Is the efficacy of the pediatric-like protocols for ALL superior to the protocols for adult ALL?

No

JM Ribera
on behalf of the PETHEMA Group.
Spanish Society of Hematology
Incidence of ALL

SEER Program (www.seer.cancer.gov)
AIEOP and GIMEMA. 5,203 ALL Patients
Distribution by age

Chiaretti S, et al, EHA 2010
Age-specific incidence of adults with acute lymphoblastic leukemia (ALL) in the North East of England by sex

US age-adjusted childhood mortality trends for lymphoma and leukemia, and all other cancer sites with annual percentage changes (APCs) for join point segments for males and females <20 yr (1975 -2006)

Childhood ALL. Overall survival

- Study 15, 2000–2005 (N=274), 96±3/84±2
- Studies 11 and 12, 1984–1991 (N=546), 74±2
- Study 10, 1979–1983 (N=428)
- Studies 5 to 9, 1967–1979 (N=825), 48±2
- Studies 1 to 4, 1962–1966 (N=90), 21±4

Years after Diagnosis

Pui CH, NEJM 2006
5-yr. survival rates for (A) ALL, (B) AML, (C) NHL, and (D) HL among children by age group and period of diagnosis, (1975-2002). SEER 9 Registries

ALL incidence and survival among adults in Sweden

Juliusson, G. et al.
Blood 2010;116:1011
OS of adults with ALL by age at diagnosis

Survival in adult ALL Has Improved in All Age Groups Except the Oldest Patients

<table>
<thead>
<tr>
<th>Age Range, % ± SE</th>
<th>1980-1984</th>
<th>2000-2004</th>
<th>Increase, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-29 yrs</td>
<td>33.7 ± 3.5</td>
<td>53.6 ± 3.2</td>
<td>19.9</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>30-44 yrs</td>
<td>20.2 ± 4.8</td>
<td>34.3 ± 3.9</td>
<td>14.1</td>
<td>.002</td>
</tr>
<tr>
<td>45-59 yrs</td>
<td>10.3 ± 4.9</td>
<td>24.3 ± 3.4</td>
<td>14.0</td>
<td>.0002</td>
</tr>
<tr>
<td>&gt; 60 yrs</td>
<td>8.4 ± 3.4</td>
<td>12.7 ± 2.9</td>
<td>4.3</td>
<td>.48</td>
</tr>
</tbody>
</table>

Reason for today’s debate on treatment of ALL in adolescent and young adults (AYA)

Retrospective comparative studies
## AL in AYA. Retrospective comparative studies

### “Pediatric” vs “adult” treatments

<table>
<thead>
<tr>
<th>Country</th>
<th>Protocol</th>
<th>Age</th>
<th>N</th>
<th>CR(%)</th>
<th>5yr.EFS(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>CCG(P)</td>
<td>16-21</td>
<td>197</td>
<td>96</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>CALGB(A)</td>
<td>16-21</td>
<td>124</td>
<td>93</td>
<td>38</td>
</tr>
<tr>
<td>France</td>
<td>FRALLE93(P)</td>
<td>15-20</td>
<td>77</td>
<td>94</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>LALA94 (A)</td>
<td>15-20</td>
<td>100</td>
<td>83</td>
<td>41</td>
</tr>
<tr>
<td>Holland</td>
<td>DCOG (P)</td>
<td>15-18</td>
<td>47</td>
<td>98</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>HOVON (A)</td>
<td>15-20</td>
<td>44</td>
<td>91</td>
<td>34</td>
</tr>
<tr>
<td>UK</td>
<td>ALL97 (P)</td>
<td>15-17</td>
<td>61</td>
<td>98</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>UKALLXII(A)</td>
<td>15-20</td>
<td>67</td>
<td>94</td>
<td>49</td>
</tr>
<tr>
<td>Italy</td>
<td>AIEOP (P)</td>
<td>14-18</td>
<td>150</td>
<td>94</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>GIMEMA (A)</td>
<td>95</td>
<td>94</td>
<td>89</td>
<td>71(2yr)</td>
</tr>
<tr>
<td>Sweden</td>
<td>NOPHO-92(P)</td>
<td>10-18</td>
<td>144</td>
<td>99</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Adult (A)</td>
<td>15-25</td>
<td>99</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>Finland</td>
<td>NOPHO (P)</td>
<td>10-25</td>
<td>128</td>
<td>96</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>ALL (A)</td>
<td>97</td>
<td>97</td>
<td>97</td>
<td>60</td>
</tr>
</tbody>
</table>

