Allogeneic HSCT for pediatric malignant diseases
Adriana Seber
Is it worth on taking your patient to transplant?
Which are the potential benefits?
What does the patient have to lose?
Transplant-related toxicities

- During the procedure
- Long-term side effects
  - sterility
  - cataract
  - hair changes
  - short stature
  - chronic graft-vs-host disease
100-day Mortality after HLA-identical Sibling Transplants, 2010-2011

- Early Disease
- Advanced Disease
- Accelerated Phase
- Other

- Intermediate Disease
- Chronic Phase
- Blast Phase

Mortality, %

AML: 22% 9%
ALL: 22%
CML: 9%
MDS/MPS
Aplastic Anemia
Immune Deficiency
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011

- Primary Disease: 49%
- GVHD: 15%
- Infection: 12%
- Organ Failure: 17%
- Second Malignancy: 1%
- Other: 5%
Transplant-related toxicities

- ✓ During the procedure
  - Long-term side effects
    - sterility
    - cataract
    - hair changes
    - short stature
    - chronic graft-vs-host disease
Transplant-related toxicities

✓ During the procedure
• Long-term side effects
  - sterility
  - cataract
  - hair changes
  - short stature
  - chronic graft-vs-host disease

Relapse of the malignant disease
HSCT in earlier phases of the disease

↓ Toxicity
↓ Long term side effects
↓ Relapse
↑ Chance of cure
Transplants should be indicated if overall survival with transplant is larger than with chemotherapy

TRANSPLANT-RELATED MORTALITY
Indications for Hematopoietic Stem Cell Transplants for Age ≤ 20 years, in the US, 2011

- Allogeneic (Total N=1,562)
- Autologous (Total N=933)

Number of Transplants

- Other Cancer
- ALL
- AML
- HD
- Other Leukemia
- NHL
- MDS/MPD
- Aplastic Anemia
- Other Non-Malignant Disease
Which patients to transplant?

- Limited resources
- Limited number of beds
- Set up priorities

Criteria

Urgency
Curability
<table>
<thead>
<tr>
<th>Doença</th>
<th>Urgência</th>
<th>Curabilidade</th>
<th>Q Constante(*)</th>
</tr>
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<tbody>
<tr>
<td>Anemia aplástica grave/síndrome mielodisplásica hipocelular / imunodeficiência combinada severa/osteopetrose</td>
<td>100</td>
<td>80</td>
<td>80</td>
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<tr>
<td>Mielofibrose primária em fase evolutiva</td>
<td>80</td>
<td>40</td>
<td>120</td>
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<tr>
<td>Leucemia aguda falha de indução</td>
<td>100</td>
<td>15</td>
<td>115</td>
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<tr>
<td>Leucemia aguda em 2ª ou remissões posteriores</td>
<td>80</td>
<td>30</td>
<td>110</td>
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<tr>
<td>Síndrome mielodisplásica em transformação</td>
<td>70</td>
<td>40</td>
<td>110</td>
</tr>
<tr>
<td>Leucemia mielóide crônica - fase acelerada (de transformação)</td>
<td>90</td>
<td>20</td>
<td>110</td>
</tr>
<tr>
<td>Leucemia aguda 1ª remissão completa</td>
<td>50</td>
<td>55</td>
<td>105</td>
</tr>
<tr>
<td>Leucemia mielóide crônica - fase crônica &lt; 1 ano diagnóstico e &lt; 20 anos de idade</td>
<td>20</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Talassemia major</td>
<td>10</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Síndromes mielodisplásicas outras /leucemia mielomonocítica crônica</td>
<td>40</td>
<td>50</td>
<td>90</td>
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<tr>
<td>Leucemia mielóide crônica - fase crônica outras</td>
<td>30</td>
<td>50</td>
<td>80</td>
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</tbody>
</table>

(*) A cada dia somam-se 0,33 (trinta e três centésimos) de pontos igualmente para todos os casos, a partir da data de inclusão do receptor na lista. Receptores menores de 13 anos, independentemente da doença, deverão ter o seu escore final acrescido de 20 pontos.
Which patients to transplant first?

- Aplastic anemia
- Osteopetrosis
- Severe combined immunodeficiency
- Acute leukemia in 2nd remission
- Myelodysplastic syndrome
- Chronic myelogenous leukemia

* Children have priority
Which patients to transplant first?

- Aplastic anemia
- Osteopetrosis
- Severe combined immunodeficiency
- Severe sickle cell anemia
- Acute leukemia in 2^{nd} remission
- Myelodysplastic syndrome
- Chronic myelogenous leukemia

* Children have priority
Which donor to use?

