Controversies in Hematology: Case-Based Discussion

Acute leukemia in Adolescents and Young adults

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Faculty of Medicine, Chiang Mai University
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Controversies in Hematology: Case-Based Discussion

ALL in Adolescents and Young adults (AYA)

• Standard risk ALL
  – Role of transplantation in 1\textsuperscript{st} CR
  – Pediatric adapted regimen for adult ALL

• Philadelphia positive ALL
  – Prognosis
  – Role of transplantation
  – Role of chemotherapy+TKI without transplantation
Case presentation

• 24 year old woman, engineer
• Presented with joint pain, anemic symptom
• Diagnosis T-ALL
• Wbc 78,500 per cu.mm. (lymphoblast 87%)
• BM chromosome – 46, XX
Case presentation

What is your treatment of choice for induction chemotherapy regimen?

A. GMALL
B. HyperCVAD or augmented HyperCVAD
C. Cancer and Leukemia Group B (CALGB study)
D. Standard or augmented Berlin-Frankfurt-Munster (BFM)
E. Pediatric inspired regimen
Case presentation

- Patient received pediatric inspired regimen (TPOG 2016) and achieved CR after induction
- She had HLA matched sibling (younger brother), SSS coverage

What is your treatment of choice for post-remission therapy?

A. Sibling allogeneic SCT
B. Continue chemotherapy
Role of transplantation in 1\textsuperscript{st} CR
Controversies in Adult ALL

2628 children with newly diagnosed ALL in 15 studies conducted at St. Jude hospital from 1962 to 2005

Controversies in Adult ALL

Around 1/3 of adult ALL, cured by standard chemotherapy

Biology of ALL according to age

After age of 10 year
- Increase of high-risk factors
- Decrease of good factors

Table 1. Incidence of Ph-like ALL across age ranges

<table>
<thead>
<tr>
<th>SR ALL children, %</th>
<th>HR ALL children, %</th>
<th>16-21 y, %</th>
<th>21-39 y, %</th>
<th>40-71 y, %</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>13</td>
<td>21</td>
<td>27</td>
<td>NR</td>
<td>16</td>
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<tr>
<td>15-18</td>
<td></td>
<td>25</td>
<td>18.7</td>
<td>11</td>
<td>93</td>
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<tr>
<td>NR</td>
<td>NR</td>
<td>~20</td>
<td>~19</td>
<td>&lt;10</td>
<td>17</td>
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</tbody>
</table>

Controversies in Adult ALL

- High remission rates in adults and children
- LFS in children 80% but only 35% in adult
- Most adults experience relapse

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission</th>
<th>Leukemia-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>80% to 90%</td>
<td>35%</td>
</tr>
<tr>
<td>Children (2-10 yrs of age)</td>
<td>97%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Controversies in Adult ALL SCT at First CR

Allo BMT vs Auto BMT in Patients With Ph- ALL: MRC UKALL XII/ECOG E2993

Patients with Ph- ALL aged < 55 yrs in complete remission after induction therapy (N = 919)

- High-Dose Methotrexate (3 doses) → Sibling Allo BMT (n = 389)
  - Yes → HLA-matched sibling donor available?
  - No → Auto BMT (n = 530)
    - Consolidation/Maintenance Chemotherapy: 2.5 years

### Controversies in Adult ALL

**SCT at First CR**

- Improved OS with allo BMT vs. auto BMT or chemotherapy in standard-risk
- 5-year OS for allo-BMT 54% vs 44%, (P < .02)
- High risk group OS was off set by TRM of SCT

#### Outcome by Risk Group, %

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Donor (n = 389)</th>
<th>No Donor (n = 530)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 5-yr survival</td>
<td>53</td>
<td>45</td>
<td>.02</td>
</tr>
<tr>
<td>High risk</td>
<td>40</td>
<td>36</td>
<td>.50</td>
</tr>
<tr>
<td>Standard risk</td>
<td>63</td>
<td>51</td>
<td>.01</td>
</tr>
</tbody>
</table>

