Ni enfants ni adultes: regard sur la biologie des LAL de l’adolescent

André Baruchel
Hôpital Robert Debré, Université Paris Diderot
Sorbonne Paris Cité

DES HEMATOLOGIE MARS 2015
AN IMPROVING OUTCOME?

**CHILDREN**

**AYA**

Stelianova-Foucher E, Lancet 2004
IS THE SPEED OF PROGRESS EQUALLY DISTRIBUTED?

**Improvement in 5-Year Relative Survival, Invasive Cancer, SEER 1975-1997**

![Graph showing improvement in 5-year relative survival by age at diagnosis (Years)].

- Average Annual Percentage Change by Age Group:
  - <5: 1.43
  - 05-9: 1.53
  - 10-14: 1.63
  - 15-19: 0.9
  - 20-24: 0.59
  - 25-29: 0.03
  - 30-34: -0.18
  - 35-39: 0.23
  - 40-44: 0.53
  - 45-49: 1.04
  - 50-54: 1.26
  - 55-59: 1.43
  - 60-64: 1.61
  - 65-69: 1.87
  - 70-74: 1.99
  - 75-79: 1.83
  - 80-84: 1.59
  - 85+: 1.15

Age at Diagnosis (Years)
Main questions about AYA and ALL

• When does adolescence begin in ALL?
  – A different biology?

• Do adolescents with ALL receive the most appropriate treatment?

• If progresses have been made, are they shared by young adults with ALL?
Main findings analysing FRALLE 93 and F2000 databases

- No difference between 10-15 years and 15-20 years in terms of:
  - Underlying biology (WBC, immunophenotype, cytogenetics, molecular genetics)
  - Early response to treatment
  - Outcome

- Both different from children 1 to 10 year-old

- « adolescence begins at 10 years in ALL »
ALL above 10 years

- more boys
- increased WBC count
- more CNS3
- more T-cell ALL
- less hyperdiploidy
- more hypodiploidy?
- much less TEL-AML1
- BCR-ABL+?

- A CYTOGENETIC AND MOLECULAR « BLACK HOLE »?

- more D8 Poor PRED response
- more D15/ D21 M2M3 marrow
- higher MRD after induction
iAMP21: intrachromosomal amplification of chr. 21

- a non Standard-risk ALL (~2-3%)
- diagnosed by FISH


iAMP21

intrachromosomal amplification of CHR 21

Left: A metaphase showing an abnormal chromosome (whole chromosome paint 21) with multiple RUNX1 (red) and two normal TEL signals.
Middle: A metaphase showing multiple RUNX1 exon signals (red) along the length of an abnormal chromosome 21
Right: Interphase cells showing clustering of the red RUNX1 and the two normal green ETV6 signals, using the LSI TEL-AML1 translocation probe (Vysis).
28 Children with iAMP21
out of 1386 Common/preB ALL in the UKALL 97/99 (2%)
International study iAMP21

- Ponte Di Legno Group: *C. Harrison et al, Leukemia 2013*
- n = 530 LAL-B iAMP21
- Median age: **9 years**
- Lésions associées:
  - RB1 (41%), ETV6 (36%),
  - IKZF1 (20%), P2RY8-CRLF2 (19%)

La chimiothérapie intensifiée (high-risk) permet de réduire le risque de rechute
IGH@ translocations

- Rearrangements of the immunoglobulin heavy chain locus (IGH@) on chromosome 14q32
- Detectable by IGH FISH
- Rare in B-ALL, occurring in <5% of cases.
- Median age: 16 years
- Peak incidence: 11% in the 20-24 year-old YA
- Poorer clinical outcome.
- Not an independent prognostic factor in children and adolescents.
- The most common IGH@ partners
  - CRLF2 (cytokine receptor-like factor 2) at the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11.3 (resulting in overexpression of CRLF2)
  - Members of the CEBP (CCAAT/enhancer binding protein) family.
  - ID4 (inhibitor of DNA binding 4) at 6p22
  - EPOR (erythropoietin receptor)

Russell LJ J Clin Oncol 2014
Figure 2: Clustering of ALL subtypes by gene-expression profiles
Hierarchical clustering of patients from the COALL (left) and DCOG (right) studies with 110 gene-probe sets selected to classify paediatric ALL. Heat map shows which gene-probe sets are overexpressed (in red) and which gene probe sets are underexpressed (in green) relative to mean expression of all gene-probe sets (see scale bar).

