La leucemia linfoblastica acuta del bambino: storia di un successo terapeutico

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Incidenza annuale dei tumori dell’età pediatrica
CHILDHOOD ACUTE LEUKEMIA

- ALL accounts for 80% of all childhood acute leukemia;

- Among childhood ALL, 80-85% of patients have BCP ALL, 15-20% T-ALL and 2-3% mature B-ALL;

- With the remarkable exception of Down-Syndrome patients, there is no genetic predisposition to develop acute leukemia.
Leucemie acute-Distribuzione per età

Picco
2-4 anni
Predominanza dei maschi
Presentation of childhood leukemia

- Hyperleukocytosis and huge organomegaly;
- Pseudoaplastic/single-bilineal cytopenia;
- «Rheumatic disease»;
- Bone pain/swelling;
- Mediastinal involvement;
- Chloroma/granulocytic sarcoma;
### LLA-Caratteristiche cliniche alla diagnosi

<table>
<thead>
<tr>
<th>Caratteristica</th>
<th>Percentuale di casi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febbre</td>
<td>61</td>
</tr>
<tr>
<td>Petecchie/Porpora</td>
<td>48</td>
</tr>
<tr>
<td>Dolori osteo-articolari</td>
<td>25</td>
</tr>
<tr>
<td>Linfadenopatia</td>
<td>50</td>
</tr>
<tr>
<td>Splenomegalia</td>
<td>63</td>
</tr>
<tr>
<td>Epatomegalia</td>
<td>68</td>
</tr>
</tbody>
</table>
LLA-Caratteristiche di laboratorio alla diagnosi

<table>
<thead>
<tr>
<th>Caratteristica</th>
<th>Percentuale di casi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conta leucocitaria</td>
<td></td>
</tr>
<tr>
<td>10,000-49,000</td>
<td>30</td>
</tr>
<tr>
<td>&lt; 10,000</td>
<td>53</td>
</tr>
<tr>
<td>&gt; 50,000</td>
<td>17</td>
</tr>
<tr>
<td>Emoglobina (g/dl)</td>
<td></td>
</tr>
<tr>
<td>≥ 11</td>
<td>12</td>
</tr>
<tr>
<td>7 – 11</td>
<td>45</td>
</tr>
<tr>
<td>&lt; 7</td>
<td>43</td>
</tr>
<tr>
<td>Conta piastrinica (mm$^3$)</td>
<td></td>
</tr>
<tr>
<td>&gt; 100K</td>
<td>25</td>
</tr>
<tr>
<td>20 - &lt; 100K</td>
<td>47</td>
</tr>
<tr>
<td>&lt; 20K</td>
<td>28</td>
</tr>
</tbody>
</table>
Classifying AML, ALL and MLL

> 95% correct diagnoses

Eterogeneità genetica nella LLA dell’infanzia

- "Normale": 24%
- 11q23: 4%
- 14q11: 3%
- Ph: 2%
- t(1;19): 4%
- TEL-AML1: 22%
- < 45 Crom: 1%
- 45 Crom: 3%
- Pseudodiploide: 10%
- 47-50 Crom: 6%
- > 50 Crom: 26%
EFS According to Genotype and Phenotype

- 91%±3% Hyperdiploidy >50 (n=205)
- 89%±3% TEL-AML1 (n=163)
- 86%±7% E2A-PBX1 (n=40)
- 82%±3% Other B-lineage (n=261)
- 73%±5% T-cell (n=135)
- 37%±12% BCR-ABL (n=22)
- 32%±12% MLL-AF4 (n=15)

The impact of a more sophisticated cytogenetic classification

Moorman AV et al. Lancet Oncology 2010;11:429-438
Figure 3. Comparison of EFS for non-Ph+ hypodiploid patients with 44 chromosomes or fewer than 44 chromosomes.
Define the molecular specific response profile

Dx expression analysis

Responsive genotype

“Conservative” therapy

Unresponsive genotype

MRD monitoring

“Hi-risk”

“Aggressive” therapy

“Conservative” therapy

“Hi-risk”