**10-yr relapse rate**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Donor (n = 389)</th>
<th>No Donor (n = 530)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>39</td>
<td>62</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Standard risk</td>
<td>27</td>
<td>50</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Controversies in Adult ALL SCT at First CR

Figure 2. Forest plot of comparison: 1 Donor versus no donor, outcome: 1.1 Overall survival (overall sample).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornelissen 2009</td>
<td>-0.21453287</td>
<td>0.283</td>
<td>5.0%</td>
<td>0.81 [0.48, 1.35]</td>
<td></td>
</tr>
<tr>
<td>De Witte 1994</td>
<td>-0.40677966</td>
<td>0.411</td>
<td>11.5%</td>
<td>0.67 [0.30, 1.49]</td>
<td></td>
</tr>
<tr>
<td>Fielding 2009</td>
<td>-0.22316556</td>
<td>0.174</td>
<td>11.5%</td>
<td>0.80 [0.57, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Goldstone 2008</td>
<td>-0.094302</td>
<td>0.086</td>
<td>46.7%</td>
<td>0.91 [0.77, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Hunault 2004</td>
<td>-0.57446808</td>
<td>0.343</td>
<td>2.9%</td>
<td>0.56 [0.29, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Labar 2004</td>
<td>-0.02020202</td>
<td>0.193</td>
<td>9.3%</td>
<td>0.98 [0.67, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Ribera 2005</td>
<td>0.21193232</td>
<td>0.298</td>
<td>3.9%</td>
<td>1.24 [0.69, 2.22]</td>
<td></td>
</tr>
<tr>
<td>Sebban 1994</td>
<td>-0.28906301</td>
<td>0.165</td>
<td>12.7%</td>
<td>0.75 [0.54, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Takeuchi 2002</td>
<td>-0.05008944</td>
<td>0.299</td>
<td>3.9%</td>
<td>0.95 [0.63, 1.71]</td>
<td></td>
</tr>
<tr>
<td>Ueda 1998</td>
<td>-0.41186736</td>
<td>0.418</td>
<td>2.0%</td>
<td>0.86 [0.29, 1.50]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
100.0%  
0.86 [0.77, 0.97]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.70$, df = 9 ($P = 0.77$); $I^2 = 0$

Test for overall effect: $Z = 2.48$ ($P = 0.01$)

Pediatric adapted regimen for adult ALL
Controversies in Adult ALL

- Summary of recent studies using pediatric-inspired protocols in AYA
- OS 60-80% and LFS 60-70%

<table>
<thead>
<tr>
<th>Study</th>
<th>Age range, y</th>
<th>Patients, n</th>
<th>CR rate</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRALLE-93 [7]</td>
<td>15–20</td>
<td>77</td>
<td>94%</td>
<td>78% 5-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72% 5-y DFS</td>
</tr>
<tr>
<td>UK ALL97 [8]</td>
<td>15–17</td>
<td>61</td>
<td>98%</td>
<td>71% 5-y OS</td>
</tr>
<tr>
<td>DCOG [9]</td>
<td>15–18</td>
<td>47</td>
<td>98%</td>
<td>79% 5-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71% 5-y DFS</td>
</tr>
<tr>
<td>DFCI [10]</td>
<td>15–18</td>
<td>51</td>
<td>94%</td>
<td>81% 5-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78% 5-y EFS</td>
</tr>
<tr>
<td>CCG [11]</td>
<td>16–20</td>
<td>197</td>
<td>90%</td>
<td>67% 7-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63% 7-y EFS</td>
</tr>
<tr>
<td>CCG 1961 [12•]</td>
<td>16–21</td>
<td>262</td>
<td>96%</td>
<td>77.5% 5-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71.5% 5-y EFS</td>
</tr>
<tr>
<td>St. Jude’s XV [13•]</td>
<td>15–18</td>
<td>44</td>
<td>98%</td>
<td>88% 5-y OS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86% 5-y EFS</td>
</tr>
<tr>
<td>PETHEMA [16]</td>
<td>15–18</td>
<td>35</td>
<td>94%</td>
<td>77% 6-y OS</td>
</tr>
<tr>
<td></td>
<td>18–30</td>
<td>46</td>
<td>100%</td>
<td>63% 6-y EFS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63% 6-y OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60% 6-y EFS</td>
</tr>
<tr>
<td>GRAALL [17]</td>
<td>15–45</td>
<td>172</td>
<td>93.5%</td>
<td>61% 3.5-y OS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57% 3.5-y EFS</td>
</tr>
<tr>
<td>PMH [18•]</td>
<td>18–35</td>
<td>42</td>
<td>98%</td>
<td>83% 5-y OS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>77% 5-y RFS</td>
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</table>