FRALLE-93 vs. LALA-94

## Global outcome
**LALA-94 / FRALLE-93**

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age *</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex **</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>WBC *</td>
<td>0.005</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B vs T **</td>
<td>0.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Cytogenetics **</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Trial ** (LALA vs. FRALLE)</td>
<td>0.04</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* : Mann-Whitney test (CR) and univariate Cox (EFS)

** : Fisher’s test (RC) and log-rank (EFS)

Reasons for the best results of pediatric protocols

• Higher dose-intensity of chemotherapy

• Higher adherence to treatment

• Better possibility to conduct clinical studies in children (ALL more frequent)

• Economic problems in emancipated AYA in certain countries
Major differences in pediatric vs. adult protocols

• **Higher dose of essential drugs**
  – Up to 3x vinca alkaloids
  – Up to 5x prednisolone
  – Up to 20x asparaginase

• **Less use of myelosuppressive drugs**
  – eg, anthracyclines, cyclophosphamide, cytarabine

• **Less use of BMT**
  – BMT only recommended by pediatricians for very high-risk ALL

• **Less delays between therapy elements**
  – Time to treatment following initial CR was 2 days in pediatric practice vs. 7 days in adult practice ($P = .002$)
Biology of Patient Affects Toxicity: L-Asparaginase

• L-asparaginase (L-asp): essential treatment component in pediatric ALL patients
  – Can also cause frequent treatment delays and toxicity (eg, increased risk of bleeding or thrombosis), compromising overall therapy

• CAPELAL: retrospective study of 214 adults with either ALL or lymphoblastic lymphoma
  – Treatment: E. coli–derived L-asp 7500 IU/m² x 6

• Toxicity effects
  – L-asp delayed in 22%, reduced dose in 41%
  – Typically due to coagulation abnormalities as well as hepatotoxicity

Biology of Patient Affects Toxicity: L-Asparaginase

- **CAPELAL study**: thrombotic events observed in 9.3% of 214 adults; none fatal\[1\]
- Worse ALL outcome in those with a thrombotic event; many discontinued L-asp
- **UKALL 2003 study**: thrombosis noted in 3% of 1824 pediatric patients receiving PEG-ASP\[2\]

Additional evidence in favor of the use of pediatric protocols for AYA

Prospective (but non-comparative) studies conducted by adult groups using “pediatric-inspired” protocols
### Prospective studies on therapy of ALL in AYA

<table>
<thead>
<tr>
<th>Group-Protocol</th>
<th>Age</th>
<th>N</th>
<th>CR(%)</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFCI 91-01,95-01</td>
<td>15-18</td>
<td>51</td>
<td>94</td>
<td>78</td>
</tr>
<tr>
<td>GRAALL-03*</td>
<td>15-45</td>
<td>172</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>PETHEMA ALL96**</td>
<td>15-18</td>
<td>35</td>
<td>94</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>19-30</td>
<td>46</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>DFCI</td>
<td>18-50</td>
<td>74</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>Toronto-Modified DFCI</td>
<td>18-60</td>
<td>85</td>
<td>89</td>
<td>71</td>
</tr>
<tr>
<td>FRALLE 93 HR-derived***</td>
<td>18-55</td>
<td>40</td>
<td>90</td>
<td>72 (OS)</td>
</tr>
</tbody>
</table>

*Increase of 8.6-fold, 3.7-fold and 16-fold in cumulated doses of PDN, VCR and L-ASP compared to ALL-94 protocol. Better results in patients up to 45 yr