The best available donor:
- Matched sibling
- Matched unrelated adult
- Unrelated cord blood
  (> 6/8: high resolution A,B,C,DR; no double mismatches, good cellularity)
- Haploidentical related donor
Which allogeneic graft to use?

- Bone marrow

- Peripheral blood
  - Risk of central lines in children
  - Risk of leukapheresis in small children
Higher Mortality After Allogeneic Peripheral-Blood Transplantation Compared With Bone Marrow in Children and Adolescents: The Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry

Mary Eapen, Mary M. Horowitz, John P. Klein, Richard E. Champlin, Fausto R. Loberiza, Jr, Olle Ringdén, John E. Wagner
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Treatment-related mortality*</td>
<td>1.89</td>
<td>1.28 to 2.80</td>
<td>.001</td>
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<tr>
<td>Relapse†</td>
<td>1.06</td>
<td>0.77 to 1.46</td>
<td>.7</td>
</tr>
<tr>
<td>Treatment failure‡</td>
<td>1.31</td>
<td>1.03 to 1.68</td>
<td>.03</td>
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<tr>
<td>Overall mortality§</td>
<td>1.38</td>
<td>1.07 to 1.79</td>
<td>.01</td>
</tr>
</tbody>
</table>

NOTE. Bone marrow recipients, the reference group, was assigned a relative risk (RR) of 1.00; RR greater than 1.0 indicate a benefit for bone marrow.

*Other significant variables associated with treatment-related mortality in both cohorts were use of growth factor within 7 days of allograft infusion for engraftment (RR, 1.80; 1.27 to 2.55; P = .001).

†Other significant variables associated with relapse in both cohorts were disease status; 1st CR (RR, 1.00, baseline), 2nd CR (RR, 1.82;
Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D., for the Blood and Marrow Transplant Clinical Trials Network*
Overall Survival (%) vs Years since Randomization for Peripheral blood and Bone marrow treatment groups.

P = 0.29
Severe Chronic GVHD

Peripheral blood >> Bone Marrow

(48% vs. 32%, p < 0.001)
Which allogeneic graft to use?

- Bone marrow
- Peripheral blood
  - Risk of central lines in children
  - Risk of leukapheresis in small children
Consensus indications

- European – EBMT
  http://ebmtonline.forumservice.net
- American – ASBMT
  www.effectivehealthcare.ahrq.gov/stem-cell-children.cfm
- British – BSBMT http://bsbmt.org
- Scottish - Royal Hospital for Sick Children
- Brazilian – SBTMO – Pediatric BMT Group
<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease status</th>
<th>Allogeneic matched related</th>
<th>Allogeneic Unrelated</th>
<th>Haploidentical related</th>
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</thead>
<tbody>
<tr>
<td><strong>Donor specifics</strong>&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td></td>
<td>10/10 sibling other 10/10 related other 9/10 related</td>
<td>10/10 adult 9-10/10 adult 4-6/6 cord</td>
<td>&lt;9/10 related</td>
</tr>
<tr>
<td><strong>Stem Cell Source</strong></td>
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<td>BM/PBPCs/cord</td>
<td>BM/PBPCs/cord</td>
<td>PBPCs/BM</td>
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<tr>
<td>AML</td>
<td>High risk CR1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>CO</td>
</tr>
<tr>
<td></td>
<td>CR≥2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>S</td>
<td>S</td>
<td>S&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>CO</td>
<td>CO</td>
<td>CO&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>ALL</td>
<td>High risk CR1&lt;sup&gt;h&lt;/sup&gt;</td>
<td>S&lt;sup&gt;h&lt;/sup&gt;</td>
<td>S&lt;sup&gt;h&lt;/sup&gt;</td>
<td>CO</td>
</tr>
<tr>
<td></td>
<td>CR2&lt;sup&gt;i&lt;/sup&gt;</td>
<td>S&lt;sup&gt;i&lt;/sup&gt;</td>
<td>S&lt;sup&gt;i&lt;/sup&gt;</td>
<td>S&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>CR3</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>GNR</td>
<td>GNR</td>
<td>GNR</td>
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<tr>
<td>CML</td>
<td>Chronic phase</td>
<td>S&lt;sup&gt;j&lt;/sup&gt;</td>
<td>S&lt;sup&gt;j&lt;/sup&gt;</td>
<td>CO&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Accelerated phase</td>
<td>S</td>
<td>S</td>
<td>CO</td>
</tr>
<tr>
<td></td>
<td>Blast crisis</td>
<td>S&lt;sup&gt;k&lt;/sup&gt;</td>
<td>S&lt;sup&gt;k&lt;/sup&gt;</td>
<td>CO&lt;sup&gt;k&lt;/sup&gt;</td>
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<tr>
<td>T-NHL</td>
<td>As per ALL&lt;sup&gt;l&lt;/sup&gt;</td>
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</table>