Outcomes in AYAs treated in fully pediatric or pediatric-inspired trials

Although the majority of recent studies demonstrate a survival benefit using intensive pediatric regimens for AYA, another recently published comparison study of an “adult” regimen (hyper-CVAD) vs a pediatric regimen (BFM-like) found equivalent EFS (~70%). Because this trial was conducted at an institution with a large, experienced leukemia program, the results may not be widely generalizable but suggest that high-volume referral centers may offer benefits beyond chemotherapeutics. In fact, recent data show that outcomes for AYAs with ALL are significantly improved if treatment is administered at a university or National Cancer Institute-sponsored cancer center with expertise in the complex regimens used to treat ALL.

Outcomes in AYAs treated in fully pediatric or pediatric-inspired trials

### Table: Outcomes in AYAs treated in fully pediatric or pediatric-inspired trials

<table>
<thead>
<tr>
<th>Age range, y</th>
<th>Median age, y</th>
<th>CR, %</th>
<th>Early death, %</th>
<th>Death in CR, %</th>
<th>HSCT, %</th>
<th>EFS/DFS/CRD</th>
<th>OS</th>
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<tbody>
<tr>
<td>15-30</td>
<td>20</td>
<td>98</td>
<td>1</td>
<td>1*</td>
<td>0*</td>
<td>6</td>
<td>EFS, 61</td>
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<tr>
<td>17-40</td>
<td>26</td>
<td>91</td>
<td>4</td>
<td>NR</td>
<td>35</td>
<td>2</td>
<td>EFS, 66</td>
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<tr>
<td>15-29</td>
<td>19</td>
<td>99</td>
<td>NR</td>
<td>NR</td>
<td>28</td>
<td>5</td>
<td>EFS, 61</td>
</tr>
<tr>
<td>16-24</td>
<td>19</td>
<td>94</td>
<td>4</td>
<td>15</td>
<td>5</td>
<td>5 DFS, 67</td>
<td>5</td>
</tr>
<tr>
<td>17-39</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>2 EFS, 66</td>
<td>2</td>
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<tr>
<td>18-50†</td>
<td>28†</td>
<td>86</td>
<td>1</td>
<td>NR</td>
<td>21</td>
<td>4</td>
<td>EFS, 58</td>
</tr>
<tr>
<td>13-39</td>
<td>22</td>
<td>93</td>
<td>1</td>
<td>8</td>
<td>10</td>
<td>3 CRD, 70</td>
<td>5</td>
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<tr>
<td>15-40</td>
<td>27</td>
<td>98</td>
<td>1</td>
<td>7</td>
<td>6</td>
<td>3 CRD, 67</td>
<td>5</td>
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<td>18-35</td>
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<td>98</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>3 DFS, 77</td>
<td>3</td>
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<tr>
<td>15-35</td>
<td>NR</td>
<td>91</td>
<td>4</td>
<td>NR</td>
<td>43</td>
<td>5 CRD, 61</td>
<td>5</td>
</tr>
<tr>
<td>15-35</td>
<td>24</td>
<td>97</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5 EFS, 59</td>
<td>5</td>
</tr>
<tr>
<td>18-45</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td>6</td>
<td>NR</td>
<td>5 EFS, 74</td>
<td>5</td>
</tr>
</tbody>
</table>