** No differences between adolescents and young adults

***Better results in patients up to 40 yr

FRALLE-93 vs EORTC ALL4

(A) Disease Free Survival

(B) Overall Survival

(C) Disease Free Survival

(D) Overall Survival

(E) Disease Free Survival

(F) Overall Survival

All patients

Patients < 40 yo

Patients ≥ 40 yo

0 365 730 1095 1460 1825

0 365 730 1095 1460 1825

0 365 730 1095 1460 1825

0 365 730 1095 1460 1825

P=0.04

P=0.05

P=0.03

P=0.03

P=0.86

P=0.90


EFS and OS for AYA (16-21 yr.)
treated on Children's Cancer Group 1961 (n = 262)

5-year EFS 71.5% (SE 3.6%); 5-year survival 77.5% (SE 3.3%)

Event-free survival
GRAALL-2003 / FRALLE-2000

![Graph showing event-free survival for GRAALL-2003 and FRALLE-2000 with p-values and percentages.]

**GRAALL-03**
- 3-y 69% (± 13)
- 3-y 66% (± 11)

**FRALLE-2000**
- 3-y 85% (± 8)

p=0.01 (Censored at allograft)
p=0.003

Courtesy of H Dombret and A Baruchel
The turtle and the hare
La tortuga y la liebre
Evidences in favor of the use of pediatric protocols for AYA

- Retrospective comparisons
- Prospective -but non-randomized- protocols in AYAs by adult teams using pediatric-inspired protocols
- Results of current pediatric protocols are improving in adolescents
However...

- **Retrospective comparisons**: weak design
- **Groups not fully comparable** in retrospective comparisons
- In some studies the protocol itself had no impact on survival in the multivariate analysis (although in others had)
- **Current adult protocols (without “pediatric inspiration”)** show promising results in young adults
- **Absence of direct prospective comparative studies ("pediatric” vs. adult-type”)**
Non full comparability of “pediatric” vs. “adult” AYA groups of patients in baseline ALL parameters (i.e.: age)

<table>
<thead>
<tr>
<th>Country</th>
<th>Protocol</th>
<th>Median age</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>FRALLE-93 (P)</td>
<td>15.9</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>LALA-94 (A)</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>Holland</td>
<td>DCOG (P)</td>
<td>15.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>HOVON (A)</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>NOPHO (P)</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>CCG (P)</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>CALGB (A)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>NOPHO (P)</td>
<td>12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>ALL (A)</td>
<td>18.9</td>
<td></td>
</tr>
</tbody>
</table>
Lack of impact of the protocol by multivariate analysis. ALL97 vs. UKALLXII/E2993

- UKALLXII/E2993 (adult) vs. ALL97 (pediatric)
- Forward and backward multivariate analysis

Prognostic factors:
- Yes: Age, Ph
- No: protocol

OS (%)

Years

<table>
<thead>
<tr>
<th>Years</th>
<th>UKALLXII/E2993</th>
<th>ALL97</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at risk:
- UKALLXII/E2993: 67, 51, 43, 32, 23, 17
- ALL97: 61, 55, 50, 43, 31, 21

P = 0.04

Current adult protocols without “pediatric inspiration” have promising results in young adults

GMALL
MRC/ECOG
MDACC
Results of Induction Therapy in Adolescents
GMALL Studies 06/99-07/03

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>CR</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>417</td>
<td>90%</td>
<td>2%</td>
</tr>
<tr>
<td>15-17 yrs</td>
<td>73</td>
<td>93%</td>
<td>3%</td>
</tr>
<tr>
<td>18-20 yrs</td>
<td>171</td>
<td>92%</td>
<td>2%</td>
</tr>
<tr>
<td>21-25 yrs</td>
<td>173</td>
<td>88%</td>
<td>2%</td>
</tr>
</tbody>
</table>

5-yr DFS: 67%

Courtesy of N Goekbuget and D Hoelzer
**MRC UKALLXII/ECOG E2993**

**ALL-96:** prospective study of pediatric regimens in adolescents and young adults with standard-risk ALL\(^1\)

**UKALLXII/ECOG E2993:** prospective study of allogeneic SCT vs autologous SCT plus chemotherapy in adults with standard-risk ALL\(^2\)

---

**Graphs:**

- **Left:**
  - Adolescents (n = 35)
  - Young adults (n = 46)
  - CR: 98%
  - 6-yr OS in young adults: 63%
  - 6-yr OS in adolescents: 77%
  - \(P = \text{NS}\)