<sup>a</sup> Recipients <br><sup>b</sup> Donor age 18-64, <br><sup>c</sup> Either mismatched of CMR 0.995, <br><sup>d</sup> CR1 18-40, CR3 41-64, <br><sup>e</sup> Other, <br><sup>f</sup> Other, <br><sup>g</sup> Other, <br><sup>h</sup> CR2 18-40, CR3 41-64, <br><sup>i</sup> CR2 18-40, CR3 41-64, <br><sup>j</sup> Chronic phase CR3 18-40, accelerated phase CR3 41-64, blast crisis CR3 >64, <br><sup>l</sup> As per ALL
<table>
<thead>
<tr>
<th>Disease</th>
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<td>BM/PBPCs/cord</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>High risk CR1 (^c)</td>
<td>S (^c)</td>
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<tr>
<td></td>
<td>CR(\geq2) (^d)</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>CO</td>
</tr>
<tr>
<td>ALL</td>
<td>High risk CR1 (^n)</td>
<td>S (^n)</td>
</tr>
<tr>
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<td>CR2 (^i)</td>
<td>S (^i)</td>
</tr>
<tr>
<td></td>
<td>CR3</td>
<td>S</td>
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<td></td>
<td>Relapse/refractory</td>
<td>GNR</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic phase</td>
<td>S (^j)</td>
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<td></td>
<td>Accelerated phase</td>
<td>S</td>
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<tr>
<td></td>
<td>Blast crisis</td>
<td>S (^k)</td>
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Pediatric Acute Lymphoblastic Leukemia

• Autologous transplants are not indicated
• Allogeneic transplants:
  ✓ Third remission
  – Second remission
  – First remission
Outcome of Myeloablative Conditioning and Unrelated Donor Hematopoietic Cell Transplantation for Childhood Acute Lymphoblastic Leukemia in Third Remission

Eneida R. Nemecek,1 Betsy W. Buck,2 Alexandra Cheerva,3 Melanie Lipshitz,4 Mary Eapen,2 Thomas E. Storer,5 Parinda A. Talan,5 Ann E. Woollard6

Figure 2. Estimates of leukemia-free survival.
Biol Blood Marrow Transplant 17:1833-1840, 2011
Pediatric Acute Lymphoblastic Leukemia

• Autologous transplants are not indicated
• Allogeneic transplants:
  ✓ Third remission
  – Second remission
  – First remission
ALL in CR2: Matched sibling donor BMT vs. Chemotherapy

Barrett 1994 NEJM 331:1253-1258
### ALL in 2nd remission

<table>
<thead>
<tr>
<th>Risk</th>
<th>Relapse</th>
<th>EFS</th>
<th>Transplant</th>
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<tbody>
<tr>
<td>High (25%)</td>
<td>Early marrow</td>
<td>5-15%</td>
<td>Any BMT</td>
</tr>
<tr>
<td></td>
<td>CNS/testes</td>
<td>20-25%</td>
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<tr>
<td>Interm (65%)</td>
<td>BM 2-4 years</td>
<td>40-60%</td>
<td>Related</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>40-60%</td>
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<tr>
<td>Low (10%)</td>
<td>non-T &gt; 4 yr-BM</td>
<td>60-70%</td>
<td>Chemo ± RT</td>
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<td></td>
<td>non-T &gt; 4 yr-EM</td>
<td>60-80%</td>
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</table>
Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - Third remission
  - Second remission
  - First remission
Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study.


![Graph showing disease-free survival comparison between chemotherapy and related-donor HCT.]
Pediatric Acute Lymphoblastic Leukemia

• Autologous transplants are not indicated
• Allogeneic transplants:
  ✓ Third remission
  ✓ Second remission
  – First remission
    • t(9;22)
    • hypodiploid (<44) chromosome number
    • induction failure (M2/3 marrow on D29)
    • 11q23
    • minimal residual disease
From the Children’s Oncology Group; Department of Pediatrics, Division of Hematology, Oncology, and Blood and Marrow Transplant, British Columbia’s Children’s Hospital, University of British Columbia, Vancouver, BC; Cook Children’s Medical Center, Hematology and Oncology, Fort Worth; Pediatric Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX; Phyllis and David Kominsky Center for Children’s Health, Weill Cornell Medical Center, New York; Department of Pediatrics, New York University Medical Center, New York, NY; Department of Pediatrics and University of Florida Shands Cancer Center, University of Florida.

# Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children’s Oncology Group Study

Kirk R. Schultz, W. Paul Bowman, Alexander Aledo, William B. Slayton, Harland Sather, Meenakshi Devidas, Chenguang Wang, Stella M. Davies, Paul S. Gaynon, Michael Trig; Dean Jorstad, Andrew Carroll, Nyla A. Heerema, Naomi Winick, and William L. Carroll, and Bruce Camitta

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cons 1 (3 wk)</th>
<th>Cons 2 (3 wk)</th>
<th>Reind 1 (3 wk)</th>
<th>Intens 1 (9 wk)</th>
<th>Reind 2 (3 wk)</th>
<th>Intens 2 (9 wk)</th>
<th>Maint 1-4 (8-wk cycles)</th>
<th>Maint 5-12 (8-wk cycles)</th>
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<tbody>
<tr>
<td>Cohort 1</td>
<td></td>
<td></td>
<td></td>
<td>Imatinib x 3 wk</td>
<td></td>
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<tr>
<td>Cohort 2</td>
<td>Imatinib x 3 wk</td>
<td>Imatinib x 3 wk</td>
<td></td>
<td>Imatinib x 3 wk</td>
<td>Imatinib x 3 wk</td>
<td>Imatinib x 3 wk</td>
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<td>Cohort 3</td>
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<td>Cohort 4</td>
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<td>Imatinib x 3 wk</td>
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<td>Cohort 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Continuous dosing of imatinib

340 mg/m²/dia
Long-term follow-up of imatinib in pediatric Ph+ ALL: Children's Oncology Group AALL0031

Additional mutations = worse prognosis

Event-Free Survival (probability)

Time (years)

Cohort 5 chemo (n = 25) N = 28
Related BMT (n = 21) N = 21
Unrelated BMT (n = 11) N = 13

P = .1438  P = 0.6

70%  65%  56%
Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - Third remission
  - Second remission
  - First remission
    - t(9;22) : chemotherapy + TKI
    - hypodiploid (<44 chromosomes)
    - induction failure (M2/3 marrow on D29)
    - 11q23
    - minimal residual disease
Philadelphia chromosome-negative very high-risk acute lymphoblastic leukemia in children and adolescents: results from Children’s Oncology Group Study AALL0031

*Leukemia* (2014) **28**, 964–967; doi:10.1038/leu.2014.29

The Children’s Oncology Group (COG) AALL0031 study included very high-risk (VHR) pediatric acute lymphoblastic leukemia (ALL) patients who had an expected 5-year event-free survival ≤45%. The chemotherapy regimen was based on previous strategies; eligible patients received 4 weeks of standard induction chemotherapy and then were enrolled on AALL0031, which included an intensive consolidation followed by a continuation regimen (Supplementary Figure 1).\(^1\) COG AALL0031 enrolled patients aged 1–21 years with VHR ALL from 14 October 2002 to 20 October 2006. Induction therapy was limited to a combination of vincristine, prednisone or dexamethasone, and asparaginase with or without daunomycin. VHR features included the following: (a) Philadelphia chromosome [t(9;22)(q34;q11.2)]; (b) hypodiploidy: defined as ≤44 chromosomes or DNA index <0.81; (c) any rearrangement of the *MLL* gene in conjunction with a slow early response ≥5% marrow blasts at day 15 and/or ≥0.1% minimal residual disease (MRD) at the end of induction as detected by multiparameter flow cytometry;\(^2,3\) and (d) induction failure (IF) defined as either >25% blasts (M3 marrow status) by histology at the end of 4 weeks of induction therapy or an M2 marrow (5–25% blasts) or MRD ≥1% by flow cytometry at the end of induction followed by an M2 (or M3) marrow or MRD ≥1% after receiving two additional weeks of induction therapy (M2/M2 IFs). The therapy was identical to that presented in a previous publication on outcomes for Ph\(^+\) ALL patients,\(^1\) except that the Ph\(^-\) patients received no imatinib (see Supplementary Figure 1).