“Aggressive” therapy

Courtesy of Jerry Radich, FHCRC
Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study

Valentino Conter,1,2 *Claus H. Bartram,3 Maria Grazia Valsecchi,4 Andre Schrauder,5 Renate Panzer-Grumayer,6 Anja Mörck,5 Maurizio Aricò,7 Martin Zimmormann,8 Georg Mann,6 Giulio De Rossi,9 Martin Stanulla,5 Franco Locatelli,10 Giuseppe Basso,11 Felix Niggli,12 Elena Barisone,13 Günter Henze,14 Wolf-Dieter Ludwig,15 Oskar A. Haas,6 Giovanni Cazzaniga,16 Rolf Koehler,3 Daniela Silvestri,4 Jutta Brudike,17 Rosanna Parasole,18 Rita Beier,8 Jacques J. M. van Dongen,19 Andrea Biondi,1,18 and Martin Schrappe5
Event-free survival (A) and cumulative incidence of relapse (B) according to PCR-MRD classification in 3184 pB-ALL patients.

**A**

N. pts | N. events | 5 yrs EFS | 7 yrs EFS
---|---|---|---
SR | 1348 | 81 | 92.3% (0.9) | 91.1% (1.2)
IR | 1647 | 288 | 77.6% (1.3) | 76% (1.4)
HR | 189 | 86 | 50.1% (4.1) | 46.6% (5.1)

p-value<0.001

**B**

N. pts | N. rel. | 5- yrs CI | 7- yrs CI
---|---|---|---
SR | 1348 | 61 | 6.0% (0.8) | 7.2% (1.2)
IR | 1647 | 266 | 21.0% (1.2) | 22.3% (1.4)
HR | 199 | 60 | 34.9% (3.8) | 38.5% (5.0)

p-value<0.001

Conter V. et al. Blood 2010;115:3206-3214
Five-year relative survival rates for selected primary cancers according to year of diagnosis (1975–2006) among children younger than 20 years of age.

PROTOCOLLI AIEOP PER LEUCEMIE LINFOBLASTICHE ACUTE

Sopravvivenza per generazione di protocollo 91.0 (89-92) Anni dalla diagnosi

<table>
<thead>
<tr>
<th>Anni dalla diagnosi</th>
<th>780</th>
<th>900</th>
<th>687</th>
<th>407</th>
<th>1191</th>
<th>1691</th>
<th>977</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>438</td>
<td>589</td>
<td>506</td>
<td>304</td>
<td>911</td>
<td>604</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>323</td>
<td>466</td>
<td>351</td>
<td>189</td>
<td>105</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>126</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
TRATTAMENTO MULTIDISCIPLINARE ARMONICO e INTEGRATO

Supporto organizzativo

Supporto sociale

Supporto psicologico

Supporto anti-infettivo

Supporto trasfusionale

Supporto metabolico


Supporto immunologico

CHIRURGIA

RADIO TERAPIA

LENI TERAPIA

CHEMIO TERAPIA

IMMUNO TERAPIA
LLA: elementi del trattamento polichemioterapico

• Fase citoreduuttiva e di induzione della remissione
• Necessità di consolidare il risultato ottenuto con la fase di Induzione.
• Reinduzione
• Trattamento specifico sul Sistema Nervoso Centrale
• Mantenimento
Protocollo AIEOP/BFM-ALL 2000

MRD Timepoints

1 1b 2

SR:
MRD neg. at tps. 1+2

R1

(3)

120Gy* only T-ALL

DEXA 140mg
Anthr 180mg
CP 2.5g

DEXA 210mg
Anthr 240mg
CPM 3g

(4)

(5)

II

III

I

I

DEXA 280mg
Anthr 240mg
CPM 3g

DEXA 720mg
Anthr 330mg
CPM 4.5g+IFO4g

DEXA 810mg
Anthr 300mg
CPM 5g+IFO4g

R2

MR - 1

MR:
- MRD level at
  tps. 2 < tps. 1;
- <10^8 at tps. 2

DEXA 210mg
Anthr 240mg
CPM 3g

R3

HR - 2 AIEOP

R1

III

H R 1’

180Gy*

HR - 2 BFM

H R 2’

II

H R 3’

120Gy*

II

H R 3’

III

H R 3’

BMT*

BM sampling

0 10 20 22 26 29 52 104 W.