- **Right:**
  - Donor (n = 239)
  - No donor (n = 323)
  - CR: 97%
  - 5-yr OS with donor: 62%
  - 5-yr OS without donor: 52%
  - \(P = .02\)

---

### HyperCVAD + Rituximab (if CD20+)

#### Whole series

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
<th>CR(%)</th>
<th>CR duration (%)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-yr.</td>
<td>5-yr.</td>
</tr>
<tr>
<td>Overall</td>
<td>282</td>
<td>95</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>≤30</td>
<td>96</td>
<td>99</td>
<td>63</td>
<td>50</td>
</tr>
<tr>
<td>31-59</td>
<td>128</td>
<td>98</td>
<td>66</td>
<td>55</td>
</tr>
<tr>
<td>≥60</td>
<td>58</td>
<td>88</td>
<td>53</td>
<td>47</td>
</tr>
</tbody>
</table>

### Modified HyperCVAD+rituximab (if CD20+)

<table>
<thead>
<tr>
<th>3-yr CRD (%)</th>
<th>Without intensification (n=126)</th>
<th>With intensification (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20-</td>
<td>CD20+</td>
<td>CD20-</td>
</tr>
<tr>
<td>≤30</td>
<td>84</td>
<td>75</td>
</tr>
<tr>
<td>31-59</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>≥60</td>
<td>71</td>
<td>65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3-yr OS (%)</th>
<th>Without intensification (n=126)</th>
<th>With intensification (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD20-</td>
<td>CD20+</td>
<td>CD20-</td>
</tr>
<tr>
<td>≤30</td>
<td>77</td>
<td>75</td>
</tr>
<tr>
<td>31-59</td>
<td>56</td>
<td>66</td>
</tr>
<tr>
<td>≥60</td>
<td>66</td>
<td>15</td>
</tr>
</tbody>
</table>

Thomas DA et al J Clin Oncol 2010; 28:3880-3889
Outcomes for pts < 60 yr with Ph-negative ALL

But we need prospective comparative studies...

Do they exist?
Phase II Study of Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia

**Type of study:** CALGB-SWOG-ECOG C10403 trial based on COG AALL0232. Intergroup phase II trial.

**Sponsors and Collaborators:** CALGB/ NCI/ ECOG/ SWOG

**Objectives:**
- To *describe the outcomes* of AYAs with ALL treated with a pediatric regimen by adult hematologists/oncologists at multiple sites.
- To *compare the outcomes* of patients treated on this protocol with similar patients treated by pediatric oncologists on protocol COG-AALL0232.
- To *evaluate the adherence* of adult hematologists/oncologists and their patients to a "pediatric" ALL treatment regimen and identify reasons for variances.
- To analyze and describe the outcomes of patients treated on this study according to baseline *psychosocial characteristics, demographics, and family support.*

**Estimated Enrollment:** 300 patients in 170 centers

**Study Start Date:** October 2007

**Estimated Primary Completion Date:** September 2012


[www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT00558519
Optimizing Treatment of ALL in AYA

Summary

• Use pediatric protocols. No mature data to date. Results of prospective trials are awaited.

• Given with a “pediatric spirit”: minimize delays and dose reductions. Yes

• Treat at large centers with experience treating this population. Yes

• Enroll patients on clinical trials if possible. Yes
AIEOP-BFM ALL 2000 study (3184 pB-ALL patients)

PETHEMA ALL-03 study (High-risk adult patients)

Conter, V. et al. Blood 2010;115:3206-3214

JM Ribera et al. ASH, 2009
MRD and Prognosis in Adult ALL

GMALL 07/03. Standard-risk ALL

NILG. Standard-risk and High-risk ALL


Final message

Either pediatric or not, use the protocol that provides the best probability of clearance of MRD!
Acknowledgments

- **PETHEMA** members
- **GMALL**: D Hoelzer, N Goekbuget
- **GRAALL**: H Dombret
- **FRALLE**: N Boissel, A Baruchel
- **GIMEMA**: S Chiaretti, G Meloni, R Foà
- **NILG**: R Bassan
- **MRC**: A Fielding, A Goldstone