Prior approval was obtained from the National Cancer Institute and the Institutional Review Boards of the COG member institutions. Informed consent was obtained in accordance with the Federal guidelines. Sixty-three hypodiploid (41) and IF (22) patients were enrolled in AALL0031 after 4 weeks of a three- or four-drug induction regimen for National Cancer Institute standard and high-risk ALL, respectively. Data on adverse events and clinically significant abnormal laboratory findings were collected using National Cancer Institute Common Terminology Criteria version 2.0. MRD was assessed by multiparameter flow cytometry.\(^2\) Samples were available from 46 of 63 (73%) patients at study entry. MRD high was defined as >0.01% and low as ≤0.01%.

The primary outcome in this report is disease-free survival (DFS). Overall survival (OS), DFS and event-free survival were all defined as the time from the end of consolidation to the first event or last contact. An event was defined as relapse at any site, secondary malignancy or death in remission. A historical control data set of hypodiploid patients included patients enrolled on the Pediatric Oncology Group 8602, 9005, 9006, 9201, 9405, 9406 and 9605 protocols for B-ALL (January 1986–November 1999).\(^3\) The percentage of patients undergoing bone marrow transplant (BMT) in these comparator studies is unknown. IF patients were excluded from post-induction therapy in the historical control trial. Estimates of DFS, event-free survival and OS were computed using the Kaplan–Meier method\(^4\) and s.e. of the estimates according to Peto and Peto.\(^5\) The log-rank test was used for comparison of survival curves.
Hypodiploid + MRD

- MRD after consolidation cycle 2

4-year DFS rates:
- MRD < 0.01% = 83% with BMT
  47% with chemotherapy
- MRD > 0.01% = 56% with BMT
  29% with chemotherapy
Pediatric Acute Lymphoblastic Leukemia

• Autologous transplants are not indicated
• Allogeneic transplants:
  ✓ Third remission
  ✓ Second remission
  – First remission
    • t(9;22) : chemotherapy + TKI
    ✓ hypodiploid (<44 chromosomes)
    • induction failure (M2/3 marrow on D29)
    • 11q23
    • minimal residual disease
Outcomes after Induction Failure in Childhood Acute Lymphoblastic Leukemia

Martin Schrappe, M.D., Stephen P. Hunger, M.D., Ching-Hon Pui, M.D., Vaskar Saha, F.R.C.P.C.H., Paul S. Gaynon, M.D., André Baruchel, M.D., Valentino Conter, M.D., Jacques Otten, M.D., Akira Ohara, M.D., Ph.D., Anne Birgitta Versluys, M.D., Gabriele Escherich, M.D., Mats Heyman, M.D., Ph.D., Lewis B. Silverman, M.D., Keizo Horibe, M.D., Ph.D., Georg Mann, M.D., Bruce M. Camitta, M.D., Jochen Harbott, Ph.D., Hansjörg Riehm, M.D., Sue Richards, D.Phil., Meenakshi Devidas, Ph.D., and Martin Zimmermann, Ph.D.
<table>
<thead>
<tr>
<th>Study group</th>
<th>Patients treated</th>
<th>Induction failures N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associazione Italiana Ematologia ed Oncologia Pediatrica (AIEOP; Italy)</td>
<td>2938</td>
<td>88 (3.0)</td>
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<tr>
<td>Berlin-Frankfurt-Münster Group (BFM; Austria, Germany, Switzerland)</td>
<td>5828</td>
<td>137 (2.3)</td>
</tr>
<tr>
<td>Children’s Cancer Group (CCG; U.S.A., Canada, Australia, New Zealand)</td>
<td>5122</td>
<td>120 (2.3)</td>
</tr>
<tr>
<td>Cooperative ALL Group (COALL; Germany)</td>
<td>1686</td>
<td>49 (2.9)</td>
</tr>
<tr>
<td>Dutch Childhood Oncology Group (DCOG; The Netherlands)</td>
<td>1729</td>
<td>30 (1.7)</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute ALL Consortium (DFCI; U.S.A., Canada)</td>
<td>1457</td>
<td>31 (2.1)</td>
</tr>
<tr>
<td>Children’s Leukemia Group of the European Organisation for Research and Treatment of Cancer, (CLG-EORTC; Belgium, France, Portugal)</td>
<td>2316</td>
<td>69 (3.0)</td>
</tr>
<tr>
<td>French Acute Lymphoblastic Leukaemia Study Group (FRALLE; France)</td>
<td>3455</td>
<td>81 (2.3)</td>
</tr>
<tr>
<td>Japanese Association of Childhood Leukemia Study (JACLS, Japan)</td>
<td>1263</td>
<td>62 (4.9)</td>
</tr>
<tr>
<td>Childrens Cancer and Leukaemia Group (CCLG; United Kingdom)</td>
<td>5100</td>
<td>139 (2.5)</td>
</tr>
<tr>
<td>Nordic Society for Pediatric Hematology and Oncology (NOPHO; Sweden, Denmark, Norway, Finland, Iceland)</td>
<td>1546</td>
<td>53 (3.4)</td>
</tr>
<tr>
<td>Pediatric Oncology Group (POG; U.S.A., Canada)</td>
<td>8511</td>
<td>119 (1.4)</td>
</tr>
<tr>
<td>St. Jude Children's Research Hospital (SJCRH; Memphis, U.S.A.)</td>
<td>929</td>
<td>14 (1.5)</td>
</tr>
<tr>
<td>Tokyo Children Cancer Study Group (TCCSG; Tokyo, Japan)</td>
<td>2137</td>
<td>49 (2.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>44017</strong></td>
<td><strong>1041 (2.4)</strong></td>
</tr>
</tbody>
</table>