* Patients with E2A-rearranged subclone (15–26% positive cells). † Right column of grey bar denotes BCR-ABL1-like cases.
COALL 92-97: 145 pts

DCOG ALL-8: 92 pts
<table>
<thead>
<tr>
<th>Chromosomal location</th>
<th>BCR-ABL1-like (n=44)</th>
<th>BCR-ABL1-positive (n=15)</th>
<th>B-other (n=25)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IKZF1 (IKAROS)</td>
<td>7p12.2</td>
<td>17 (39%)</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>TCF3 (E2A)</td>
<td>19p13.3</td>
<td>3 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>EBF1</td>
<td>5q33.3</td>
<td>6 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>PAX5</td>
<td>9p13.2</td>
<td>16 (36%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>VPREB1</td>
<td>22q11.22</td>
<td>15 (34%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Total†</td>
<td>..</td>
<td>36 (82%)</td>
<td>12 (80%)</td>
</tr>
</tbody>
</table>

No aberrations were found in other transcription factors, including SPI1, BCL11A, E2-2, FOXP1, and LEF1. Abnormalities in the B-other group differed from both the BCR-ABL1-like (p=0.0002) and the BCR-ABL1-positive (p=0.0098) groups. *Precursor B-ALL cases excluding BCR-ABL1-like, BCR-ABL1-positive, and hyperdiploid cases. †Patients can have more than one gene deleted, hence, the total sum of patients with deleted genes does not equal the sum of individual genes.

*Table 5: Common deletions of B-cell development genes characteristic for BCR-ABL1-like and BCR-ABL1-positive ALL*
The BCR–ABL1-like leukaemic cells were a median of 73 times (p=0.001) more resistant to L-asparaginase and 1.6 times (p=0.017) more resistant to daunorubicin than were other precursor B-ALL cases, whereas no significant n. difference was seen in cytotoxic effects of prednisolone and vincristine (figure 4).
This study comprised 1128 children with newly diagnosed ALL in 3 consecutive Dutch Childhood Oncology Group trials (DCOG ALL-8, ALL-9, and ALL-10)\textsuperscript{21} and 2 German Cooperative ALL trials (COALL 06-97 and 07-03)\textsuperscript{22}

Figure 1. CIR for the BCR-ABL1-like expression signature, IKZF1-deleted, and high CRLF2 mRNA expression in newly diagnosed children with BCR-ABL1-negative, MLL wild-type BCP-ALL. CIR with death as a competing event was calculated using the method of Fine and Gray\textsuperscript{25} in a pooled analysis of all 4 study cohorts and plotted against the time from initial diagnosis. For each feature, CIR at the 5-year follow-up is given in parentheses. (A) CIR of 94 BCR-ABL1-like and 442 non–BCR-ABL1-like BCP-ALL cases. (B) CIR of 136 IKZF1-deleted (DEL) and 721 IKZF1 wild-type (WT) cases. (C) Comparison between 55 cases with high CRLF2 expression and 481 cases with low CRLF2 expression.
BCP-ALL

Ph /BCR-ABL like ALL and AYA

<table>
<thead>
<tr>
<th></th>
<th>SR-ALL children</th>
<th>HR-ALL children</th>
<th>16-21</th>
<th>YA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>10%</td>
<td>13%</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>5y EFS</td>
<td>58%</td>
<td>41%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>5y OS</td>
<td>73%</td>
<td>66%</td>
<td>26%</td>
<td></td>
</tr>
</tbody>
</table>

Roberts K et al, NEJM 2014
Incidence of Ph-like and Ph-positive Acute Lymphoblastic Leukemia (ALL), According to Age.

BCR-ABL1-like: prognostic but druggable?

Frequency of genomic lesions in Ph like ALL:

- JAK2-translocations: 3/15 (20%)
- ABL1-translocations: 5/15 (33%)
- IGH@-translocations: 4/15 (25%)

Roberts K et al, Cancer Cell 2012
EBF1-PDGFRB and BCP-ALL

- Roberts K et al Cancer Cell 2012

- **Weston BW et al J Clin Oncol 2013**
  - 10 y-old boy; WBC: 3.1G/L; BCP-ALL; normal CG
  - 4 drug induction → Induction failure
  - Del 5q33: PDGFRB rearranged; Fusion transcript: EBF1-PDGFRB
  - Imatinib + chemo: 14 days later CR (CMF MRD:0.05%)
  - Imatinib + chemo: CCR at 10 months