**Fully pediatric or pediatric-inspired trials**
- Split into age groups of 18 to 25 years and 26 to 45 years

Controversies in Adult ALL

Induction (4 weeks)
- Prednisone: 10 mg PO QID Days 0–28
- Doxorubicin: 30 mg/m² IV Days 0 and 1
- Vincristine: 2 mg IV Days 0, 7, 14, 21
- Methotrexate: 4 g/m² IV over 1 h Day 2 (with leucovorin rescue)
- Asparaginase: 25 000 IU/m² IM Day 4
- Cyt/Mtx/HC*: 40/12/15 mg IT Days 0, 14

CNS therapy (3 weeks)
- Doxorubicin: 30 mg/m² IV Day 1
- Vincristine: 2 mg IV Day 1
- 6-Mercaptopurine: 50 mg/m² PO QHS Days 1–14
- Cranial radiation: 1200 cGy Over 8 d
- Cyt/Mtx/HC*: 40/12/15 mg IT Days 1, 4, 8, 11

Intensification therapy: 30 weeks (10 cycles–21 d/cycle)
- Doxorubicin: 30 mg/m² IV Day 1 (cycles 1–7 only)
- Vincristine: 2 mg IV Day 1
- 6-Mercaptopurine: 50 mg/m² PO QHS Days 1–14
- Dexamethasone: 9 mg/m² PO BID Days 1–5
- Asparaginase: 12 500 IU/m² IM Days 1, 8, 15
- Methotrexate: 30 mg/m² IV Days 2, 9, 16 (cycles 8–10 only)
- Cyt/Mtx/HC*: 40/12/15 mg IT Every 18 weeks

Maintenance therapy: 72 weeks (24 cycles–21 d/cycle)
- Vincristine: 2 mg IV Day 1
- 6-Mercaptopurine: 50 mg/m² PO QHS Days 1–14
- Dexamethasone: 6 mg/m² PO BID Days 1–5
- Methotrexate: 30 mg/m² IV/IM Days 1, 8, 15
- Cyt/Mtx/HC*: 40/12/15 mg IT Every 18 weeks

Storr JM, et al. BJH, 146,76–85.
St. Jude’s data reported significant toxicities

- 11.7, 32.9, 23.8, 27.7% in 3-year cumulative risks
- Grade 4 to 5 severe infection, grade 3 to 4 osteonecrosis, grade 2 to 4 thrombosis, and grade 3 to 4 hyperglycemia
- Others: neuropathy, neuro-cognitive dysfunction, pancreatitis, cardiac toxicity, and secondary malignancies
Thai Pediatric Oncology Group (TPOG) regimen

- Pediatric inspired regimen – dose adapted
- Remain CNS irradiation – reduced dose

Treatment protocol for very high risk acute lymphoblastic leukemia [ThaiPOG-ALL-1303]

Protocol name: ThaiPOG-ALL-1303
Protocol for: Very High Risk ALL
Reference: COG AALL1131
Open date: January 2014 (revised October 2015)

Patient eligibility:
- Precursor B-cell ALL with
  - Age at diagnosis ≥14 years old
  - CNS-3
  - Induction failure (≥M2 at day 20)
  - Previous SR and HR with Day 29 BM MRD ≥ 0.01% with no Favorable cytogenetic
- T-cell ALL with
  - CNS-3
  - Day 29 BM MRD ≥0.01%

Exclusion criteria: Burkitt leukemia

Treatment schema:
- SR-Induction
- HR/VHR-Induction
- Day 29 assessment

VHR features
- VHR-Aug-Consolidation
- Induction failure, Hypodiploidy
- HSCT
- VHR-Aug-IM-I
- VHR-Aug-DI
- VHR-IM-II
- Aug-Maintenance
Superiority of Pediatric CMT over allo-HCT for Adult ALL in 1st CR

A Combined Analysis of Dana-Farber ALL Consortium and CIBMTR Cohorts

Caveat:
• Aged 18-50 years
• HCT cohort was older (34 vs. 30 y, p=0.001) and higher WBC
• RCT is needed