14 cooperative groups 1985 – 2000
44.017 children 1.041 induction failures (2.4%)
Pediatric ALL with induction failure

- High hyperdiploid, 71±6% (N=55, 16 deaths)
- Normal karyotype, 36±4% (N=159, 98 deaths)
- Other chromosomal aberrations, 30±3% (N=250, 171 deaths)
- 11q23/MLL, 16±5% (N=50, 42 deaths)
- t(9;22)/BCR-ABL1, 11±3% (N=110, 97 deaths)

P<0.001 by log-rank test
B-lineage ALL (non-MLL) < 6 years of age

Chemotherapy only
72±5% (N=95, 24 deaths)

Matched related donor SCT
59±12% (N=17, 7 deaths)

Other types of allogeneic SCT
57±14% (N=15, 6 deaths)

Chemotherapy vs. all types of allogeneic SCT,
P=0.007 by Mantel–Byar method

ALL – T lineage

Overall Survival (%)

Years after Diagnosis

Other types of allogeneic SCT
45±8% (N=39, 21 deaths)

Matched related donor SCT
40±9% (N=32, 19 deaths)

Chemotherapy only
26±4% (N=97, 72 deaths)

Chemotherapy vs. all types of allogeneic SCT,
P=0.06 by Mantel–Byar method

Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - Third remission
  - Second remission
  - First remission
  - \text{t}(9;22)
  - Hypodiploid (<44) chromosome number
  - Induction failure (M2/3 marrow on D29)
  - \text{11q23}
  - MRD D29 >0.1%
Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with *mixed-lineage-leukemia (MLL)*-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study

Georg Mann, Andishe Attarbaschi, Martin Schrappe, Paola De Lorenzo, Christina Peters, Ian Hann, Giulio De Rossi, Maria Felice, Birgitte Lausen, Thierry LeBlanc, Tomasz Szczepanski, Alina Ferster, Gritta Janka-Schaub, Jeffrey Rubnitz, Lewis B. Silverman, Jan Stary, Myriam Campbell, Chi Kong Li, Ram Suppiah, Andrea Biondi, Ajay Vora, Maria Grazia Valsecchi, Rob Pieters and on behalf of the Interfant-99 Study Group
QT  N = 170

TMO  N = 11

\[ P\text{-value} = .32 \]
MLL+ and age < 6 months and:

- > 300,000 leukocytes at diagnosis or
- > 1000 blasts PB after 8 days on steroids
Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - Third remission
  - Second remission
  - First remission
    - $t(9;22)$
    - Hypodiploid (<44) chromosome number
    - Induction failure (M2/3 marrow on D29)
    - 11q23
    - Minimal Residual Disease D29 >0.1%

[D+78]
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


Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study

<table>
<thead>
<tr>
<th>TP1</th>
<th>TP2</th>
<th>N.pts</th>
<th>N. rel.</th>
<th>5-yrs Cl</th>
<th>7-yrs Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10-3</td>
<td>NEG</td>
<td>866</td>
<td>95</td>
<td>14.8%(1.5)</td>
<td>16.2%(1.8)</td>
</tr>
<tr>
<td>&lt;10-3</td>
<td>POS</td>
<td>259</td>
<td>46</td>
<td>21.8%(3.1)</td>
<td>23.3%(3.4)</td>
</tr>
<tr>
<td>&gt;=10-3</td>
<td>NEG</td>
<td>257</td>
<td>45</td>
<td>20.7%(2.9)</td>
<td>23.0%(3.6)</td>
</tr>
<tr>
<td>&gt;=10-3</td>
<td>POS</td>
<td>395</td>
<td>130</td>
<td>40.7%(3.0)</td>
<td>42.4%(3.3)</td>
</tr>
</tbody>
</table>