- **Lengline E et al, Haematologica 2013**

- ~ 3% of childhood BCP-ALL
A 16 year-old boy with poor early response to induction chemotherapy
LAL Ph+ like: problèmes

• Comment les repérer?
  – Phospho-flow
  – LDA cards
  – B-other + FISH+ Biol Mol: CGH/multiplex PCR/RNA seq

• Comment introduire les ITK?
  – Si échec d’induction et MRD tardive high: « facile »
  – Autres cas?
    • Sortir du protocole
    • « Déviation » prévue dans le protocole mais interaction avec les autres questions
    • Protocole international type Eshopall

• Comment introduire les autres médicaments?
  – Ex Ruxolitinib
ALL above 10 years

- more boys
- increased WBC count
- more T-cell ALL
- less hyperdiploidy
- more hypodiploidy?
- much less TEL-AML1
- BCR-ABL+?

- more iAMP 21
- more IgH@ translocations
- more IKZF1 deletions
- more CRLF2 lesions
- more « BCR-ABL like »

- more D8 Poor PRED resistance
- more D15/ D21 M2M3 marrow
- higher MRD after induction
Patients (N=177)

- Inclusion date: 06/93 10/94
- Point date: 07/2000
- Patients: 77 106
- Evaluable: 77 100

Boissel N et al, J Clin Oncol 2003
### Outcome according to protocol

<table>
<thead>
<tr>
<th></th>
<th>Total N= 177</th>
<th>FRALLE 93 N= 77</th>
<th>LALA 94 N= 100</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MFU (y)</strong></td>
<td>3.7</td>
<td>3.5</td>
<td>3.8</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>88%</td>
<td>94%</td>
<td>83%</td>
<td>.04</td>
</tr>
<tr>
<td><strong>5y OS</strong></td>
<td>59 ±8%</td>
<td>78 ±11%</td>
<td>45 ±11%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>5y DFS</strong></td>
<td>60 ±9%</td>
<td>72 ±13%</td>
<td>49 ±11%</td>
<td>.0004</td>
</tr>
<tr>
<td><strong>5y RFS</strong></td>
<td>62 ±9%</td>
<td>77 ±13%</td>
<td>49 ±12%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>5y EFS</strong></td>
<td>52 ±8%</td>
<td>67 ±13%</td>
<td>41 ±14%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Boissel N et al, J Clin Oncol 2003
EFS (N=177)

Boissel N et al, J Clin Oncol 2003
EFS – Prognostic Factors

Multivariate analysis (Cox model)

- **Trial** (LALA vs FRALLE) \(<0.0001\)
- **WBC** \(0.0002\)
- **Cytogenetics** \(0.1\)
- **B vs T** \(0.4\)

*Boissel N et al, J Clin Oncol 2003*
## COMPARISON OF ADULT AND PEDIATRIC PROTOCOLS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Years</th>
<th>Age range (years)</th>
<th>Adolescent age range (years)</th>
<th>n</th>
<th>CR rate (%)</th>
<th>EFS</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRALLE 83, LALA 85</td>
<td>1983–87</td>
<td>0–20</td>
<td>15–20</td>
<td>48</td>
<td>89</td>
<td>–</td>
<td>47.5 (6 years)</td>
<td>–</td>
</tr>
<tr>
<td>FRALLE 93, LALA 94</td>
<td>1993–99</td>
<td>0–20</td>
<td>15–20</td>
<td>77</td>
<td>94</td>
<td>67 (5 years)</td>
<td>72 (5 years)</td>
<td>78 (5 years)</td>
</tr>
<tr>
<td></td>
<td>1994–2000</td>
<td>15–adult</td>
<td>15–20</td>
<td>100</td>
<td>83</td>
<td>41 (5 years)</td>
<td>49 (5 years)</td>
<td>45 (5 years)</td>
</tr>
<tr>
<td>CCG 1882,1901 CALGB</td>
<td>1989–95</td>
<td>0–21</td>
<td>16–20</td>
<td>197</td>
<td>90</td>
<td>63 (7 years)</td>
<td>–</td>
<td>67 (7 years)</td>
</tr>
<tr>
<td></td>
<td>1988–98</td>
<td>16–adult</td>
<td>16–20</td>
<td>124</td>
<td>90</td>
<td>34 (7 years)</td>
<td>–</td>
<td>46 (7 years)</td>
</tr>
<tr>
<td>AIEOP ALL 95, 2000</td>
<td>1996–2003</td>
<td>0–18</td>
<td>14–18</td>
<td>150</td>
<td>94</td>
<td>–</td>
<td>–</td>
<td>80 (2 years)</td>
</tr>
<tr>
<td>DCOG 6-9, HOVON ALL-5, 18</td>
<td>1985–99</td>
<td>0–18</td>
<td>15–18</td>
<td>47</td>
<td>98</td>
<td>69 (5 years)</td>
<td>71 (5 years)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>1985–99</td>
<td>15–adult</td>
<td>15–18</td>
<td>44</td>
<td>91</td>
<td>34 (5 years)</td>
<td>37 (5 years)</td>
<td>–</td>
</tr>
<tr>
<td>NOPHO SAALLG</td>
<td>1992–2000</td>
<td>0–18</td>
<td>15–20</td>
<td>36</td>
<td>99</td>
<td>74 (5 years)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MRC ALL97/99ukall XII/E2993</td>
<td>1997–2002</td>
<td>0–17</td>
<td>15–17</td>
<td>61</td>
<td>98</td>
<td>65 (5 years)</td>
<td>–</td>
<td>71 (5 years)</td>
</tr>
<tr>
<td></td>
<td>1997–2002</td>
<td>15–55</td>
<td>15–17</td>
<td>67</td>
<td>94</td>
<td>49 (5 years)</td>
<td>56 (5 years)</td>
<td>–</td>
</tr>
</tbody>
</table>

