<th>Clinical Dx</th>
<th>Affected vessels confirmed by histology</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 yr/M</td>
<td>ALL</td>
<td>CY, TBI</td>
<td>MSD-BM</td>
<td>–</td>
<td>+44 d</td>
<td>IP</td>
<td>Venules</td>
<td>None</td>
<td>Dead</td>
</tr>
<tr>
<td>1</td>
<td>4 yr/M</td>
<td>ALL</td>
<td>CY, VP, BCNU</td>
<td>Allo-sib</td>
<td>–</td>
<td>+60 d</td>
<td>PVOD</td>
<td>n/a</td>
<td>Steroid</td>
<td>Alive +230 d</td>
</tr>
<tr>
<td>1</td>
<td>39 yr/M</td>
<td>NHL</td>
<td>CY, VP, BCNU, DTIC</td>
<td>Auto-BM</td>
<td>–</td>
<td>+52 d</td>
<td>PVOD</td>
<td>Venules</td>
<td>Steroid</td>
<td>Dead</td>
</tr>
<tr>
<td>1</td>
<td>36 yr/F</td>
<td>ALL</td>
<td>CY, VP, Mel, TBI, TLI</td>
<td>Allo-BM</td>
<td>+</td>
<td>+6 d</td>
<td>PVOD</td>
<td>Venules</td>
<td>None</td>
<td>Alive +27 d</td>
</tr>
<tr>
<td>1</td>
<td>20 yr/M</td>
<td>NHL</td>
<td>CA, CY, TBI</td>
<td>MSD-BM</td>
<td>+</td>
<td>+73 d</td>
<td>PVOD</td>
<td>Venules and arterioles</td>
<td>Steroid</td>
<td>Dead from NHL +230 d</td>
</tr>
<tr>
<td>1</td>
<td>2 yr/M</td>
<td>NB</td>
<td>CB, CA, VP, Mel</td>
<td>Auto-PBSC</td>
<td>–</td>
<td>+17 d</td>
<td>PVOD</td>
<td>Venules and arterioles</td>
<td>Steroid, heparin, milrinone, NO</td>
<td>Dead +49 d</td>
</tr>
<tr>
<td>1</td>
<td>48 yr/M</td>
<td>MM</td>
<td>Mel</td>
<td>Auto-PBSC</td>
<td>–</td>
<td>+11 d</td>
<td>PVOD</td>
<td>n/a</td>
<td>None</td>
<td>Alive +49 d</td>
</tr>
<tr>
<td>6</td>
<td>8 mo/M</td>
<td>OS, BU, CY, VP</td>
<td>MSD-BM</td>
<td>–</td>
<td>+70 d</td>
<td>PAH</td>
<td>Arterioles</td>
<td>CCB</td>
<td>Alive +840 d</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4 mo/M</td>
<td>IM</td>
<td>BU, CY</td>
<td>MSD-BM</td>
<td>+</td>
<td>+21 d</td>
<td>PAH</td>
<td>Arterioles</td>
<td>CCB</td>
<td>Dead +32 d</td>
</tr>
<tr>
<td>8</td>
<td>8 mo/F</td>
<td>SCID</td>
<td>BU, CY</td>
<td>URD-BM</td>
<td>+</td>
<td>+70 d</td>
<td>PAH</td>
<td>n/a</td>
<td>NO, sildenafil</td>
<td>Alive +140 d</td>
</tr>
<tr>
<td>8</td>
<td>2 mo/M</td>
<td>OS</td>
<td>BU, CY</td>
<td>Haplo-BM</td>
<td>+</td>
<td>+57 d</td>
<td>PAH</td>
<td>n/a</td>
<td>NO</td>
<td>Dead +58 d</td>
</tr>
<tr>
<td>9</td>
<td>1 mo/M</td>
<td>MIOP</td>
<td>BU, CY</td>
<td>Haplo-BM</td>
<td>+</td>
<td>+20 d</td>
<td>IP, PAH</td>
<td>n/a</td>
<td>NO, PG12, CCB</td>
<td>Dead +34 d</td>
</tr>
<tr>
<td>9</td>
<td>2 mo/F</td>
<td>MIOP</td>
<td>BU, CY</td>
<td>PMRD-BM</td>
<td>+</td>
<td>+48 d</td>
<td>PAH</td>
<td>n/a</td>
<td>NO, PG12, DF</td>
<td>Alive +750 d</td>
</tr>
<tr>
<td>9</td>
<td>2 mo/F</td>
<td>MIOP</td>
<td>BU, CY</td>
<td>PMRD-BM</td>
<td>+</td>
<td>+49 d</td>
<td>PAH</td>
<td>Venules</td>
<td>NO, PG12, surfactant</td>
<td>Dead +84 d</td>
</tr>
<tr>
<td>9</td>
<td>3 mo/F</td>
<td>MIOP</td>
<td>BU, CY</td>
<td>MSD-BM</td>
<td>–</td>
<td>+53 d</td>
<td>IP, PAH</td>
<td>n/a</td>
<td>NO, PG12</td>
<td>Alive +930 d</td>
</tr>
<tr>
<td>9</td>
<td>1 mo/F</td>
<td>MIOP</td>
<td>BU, CY</td>
<td>Haplo-BM</td>
<td>–</td>
<td>+65 d</td>
<td>PAH</td>
<td>n/a</td>
<td>NO</td>
<td>Dead +111 d</td>
</tr>
<tr>
<td>10</td>
<td>21 yr/M</td>
<td>AML</td>
<td>GO, Flu, Mel, TBI</td>
<td>PMRD-BM</td>
<td>–</td>
<td>+35 d</td>
<td>PVOD</td>
<td>n/a</td>
<td>Steroid</td>
<td>Dead +260 d</td>
</tr>
<tr>
<td>This case</td>
<td>7 mo/M</td>
<td>ALL</td>
<td>BU, CY, VP</td>
<td>CB</td>
<td>+</td>
<td>+53 d</td>
<td>PVOD</td>
<td>n/a</td>
<td>Beraprost, sildenafil</td>
<td>Alive +350 d</td>
</tr>
</tbody>
</table>