Figure 4. Prognostic value of TP1 and TP2 in 1777 non–MRD-HR patients (ie, patients with MRD < 10^{-3} at TP2) who are MRD positive at TP1.
<table>
<thead>
<tr>
<th>MRD Level</th>
<th>N. pts</th>
<th>N. rel.</th>
<th>7-yr CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEG</td>
<td>222</td>
<td>18</td>
<td>8.5% (1.9)</td>
</tr>
<tr>
<td>&lt;10E-3</td>
<td>145</td>
<td>38</td>
<td>26.3% (3.7)</td>
</tr>
<tr>
<td>10E-3</td>
<td>59</td>
<td>19</td>
<td>33.0% (6.2)</td>
</tr>
<tr>
<td>&gt;10E-3</td>
<td>38</td>
<td>17</td>
<td>44.7% (8.1)</td>
</tr>
</tbody>
</table>

Figure 5. Cumulative incidence of relapse in 464 T-ALL patients by MRD levels at TP2.
Survival after HLA-identical Sibling Donor Transplants for ALL, Age < 20 years, 2001-2011

- Early (N=833)
- Intermediate (N=1,159)
- Advanced (N=196)

P < 0.001

By Disease Status
Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Lymphomas
<table>
<thead>
<tr>
<th>Stem Cell Source</th>
<th>Disease status</th>
<th>Allogeneic matched related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor specifics</td>
<td>10/10 sibling</td>
<td>10/10 sibling other</td>
</tr>
<tr>
<td>Stem Cell Source</td>
<td>other 10/10 related</td>
<td>other 9/10 related</td>
</tr>
<tr>
<td>BM/PBPCs/cord</td>
<td>BM/PBPCs/cord</td>
<td>BM/PBPCs/cord</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease status</th>
<th>Allogeneic matched related</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>High risk CR1</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>CR≥2</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>CO</td>
</tr>
<tr>
<td>ALL</td>
<td>High risk CR1</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>CR2</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>CR3</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>GNR</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic phase</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Accelerated phase</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Blast crisis</td>
<td>S</td>
</tr>
</tbody>
</table>
Pediatric Acute Lymphoblastic Leukemia

- Autologous transplants are not indicated
- Allogeneic transplants:
  - Third remission
  - Second remission
  - First remission
- \( t(9;22) \) hypodiploid (< 44) chromosome number
- Induction failure (M2/3 marrow on D29)
- 11q23
- Minimal Residual Disease D29 > 0.1%

Pediatric leukemia: Cytogenetics and/or Molecular markers Measure response
Survival after HLA-identical Sibling Donor Transplants for AML, Age < 20 years, 2001-2011

- Early (N=1,265)
- Intermediate (N=269)
- Advanced (N=251)

P < 0.001

By Disease Status
Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Lymphomas
Overall survival after myeloablative transplants for Myelodysplastic Syndrome 1996-2001

Early diagnosis and transplant referral

HLA-identical sibling RA/RARS (N = 48)

HLA-identical sibling, RAEB RAEB-T (N = 88)

P = 0.0004
Pediatric Malignant Diseases Treated with Allogeneic Transplantation

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Myelodysplastic syndrome
- Chronic myelogenous leukemia
- Lymphomas
<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease status</th>
<th>Allogeneic matched related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor specifics(^a,b)</td>
<td></td>
<td>10/10 sibling other 10/10 related other 9/10 related</td>
</tr>
<tr>
<td>Stem Cell Source</td>
<td></td>
<td>BM/PBPCs/cord</td>
</tr>
<tr>
<td>AML</td>
<td>High risk CR1(^c)</td>
<td>S(^c)</td>
</tr>
<tr>
<td></td>
<td>CR(\geq2)(^d)</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>CO</td>
</tr>
<tr>
<td>ALL</td>
<td>High risk CR1(^n)</td>
<td>S(^n)</td>
</tr>
<tr>
<td></td>
<td>CR2(^i)</td>
<td>S(^i)</td>
</tr>
<tr>
<td></td>
<td>CR3</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Relapse/refractory</td>
<td>GNR</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic phase</td>
<td>S(^j)</td>
</tr>
<tr>
<td></td>
<td>Accelerated phase</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>Blast crisis</td>
<td>S(^k)</td>
</tr>
</tbody>
</table>
Survival after HLA-identical Sibling Donor Transplants for CML, 2001-2011