* presymptomatic cranial irradiation (18Gy for CNS pos. pts)

* selected indications for allo-BMT: as in HR-95; new: MRD >=10^8 at tps. 2, or MRD tp2 > tp1, or MRD at tp1+2 =10^8

‡ Prot. I-DEXA: add 210mg DEXA
Prot. I-PRED: add 1260mg PRED
AIEOP-BFM ALL 2009 outline with randomized studies

**T/non-HR**

- IA<sub>D</sub>  IB  M  II
- IA  IB  M  II
- IA  IB  M  II
- IA'  
- IA<sub>CPM</sub>

**pB<sup>+</sup>/non-HR**

- IA  IB  M  II  SR  II
- IA  IB  M  II  MR
- IA'  
- IA<sub>CPM</sub>

**HR**

- IA<sub>HR</sub>  IB<sup>+</sup>  HR<sub>1</sub>  HR<sub>2</sub>  HR<sub>3</sub>  III  III  III

PEG-ASP 2500 IU/m<sup>2</sup> 1 dose vs 10 doses, over 20 weeks in total

PEG-ASP 4 x 2500 IU/m<sup>2</sup> over 4 weeks

104 wks.
Transcription and translation

Inhibition by imatinib

Constitutive tyrosine kinase

Phosphorylation of multiple substrates

Mitogenic signaling and genomic instability increased
Apoptosis and stromal regulation decreased

Chronic myelogenous leukemia

- AALL0031 (n = 44)
- Historical controls (n = 120)

\[ P < .0001 \]
Probability of OS in adolescents treated in pediatric Institutions with pediatric protocols or in adult Institutions with adult protocols

Quel che rimane ancora da superare.............
AVN – CCG 1961

- 7/769 Patients < 10 Years Developed AVN – 1%

- 126/1287 Patients ≥ 10 Years Developed AVN – 9.8%
  - 10-12 Years 32/505 7%
  - 13-15 Years 53/520 12.6%
  - 16+ Years 41/262 18.5%

- Incidence of AVN Twice As High In Females
CCG-1961 AVN by RER Groups
(Age 10+ Yrs)

Probability

Years Followed

0 1 2 3 4 5 6 7

0 0.05 0.1 0.15 0.2 0.25 0.3

Log rank p = .002

Continuous DEX
Discontinuous DEX

5 Yr Rate  RHR
Continuous DEX  14.6%  2.08
Discontinuous DEX  7.6%  Baseline

Continuous DEX
(N=398)
Discontinuous DEX
(N=421)

5 Yr Rate

RHR

Children's Oncology Group

Continuous DEX

Discontinuous DEX
AVN Incidence In 16+ Patients
Continuous vs. Discontinuous Dexamethasone

Continuous Dex

Discontinuous Dex

P = .0003
**Interfant-06**

**Overall outcome**

![Graph showing survival and EFS probabilities over years from diagnosis.]

<table>
<thead>
<tr>
<th>N. pts. (relapses)</th>
<th>N. events</th>
<th>EFS (SE) 3-year</th>
<th>EFS (SE) 4-year</th>
<th>N. deaths</th>
<th>Survival (SE) 3-year</th>
<th>Survival (SE) 4-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>385</td>
<td>168 (102)</td>
<td>47.3 (3.0)</td>
<td>47.3 (3.0)</td>
<td>131</td>
<td>56.0 (3.1)</td>
<td>56.0 (3.1)</td>
</tr>
</tbody>
</table>

Median follow-up (min-max) month: 26 (1 - 81)

NOTE: The EFS curve do not show 1 relapse in BM that occurred at 4.3 years (is alive in CR at last follow-up)

**Outcome in Interfant99**

Update at Dec 2007, median follow-up (min-max) month: 58 (1 - 102)