Kawashima N. *Int J Hematol* 2013
## Long term adverse events in infant ALL survivors

39/41 MLL-r & 18/21 MLL-g survivors were evaluated. Median age; 7.7 years (range, 1.1 – 10.4 years)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic GVHD (extensive type)</td>
<td>12 %</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12 %</td>
</tr>
<tr>
<td><strong>Short stature (&lt; -2.0SD or receiving GH therapy)</strong></td>
<td>58 %</td>
</tr>
<tr>
<td>Skin complications (alopecia, scleroderma, pigmentation)</td>
<td>30 %</td>
</tr>
<tr>
<td>Dental abnormalities</td>
<td>15 %</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>5 %</td>
</tr>
<tr>
<td>Neurocognitive deficits (learning disability, autism)</td>
<td>10 %</td>
</tr>
<tr>
<td>Ophthalmologic complications (dry eye, corneal opacity, retinitis)</td>
<td>12 %</td>
</tr>
<tr>
<td>Pulmonary complications (interstitial pneumonia, BO)</td>
<td>15 %</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>2 %</td>
</tr>
</tbody>
</table>

※ No secondary malignancies or cardiac dysfunctions
MLL-10 (2011-2015)

Infants with ALL

MLL-g

Regimen A

MLL96/98 chemotherapy regimen

MLL-r

Regimen B

Interfant-99 induction + Modified COG P9407 post-remission chemotherapy regimen

HR cases
- Age <6 months
- CNS-3

Allo HSCT

*MRD (flow, IgH/TCR, chimeric transcripts) checked at BMA-1,-2,-3,& -4.
Severe life-threatening T-cell immunodeficiency in infants following ALL chemotherapy

- Case report on 5 infants with ALL (3 MLL-r & 2 MLL-g)
- All received COG/CCG chemotherapy
- All developed multiple severe opportunistic infections after 2-13 months (median, 3 months) of therapy completion (e.g., CMV, HSV, HHV-6, parainfluenza-3, corona virus, Clostridium difficile colitis, Mycobacterium, candida esophagitis, pulmonary aspergillosis)
- Extremely low CD3+, CD4+, CD8+ T-cell populations with varying B- and NK-cell depletion
- No apparent underlying immunodeficiencies; all were HIV negative, normal newborn TREC screening (N=2), normal SCID-related gene mutation test (N=1).
- 4 died and one alive after SCT for immunodeficiency.