Poor prognostic factors in ALL

**B-lineage ALL**
- Age > 35 years
- WBC > 30,000/µL
- Pro-B ALL
- t(9;22)[BCR/ABL]
- t(4;11)[AF4/MLL]
- CR > 4 weeks

**T-lineage ALL**
- WBC > 100,000/µL
- Early-T or mature-T
- CR > 4 weeks

German Multicenter ALL Group 2000
BCR-ABL1–like ALL

- 15% of BCP-ALL
  - Unusual specific genetic subgroup
- High risk of relapse and poor outcome
- Similar gene expression signature to BCR-ABL1–positive

**BCR-ABL1–like ALL**

- 50% had CRLF2 high expression
- 30% had JAK2 mutations
- The remainder had ABL1, JAK2, PDGFRB, and other kinase rearrangements and sequence mutations

Secondary chromosomal and genomic abnormalities

The 4 most prevalent ACA

- Deletions of CDKN2A/B (30–40%)
- Deletions/mutations of IKZF1 (20%)
- Deletions/mutations/amplifications of PAX5 (20%)
- Deletions of ETV6 (10–15%)

Controversies in Adult ALL

Status of minimal residual disease post induction predicts outcome in adult ALL

Ped: MRD at day 33 and day 78 the most important prognosis

GMALL: MRD negativity ($<10^{-4}$) at day 71 and week 16 showed clinical benefit independent of pre-therapeutic risk factors

Holowiecki J, et al. BJH, 142, 227–237.
## Characteristics of MRD methods

<table>
<thead>
<tr>
<th>MRD technique</th>
<th>Conventional flow cytometry</th>
<th>RQ-PCR of IG/TR genes or breakpoint regions of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated sensitivity</td>
<td>$3-4$ colors: $10^{-3}-10^{-4}$</td>
<td>$10^{-4}-10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>$6-8$ colors: $10^{-4}$</td>
<td></td>
</tr>
<tr>
<td>Applicability</td>
<td>BCP-ALL: $&gt;90%$</td>
<td>BCP-ALL: $95%$</td>
</tr>
<tr>
<td></td>
<td>T-ALL: $&gt;90%$</td>
<td>T-ALL: $90-95%$</td>
</tr>
<tr>
<td>Advantages</td>
<td>Fast</td>
<td>Applicable in virtually all BCP-ALL and T-ALL</td>
</tr>
<tr>
<td></td>
<td>Analysis at cell population level or single cell level</td>
<td>Sensitive</td>
</tr>
<tr>
<td></td>
<td>Easy storage of data</td>
<td>Well standardized + regular international QA rounds</td>
</tr>
<tr>
<td></td>
<td>Information about the whole sample cellularity</td>
<td></td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Variable sensitivity, because of similarities between normal (regenerating) cells and malignant cells</td>
<td>Time-consuming</td>
</tr>
<tr>
<td></td>
<td>Limited standardization, no QA results</td>
<td>Expensive</td>
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<tr>
<td></td>
<td></td>
<td>Requires extensive experience and knowledge</td>
</tr>
</tbody>
</table>

Supplemental Figure 1: GMALL 07 Trial Overview for Ph-negative ALL

Stratification I according to risk factors

Stratification II according to MRD

* If donor or autologous stem cells available

Principle of pediatric inspired regimen

- Mostly based on Berlin-Frankfurt-Munster
- Multiple cycle of non-cross-resistant agents
- Repeated dosed of L-as, vincristine, steroid
- Early and frequent CNS prophylaxis (omit RT)
- Delay intensification
- Prolonged maintenance
- Higher cumulative doses of active agents
- But Less myelosuppression
Controversies in Adult ALL

• Standard risk ALL
  – Pediatric adapted regimen for adult ALL
    • Yes, if applicable
    • But availability of drug and treatment related toxicity
  – Transplantation in 1\textsuperscript{st} CR
    • Yes, if use standard adult ALL regimen
    • No RCT in the era of Pediatric adapted regimen
Controversies in Adult ALL