<table>
<thead>
<tr>
<th>N. pts. (relapses)</th>
<th>N. events</th>
<th>EFS (SE) 3-year</th>
<th>EFS (SE) 6-year</th>
<th>N. deaths</th>
<th>Survival (SE) 3-year</th>
<th>Survival (SE) 6-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>478</td>
<td>249 (193)</td>
<td>47.9 (2.3)</td>
<td>46.5 (2.3)</td>
<td>206</td>
<td>59.3 (2.3)</td>
<td>53.8 (2.5)</td>
</tr>
</tbody>
</table>
**Interfant-06**

EFS by age at diagnosis

![Graph showing EFS by age at diagnosis](image)

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>N. pts.</th>
<th>N. events</th>
<th>3-year EFS (SE)</th>
<th>p-value</th>
<th>Interfant99 3-year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 months</td>
<td>80</td>
<td>53</td>
<td>25.3 (5.5)</td>
<td></td>
<td>27.9 (4.4)</td>
</tr>
<tr>
<td>3 - 6 months</td>
<td>108</td>
<td>55</td>
<td>37.6 (5.8)</td>
<td>&gt;0.0001</td>
<td>38.3 (4.6)</td>
</tr>
<tr>
<td>6 - 9 months *</td>
<td>108</td>
<td>42</td>
<td>53.0 (5.7)</td>
<td>*</td>
<td>53.2 (4.6)</td>
</tr>
<tr>
<td>9-12 months</td>
<td>89</td>
<td>18</td>
<td>72.1 (6.0)</td>
<td></td>
<td>68.5 (4.1)</td>
</tr>
</tbody>
</table>

* The curve do not show 1 event that occurred at 4.3 years (1 relapse in BM).
## Interfant-06
### EFS by MLL Status

![Graph showing EFS by MLL Status](image)

<table>
<thead>
<tr>
<th>MLL Status</th>
<th>N. pts.</th>
<th>N. events</th>
<th>3-year EFS (SE)</th>
<th>p-value</th>
<th>Interfant99 3-year EFS (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rearranged</td>
<td>285</td>
<td>145</td>
<td>38.0 (3.5)</td>
<td>&lt;0.0001</td>
<td>37.3 (2.8)</td>
</tr>
<tr>
<td>Germline*</td>
<td>96</td>
<td>20</td>
<td>74.6 (5.2)</td>
<td></td>
<td>76.6 (4.7)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

* The curve do not show 1 event that occurred at 4.3 years (1 relapse in BM).
Factors influencing the prognosis of children with relapsed ALL

**Major variables**
- Duration of first CR
- Site of relapse
- Immunophenotype

**Minor variables**
- Sex
- Age
- PB blast count at time of relapse
# BFM Classification of Relapsed Childhood ALL

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>1. Late extramedullary relapses.</td>
</tr>
<tr>
<td>S2</td>
<td>1. Early extramedullary relapses;</td>
</tr>
<tr>
<td></td>
<td>2. Very early extramedullary relapses;</td>
</tr>
<tr>
<td></td>
<td>3. Non-T late bone marrow relapses;</td>
</tr>
<tr>
<td></td>
<td>4. Non-T combined early / late relapses.</td>
</tr>
<tr>
<td>S3</td>
<td>1. Non-T early bone marrow relapses.</td>
</tr>
<tr>
<td>S4</td>
<td>1. Very early bone marrow relapses;</td>
</tr>
<tr>
<td></td>
<td>2. Very early combined relapses;</td>
</tr>
<tr>
<td></td>
<td>3. T phenotype bone marrow relapses.</td>
</tr>
</tbody>
</table>

- **Very early relapse**: \( < 18 \) months from diagnosis.
- **Early relapse**: \( \geq 18 \) months from diagnosis, but \( < 6 \) months from treatment discontinuation.
- **Late relapse**: \( \geq 6 \) months from treatment discontinuation.
EFS of childhood relapsed ALL
ALL-REZ BFM 83-90 (SCT censored) versus 2002

ALL-REZ BFM 83-90
SCT censored

S1:  n = 51; cens. = 40; pEFS = .75 ± .06
S2:  n = 577; cens. = 277; pEFS = .38 ± .02
S3:  n = 153; cens. = 46; pEFS = .02 ± .02
S4:  n = 252; cens. = 60; pEFS = .04 ± .02
p < 0.001