CP, 2001-2011 (N=2,560)

AP, 2001-2011 (N=378)

P < 0.005
Stem cell transplantation for chronic myeloid leukemia in children

Kate Cwynarski, Irene A. G. Roberts, Simona Iacobelli, Anja van Biezen, Ronald Brand, Agnes Devergie, Jaak M. Verhoef, William Arcese, Franco Locatelli, Giorgio Dini, Dietrich Niethammer, Dietger Niederwieser, and Jane F. Apperley, for the Chronic Leukaemia Working Parties of the European Group for Blood and Marrow Transplantation

- EBMT
- BMT Jan, 1985 - Dec, 2001
- N = 314 children
- Median 14 years
  - 182 MSD; 132 MUD
- Bone Marrow

Stem cell transplantation for chronic myeloid leukemia in children


Table 2. HLA-identical sibling recipients

<table>
<thead>
<tr>
<th></th>
<th>N, 3y</th>
<th>Survival, %</th>
<th>LFS, %</th>
<th>Relapse, %</th>
<th>TRM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td>71</td>
<td>59</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP1</td>
<td>93</td>
<td>75</td>
<td>63</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>No CP1</td>
<td>7</td>
<td>46</td>
<td>35</td>
<td>49</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 3. VUD recipients

<table>
<thead>
<tr>
<th></th>
<th>N, 3 y</th>
<th>Survival, %</th>
<th>LFS, %</th>
<th>Relapse, %</th>
<th>TRM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>58</td>
<td>57</td>
<td>50</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP1</td>
<td>47</td>
<td>65</td>
<td>56</td>
<td>13</td>
<td>31</td>
</tr>
<tr>
<td>No CP1</td>
<td>11</td>
<td>39</td>
<td>34</td>
<td>20</td>
<td>46</td>
</tr>
</tbody>
</table>
Overall survival

CP1 (n=253)

AP (n=61)

$P = .001$

Cwynarski, 2003
Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: transplant activity, long-term data and current results. An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Alois Gratwohl

Haematologica 2006; 91:513-521
Figure 3. Survival probability of 2,628 patients transplanted between 1980 and 1990. CP-1: first chronic phase; AP: acute phase; BC: blast crisis; other: other subtypes.
Table 2. Probability of survival and cure undergoing allogeneic HSCT for CML

<table>
<thead>
<tr>
<th>At Tx</th>
<th>N</th>
<th>At 2 years</th>
<th>N</th>
<th>SURV</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>2628</td>
<td>1365</td>
<td>50%</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-id sibling</td>
<td>2238</td>
<td>1228</td>
<td>53%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Twin</td>
<td>40</td>
<td>28</td>
<td>69%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>164</td>
<td>56</td>
<td>32%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>186</td>
<td>53</td>
<td>27%</td>
<td>58%</td>
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</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st chronic phase</td>
<td>1828</td>
<td>1069</td>
<td>57%</td>
<td>–</td>
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</tr>
<tr>
<td>Accelerated phase</td>
<td>444</td>
<td>175</td>
<td>35%</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First c phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-id</td>
<td></td>
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</tr>
</tbody>
</table>

At 15 years

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>SURV</th>
<th>TRM</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pt</td>
<td>255</td>
<td>34%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MSD</td>
<td>241</td>
<td>36%</td>
<td>44%</td>
<td>26%</td>
</tr>
</tbody>
</table>
IBFM-Protocol on Allogeneic Stem Cell Transplantation in Paediatric CML

Study Title:
Allogeneic stem cell transplantation for children and adolescents with CML: Conditioning regimen, donor selection, supportive care and diagnostic procedures.

Short title: CML-SCT

Study coordinator
Univ.Doz. Dr. Susanne Matthes-Martin
Department for Stem Cell Transplantation
St Anna Children’s Hospital

Conditioning regimen:
Fludarabine 40 mg/m²/d on 4 days, Melphalan 140 mg/m²/d on 1 day and Thiotepa 2 x 5 mg/kg/d on 1 day + ATG
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| T-NHL                           | As per ALL |$
| Lymphoblastic (non-Burkitt) B-NHL| As per ALL |
| ALC+                            | CR2       |
|                                | CR≥3      |
|                                | Refractory|
| Burkitt NHL                     | CR2       |
|                                | Refractory|
| Anaplastic Large Cell Lymphoma  | S         |
|                                 | S         |
|                                 | S         |

R-ICE: Rituximab + Ifosfamide – Carboplatin – Etoposide

**Autologous BMT**
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Obrigada