• Standard risk ALL
  – Pediatric adapted regimen for adult ALL
    • Yes, strongly encourage
    • Protocol adaptation, treatment related toxicity (TPOG)
    • Check your protocol
  – Transplantation in 1st CR
    • Yes, if use standard adult ALL regimen
    • High risk and positive MRD
    • No RCT in the era of Pediatric adapted regimen
Controversies in Adult ALL

Outcome of 609 relapse adults ALL; MRC UKALL12/ECOG 2993 study

Philadelphia positive ALL
Controversies in Hematology: Case-Based Discussion

ALL in Adolescents and Young adults (AYA)

• Standard risk ALL
  – Role of transplantation in 1st CR
  – Pediatric adapted regimen for adult ALL

• Philadelphia positive ALL
  – Prognosis
  – Role of transplantation
  – Role of chemotherapy+TKI without transplantation
Case presentation

• 17 year old woman, student
• Presented with joint pain, prolonged fever
• Diagnosis CALLA-B-ALL
• Wbc 6,620 per cu.mm. (lymphoblast 90%)
• BM chromosome – 47, XX, i(7q), der(8), t(9;22),+mar[5]/ 46, XX, t(9;22)[2], 46,XX[10]
Case presentation

What is your treatment of choice for induction chemotherapy regimen plus TKI?

A. GMALL
B. HyperCVAD
C. Cancer and Leukemia Group B (CALGB study)
D. Standard or augmented Berlin-Frankfurt-Munster (BFM)
E. Pediatric inspired regimen
Case presentation

• Patient received HyperCVAD plus imatinib 600 mg/day achieved CR after induction (1st cycle)
• She had HLA matched sibling (younger sister), UC scheme

What is your treatment of choice for post-remission therapy?

A. Sibling allogeneic SCT
B. Continue chemotherapy
Controversies in Adult Ph+ ALL

- Philadelphia positive ALL
  - One of the worst prognosis factors
  - Role of transplantation in TKI era
  - Role of chemotherapy plus TKI without transplantation
Controversies in Adult Ph+ ALL

• In the past
  – Poorly tractable therapeutic disease
  – Associated with at least a 10% lower chance of complete remission (CR)
  – Extremely poor prognosis overall
  – Median survival of 8 months

• In TKI era
  – Tyrosine kinase inhibitor has changed the outcome and prognosis of Adult Ph+ ALL
Induction therapy

• TKI in the induction phase - Gold-standard
  – Much higher CR rates
  – Improved long-term outcome
  – Disease-free survival (DFS)/overall survival (OS)
  – Increasing the likelihood of allo-SCT

• Compared with historical controls

## Controversies in Adult Ph+ ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Study group</th>
<th>Drug, dose, mg</th>
<th>N</th>
<th>CR, %</th>
<th>Transplantation rate, %</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Published studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas</td>
<td>MD Anderson</td>
<td>Im 400</td>
<td>20</td>
<td>93</td>
<td>50</td>
<td>75% at 20 mo</td>
</tr>
<tr>
<td>Yanada</td>
<td>JALSG</td>
<td>Im 600</td>
<td>80</td>
<td>96</td>
<td>61</td>
<td>75% at 1 year</td>
</tr>
<tr>
<td>Wassmann</td>
<td>GMALL</td>
<td>Im 4–600</td>
<td>92</td>
<td>95</td>
<td>77</td>
<td>36% (alternating schedule)</td>
</tr>
<tr>
<td>De Labarathe</td>
<td>GRAALL</td>
<td>Im 600</td>
<td>45</td>
<td>96</td>
<td>48</td>
<td>65% at 18 mo</td>
</tr>
<tr>
<td>Vignetti</td>
<td>GIMEMA</td>
<td>Im 800</td>
<td>30</td>
<td>100</td>
<td>N/A</td>
<td>74% at 12 mo</td>
</tr>
<tr>
<td>Ottman</td>
<td>GMALL</td>
<td>Im 600</td>
<td>55</td>
<td>96 (imatinib) 50 (chemo)</td>
<td>N/A</td>
<td>42% at 24 mo</td>
</tr>
<tr>
<td>Ribera</td>
<td>PETHEMA</td>
<td>Im 400</td>
<td>30</td>
<td>90</td>
<td>70</td>
<td>N/A</td>
</tr>
<tr>
<td>Bassan</td>
<td>NILG</td>
<td>Im 340/m²</td>
<td>59</td>
<td>92</td>
<td>63</td>
<td>30% at 4 y</td>
</tr>
<tr>
<td>Schultz</td>
<td>COG</td>
<td>Im 340/m²</td>
<td>92</td>
<td>Not stated</td>
<td>N/A*</td>
<td>38% at 5 y</td>
</tr>
<tr>
<td>Ravandi</td>
<td>MD Anderson</td>
<td>Das 50 bd (or 100 od)</td>
<td>35</td>
<td>94</td>
<td>N/A</td>
<td>80% (EFS) at 3 y</td>
</tr>
</tbody>
</table>