IntReALL 2010
ALL-REZ BFM 03/11

S1:  n = 35; cens = 26; pEFS = .70 ± .09
S2:  n = 390; cens = 271; pEFS = .61 ± .03
S3:  n = 80; cens = 33; pEFS = .29 ± .06
S4:  n = 134; cens = 41; pEFS = .27 ± .04
P < 0.001
ALL in 2nd CR – MUD HSCT
Disease-free survival by year of HSCT

2005 - 2009 = 60% (51-69)

2000 - 2004 = 46% (36-57)

1995 - 1999 = 36% (22-51)

P = 0.0152

2005 - 2009: N = 110; E = 44
2000 - 2004: N = 84; E = 45
1995 - 1999: N = 44; E = 28

AIEOP BMT Registry
January 2012
Blinatumomab (MT103), a T Cell-engaging BiTE® Antibody

(A) BiTE antibody blinatumomab is derived by linking the variable regions \( V_H \) and \( V_L \) of two parental murine antibodies via short linker sequences.

(B) The mode of action of blinatumomab involves polyclonal activation and proliferation of T cells and redirected lysis of B lymphoma cells, resulting in apoptotic B lymphoma cell death.
### Hematologic and Molecular Remission Rate within 2 Cycles of Treatment

<table>
<thead>
<tr>
<th></th>
<th>15 µg/m²/d Cohort 1 (n = 7), n (%)</th>
<th>5-15-30 µg/m²/d Cohort 2b (n = 6), n (%)</th>
<th>5-15 µg/m²/d Cohorts 2a + 3 (n = 12), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRh*</td>
<td>5 (71)</td>
<td>3 (50)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (29)</td>
<td>3 (50)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>CRh*</td>
<td>3 (43)</td>
<td>0</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Nonresponder</td>
<td>1 (14)</td>
<td>3 (50)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- All patients with CR/CRh* achieved MRD-response (defined as MRD < $10^{-4}$ measured by PCR evaluation of individual rearrangements of immunoglobulin or TCR genes in a central laboratory)
- High response rate in all patient subgroups (including Ph+ ALL and t(4,11) translocation)
Clinical Trial MT103-205

A Single-Arm Multicenter Phase II Study preceded by Dose Evaluation to Investigate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab (MT103) in Pediatric and Adolescent Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL)
Coordinating Investigators

- **I-BFM**: Arend von Stackelberg
- **COG**: Lia Gore
- **Country Coordinating Investigators:**
  - Christina Peters, Austria
  - James Whitlock, Canada
  - Pierre-Simon Rohrlich, France
  - Arend von Stackelberg, Germany
  - Franco Locatelli, Italy
  - Michel Zwaan, The Netherlands
  - Lia Gore, USA
Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell–engaging CD19/CD3-bispecific BiTE antibody blinatumomab

Matthias Klinger,¹ Christian Brandl,¹ Gerhard Zugmaier,¹ Youssef Hijazi,¹ Ralf C. Bargou,² Max S. Topp,² Nicola Gökgület,³ Svenja Neumann,⁴ Mariele Goebeler,⁵ Andreas Viardot,⁶ Matthias Stelljes,⁶ Monika Brüggemann,⁶ Dieter Hoelzer,³ Evelyn Degenhard,¹ Dirk Nagorsen,¹ Patrick A. Baueierle,¹ Andreas Wolf,¹ and Peter Kuzer¹

A  B Cell Depletion (to ≤1/μL)

B  B Cell Kinetics

N = 20
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose level (\mu g/m^2/day)</th>
<th>Patients Treated, n</th>
<th>No of SAEs regardless of causality</th>
<th>No of DLTs</th>
<th>Cytological complete remission (CR) / molecular remission (MR) in bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>2 CR and 2 MR</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>4 CR and 4 MR</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>2 CR and 2 MR</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>8 CR and 8 MR</td>
</tr>
</tbody>
</table>