RANGE OF DIFFERENCE IN EFS: 16-35%
Progresses in adolescents with ALL?

• A review of three eras of FRALLE protocols
  – Continuous progress since the 80’S
    • Main jump in prognosis due to the adoption of delayed intensification(s)
  – Despite less indication of HSCT
    • Close to 10% currently
  – Current 5 y EFS around 72%
Some hurdles in AYA during ALL treatment

- Increased toxicity
- Compliance issues
- Psycho-social specific needs
Drug disposition in the adolescent

- Change in body composition
- Increase in height and weight
- Tobacco, alcohol, drug use
- Oral contraceptives
- High/low BMI
- Compliance with treatment plan
- Hormonal environment
- Organogenesis

Veal GJ, J Clin Oncol 2010
More toxicities in AYAs

- More asparaginase-related complications
  - pancreatitis
  - thromboembolism
- More corticosteroid-related complications
  - diabetes
  - osteonecrosis
- More infections
- More toxic deaths
- More complications after HSCT
Table 3. Summary of Selected Toxicities by Age Group in Study XV

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>1-14 Years (n = 453)</th>
<th>15-18 Years (n = 45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>SE*</td>
<td>%</td>
</tr>
<tr>
<td>Seizures, grade 2, 3, or 4</td>
<td>4.6</td>
<td>1.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Severe infection, grade 4 or 5†</td>
<td>3.9</td>
<td>0.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Disseminated fungal infection</td>
<td>5.8</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reactions to asparaginase, grade 2, 3, or 4</td>
<td>41.9</td>
<td>2.4</td>
<td>32.8</td>
</tr>
<tr>
<td>Osteonecrosis, grade 3 or 4‡</td>
<td>5.8</td>
<td>1.2</td>
<td>32.9</td>
</tr>
<tr>
<td>Thrombosis, grade 2, 3, or 4</td>
<td>6.0</td>
<td>1.1</td>
<td>23.8</td>
</tr>
<tr>
<td>Hyperglycemia, grade 3 or 4</td>
<td>6.6</td>
<td>1.2</td>
<td>27.7</td>
</tr>
</tbody>
</table>
Avascular necrosis of the bone(s)

- a major problem above 10 years of age
- steroids (dex++) but not only
- reduced but not zeroed by alternate week scheme of dexamethasone (CCG1961)

Mattano LA et al, Lancet Oncology 2012
Adherence if < 12 vs ≥ 12 years

« 59% of the relapses attributable to non adherence »

Bhattia S et al, J Clin Oncol 2012
Impact of adolescents results on older young adults with ALL?

- Fully integrated pediatric protocols
  - DFCI (US), MD Anderson, others (US)
  - COG-CALGB- others: intergroup trial C10403 (US)
  - PETHEMA (Spain)

- “Inspired” by...
  - GRAALL (France)
Acknowlegments

• Marie-Françoise Auclerc
  and all FRALLE group members
• Hervé Dombret, Nicolas Boissel
  for the GRAALLL group