### Transplantation rate, %

- 50%
- 61%
- 77%
- 48%
- N/A
- 70%
- N/A
- 70%
- N/A
- 44%
- 62%
- N/S
- 80.7%
- Median 27.1 mo

### OS

- 75% at 20 mo
- 75% at 1 year
- 36% (alternating schedule)
- 43% (concurrent schedule at 2 y)
- 65% at 18 mo
- 74% at 12 mo
- 42% at 24 mo
- 30% at 4 y
- 38% at 5 y
- 80% (EFS) at 3 y
- 64% at 24 mo
- 43% at 3 y
- 62% at 2 y
- 80.7% at 10 mo
- Median 27.1 mo

Controversies in Adult Ph+ ALL

Chemotherapy +/- TKI in Elderly ALL, Overall survival

Ph Pos (n = 7) 36%
Ph Neg (n = 25) 0%
p = 0.81

Pitfall in diagnosis

• Better identified by FISH/preferably by RT-PCR
• B-ALL esp. CALLA(+) (CD10)
• In the past conventional cytogenetics
• RT-PCR
  – Type of transcript
    • p190 (e2a2) (more common)
    • p210 (b2a2, b3a2)

Conventional cytogenetic

<table>
<thead>
<tr>
<th>CALLA(+) ALL (N=34)</th>
<th>CML (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>6</td>
<td>118</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>No metaphase</td>
<td>No metaphase</td>
</tr>
<tr>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

PCR (+) in all cases (%): $P_{190} = 7$, $P_{210} = 4$, $P_{190,210} = 2$

FISH (+) in all 5 cases

Allogeneic BMT in Adult Ph+ ALL

- The 2 large studies conducted prospectively
- Myeloablative sibling alloHSCT much better outcome than chemo
- No RCT has been done in TKI era
  - Compared TKI vs. BMT

**UK ALL XII/ECOG 2993**

<table>
<thead>
<tr>
<th>Outcome by Risk Group, %</th>
<th>Donor (n = 389)</th>
<th>No Donor (n = 530)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 5-yr survival</td>
<td>53</td>
<td>45</td>
<td>.02</td>
</tr>
<tr>
<td>□ High risk</td>
<td>40</td>
<td>36</td>
<td>.50</td>
</tr>
<tr>
<td>□ Standard risk</td>
<td>63</td>
<td>51</td>
<td>.01</td>
</tr>
<tr>
<td>10-yr relapse rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ High risk</td>
<td>39</td>
<td>62</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>□ Standard risk</td>
<td>27</td>
<td>50</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

- 5-year OS for allo BMT 53% vs 45%, (P < .02)
- High risk group – treatment related mortality
- De-intensified induction treatment

Allogeneic stem cell transplant

- Allo-SCT still remains the only truly curative option for Ph+ ALL
- Mostly for younger adult patients

**UKALLXII/ECOG2993**
- 4-y OS - imatinib cohort
- alloHSCT benefit to EFS (HR for EFS = 0.64, 95% CI (0.44-0.93), P = .02)
- But not OS