Geerlinks AV. Pediatr Blood Cancer 2016

- 2 similar cases in the Japanese MLL-10 study. (Tomizawa D. Unpublished data)
- No similar cases in the Interfant database (Pieters R. personal communication)
Results of the infant ALL studies published from the major study groups

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Study acronym &amp; inclusion time</th>
<th>No. of Pts (MLL-r/MLL-g)</th>
<th>No. of Pts HSCT in 1CR</th>
<th>CR (%)</th>
<th>EFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JILSG</td>
<td>MLL96/98 (1995-2001)</td>
<td>102 (80/22)</td>
<td>49</td>
<td>94.1</td>
<td>4-yr 50.9</td>
<td>4-yr 60.5</td>
</tr>
<tr>
<td>JPLSG</td>
<td>MLL03 (2004-2009)</td>
<td>62 (62/-)</td>
<td>44</td>
<td>80.6</td>
<td>4-yr 43.2</td>
<td>4-yr 67.2</td>
</tr>
<tr>
<td>Interfant</td>
<td>Interfant-99 (1999-2005)</td>
<td>482 (314/82)</td>
<td>37</td>
<td>94</td>
<td>4-yr 47.0</td>
<td>4-yr 55.3</td>
</tr>
<tr>
<td>CCG</td>
<td>CCG1953 (1996-2000)</td>
<td>115 (79/82)</td>
<td>37</td>
<td>82.5</td>
<td>5-yr 41.7</td>
<td>5-yr 44.8</td>
</tr>
<tr>
<td>COG</td>
<td>COG P9407 (2001-2006)</td>
<td>147 (100/35)</td>
<td>0</td>
<td>91.8</td>
<td>5-yr 42.3</td>
<td>5-yr 52.9</td>
</tr>
</tbody>
</table>
Contents

• Infant ALL overview

• Treatment: the Japanese experience

• Development of novel therapeutic strategy
Clofarabine

- Novel purine nucleoside analogue
- Approved for children & adults with R/R ALL
- Highly active against MLL-r ALL cells \textit{in vitro}
- Synergistic cytotoxic effects with Ara-C combination
- Induce demethylation of the promoter region of FHIT, which is often hyper-methylated in MLL-r ALL

\text{(Stumpel DJPM, Stam RW. \textit{Eur J Cancer} 2015)}

- Clo/VP-16/CPM tested in St.Jude Total XVI for infant ALL
- Clo/VP-16/CPM arm was suspended in COG HR B-ALL trial (AALL1131) because of excess infectious toxicities
MLL-17: Treatment Schema

Newly diagnosed infant ALL

MLL-g ALL

MLL-r ALL

LR regimen

IR/HR Regimen

Induction

TP1

CLO/CA

TP2

MARMA

TP3

OCTADAD

TP4

CLO/CA

maintenance

SCT

HR

• MLL rearranged, AND
• Age at diagnosis < 6mo, AND
• WBC ≥ 300 x 10⁹/L OR PPR

PCR-MRD positive

Interfant Backbone

Off protocol

Non CR

MLL96/98
MLL-10
LR regimen

Regimen G

TP0
FLT3 overexpression in infant MLL-r ALL

Armstrong SA. Nat Genetics 2002;30;41-47
COG AALL0631: Lestaurtinib (FLT3 inhibitor) study

During Efficacy Phase
- All institutions

Enroll

Induction

MLL-G (SR)
- A

MLL-R (IR/HR)
- B

Randomize

Arm A
- SR

Arm B (w/o Lestaurtinib)
- IR/HR
- IR
- HR

Arm C (with Lestaurtinib)
- IR/HR
- IR
- HR

*Safety/Activity phase done prior to the Efficacy phase

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>3y-EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>64</td>
<td>87%</td>
</tr>
<tr>
<td>Arm B (w/o Lestaurtinib)</td>
<td>54</td>
<td>37%</td>
</tr>
<tr>
<td>Arm C (with Lestaurtinib)</td>
<td>67</td>
<td>37%</td>
</tr>
</tbody>
</table>