Randomized study of reduced-intensity chemo with imatinib

<table>
<thead>
<tr>
<th>Cycle 1 arm A</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR</td>
<td>2 mg/day IV</td>
<td>Day 1, 8, 15, and 22</td>
<td></td>
</tr>
<tr>
<td>DXM</td>
<td>40 mg/day PO</td>
<td>Day 1-2, 8-9, 15-16, and 22-23</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>400 mg bid PO</td>
<td>Day 1 to 28</td>
<td></td>
</tr>
<tr>
<td>Filgrastim</td>
<td>5 μg/kg/day SC/IV</td>
<td>From Day 15 to PMN recovery</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle 1 arm B</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR</td>
<td>2 mg/day IV</td>
<td>Day 4 and 11</td>
<td></td>
</tr>
<tr>
<td>DXM</td>
<td>40 mg/day PO</td>
<td>Day 1-4, and 11-14</td>
<td></td>
</tr>
<tr>
<td>DXR</td>
<td>50 mg/m²/day CIV</td>
<td>Day 4</td>
<td></td>
</tr>
<tr>
<td>CPM</td>
<td>300 mg/m²/12h IV</td>
<td>Day 1-3</td>
<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>400 mg bid PO</td>
<td>Day 1 to 14</td>
<td></td>
</tr>
<tr>
<td>Filgrastim or Peg-filgrastim</td>
<td>5 μg/kg/day SC/IV</td>
<td>From Day 15 to PMN recovery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mg SC</td>
<td>Day 6</td>
<td></td>
</tr>
</tbody>
</table>

- Reduced-intensity of chemotherapy
- Lower early mortality and higher CR rate
- 5-year EFS and OS without difference

Role of chemotherapy plus TKI without transplantation

- Phase 2 study
- N = 35 pts
- Median follow-up of 14 months (4-37)
- Dasatinib was continued indefinitely
- Treatment related toxicities is quite high

Final Report Of CMT+Dasatinib For Ph+ ALL

- 63 pts with untreated, 9 patients with prior
- Median follow up of 48 months
- 6 relapsed, ABL mutations (4 T315I, 1 F359V, 1 V299L)

Hyper-CVAD + ponatinib vs. dasatinib

- Propensity score matching
- The 3-year EFS rates in ponatinib and dasatinib were 69% and 46%, respectively (p=0.04)
- The 3-year OS rates were 83% and 56%, respectively (p=0.03)

Hyper CVAD/Ponatinib in Ph+ ALL

- Hyper-CVAD/ponatinib
- 2-year EFS rate was 81%
- > Gr 3 toxicity in 54%
  - Thrombotic events (8%), myocardial infarction (8%), hypertension (16%) and pancreatitis (16%)

Hyper CVAD/Ponatinib in Ph+ ALL

MRD status by PCR and flow cytometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR *</td>
<td>36/36 (100)</td>
</tr>
<tr>
<td>CCyR **</td>
<td>32/32 (100)</td>
</tr>
<tr>
<td>MMR</td>
<td>35/37 (95)</td>
</tr>
<tr>
<td>CMR</td>
<td>29/37 (78)</td>
</tr>
<tr>
<td>Flow negativity ***</td>
<td>35/36 (97)</td>
</tr>
<tr>
<td>Early death</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Controversies in Adult Ph+ ALL

- Philadelphia positive ALL
  - One of the worst prognosis factors
    - Not anymore with TKI treatment
  - Role of transplantation in TKI era
    - Yes if applicable
  - Role of chemotherapy plus TKI without transplantation
    - No but reasonable in some circumstances which transplantation is not applicable, require more study
Controversies in Adult Ph+ ALL

- Philadelphia positive ALL
  - One of the worst prognosis factors
    - Not sure with TKI treatment
  - Role of transplantation in TKI era
    - Yes but need prospective RCT
  - Role of chemotherapy plus TKI without transplantation
    - Yes if transplantation is not applicable
    - DMR and MRD needed
Monoclonal Ab and Immuno-oncology in ALL
ALL treatment paradigm

Diagnosis

High risk
  - MRD positive: Stem cell transplantation

Standard risk
  - Not CR: Chemotherapy
  - MRD negative: Chemotherapy
Thank you for your attention