Chemo Backbone: POG 9407
- Induction: VPLD + CPM
- Intensification: HD Mtx x2, VP16/CPM
- Reinduction: 4 drug (dex) + CPM
- Consolidation: HD Mtx x2, VP16/CPM, Capizzi II “Maintenance”

Brown P. SIOP2016 abstract #O-001

+/- Lestaurtinib
Other Molecular targets?

Epigenetics?
Molecular actions induced by KMT2A/MLL fusion

- KMT2A/MLL fusion
- Recruitment of aberrant DOT1L
- Site-specific hyper-methylation
- Inappropriate transcription of leukemogenic genes

MLL-r ALL
MLL-r ALL: genes affected by abnormal methylations


**Hyper-methylated:**
- DNA repair genes
- Tumor suppressor genes
- Cell cycle regulators
- Pro-apoptotic genes

**Hypo-methylated:**
- Anti-apoptotic genes
- Proto-oncogenes
Hypomethylating agents for MLL-r ALL

in vitro study

- Zebularine (similar data exists for Decitabine)

Stumpel et al., Blood 2009
Azacitidine successfully maintained the second remission in an infant with KMT2A-rearranged acute lymphoblastic leukemia who relapsed after unrelated cord blood transplantation.
## Infant MLL-r ALL trials testing epigenetic drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>COG: AALL15P1 (NCT02828358) for newly diagnosed infant MLL-r ALL</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>NCCHD (Japan): AZA-MLL-P16 (UMIN000029275) for R/R infant MLL-r ALL</td>
</tr>
<tr>
<td>Bortezomib/Vorinostat</td>
<td>St.Jude: Total Therapy for Infants with ALL I (NCT02553460) for newly diagnosed infant ALL</td>
</tr>
<tr>
<td>Panobinostat/Ara-C</td>
<td>TACL Phase 1 trial for children with R/R leukemia and lymphoma (NCT01321346)</td>
</tr>
<tr>
<td>Pinometostat (EPZ-5676; DOT1L inhibitor)</td>
<td>Phase 1 dose escalation trial for R/R children with MLL-r acute leukemia (NCT02141828) (Shulka N. ASH 2016)</td>
</tr>
</tbody>
</table>
CD19 targeted immunotherapy

**CAR T cells & BiTE® antibodies**

Blinatumomab pilot study to the Interfant-06 backbone for newly diagnosed infant MLL-r ALL is ongoing (EudraCT #2016-004674-17)

Suzuki M. *Pediatr Blood Cancer* 2015
• An infant girl with t(11;19) B-ALL
• BM relapse 3 months after BMT
• Failed Blinatumomab therapy
• Unable to generate donor-derived CAR19 T cells

• Received third-party CAR19 (UCART19) cells following lymphodepleting chemotherapy
• UCART19 is manufactured by disrupting TCRα and CD52 to avoid rejection/GVHD by TALEN® gene editing
• Molecular remission achieved within 28 days
• Underwent 2\textsuperscript{nd} BMT

Qasim W. Sci Transl Med 2017
Issues on CD19-targeted immunotherapy

- CD19-negative ALL relapse

- Lineage switch to CD19-negative myeloid leukemia

Mejstrikova E. *Blood Cancer J* 2017

pre-Blina (orange)  post-Blina (green)
Conclusions

✓ Infant MLL-r ALL is still one of the most difficult to cure among all the subtypes of pediatric ALL
✓ Current standard of care for infant MLL-r ALL is accompanied by high-risk of severe acute and late toxicities.
✓ Development of novel therapeutic strategies such as epigenetic therapy and immunotherapy is in progress
✓ International collaborations among the major study groups would be a key solution to overcome this rare and difficult disease, which is under way
Acknowledgment

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