Definitions
Patients were considered in morphological complete remission (CR) if they had normal neutrophil and platelet counts, less than 5% blast cells in a bone marrow (BM) smear and no extramedullary disease. All patients had a lumbar puncture before hematopoietic stem cell transplantation (HSCT) to document cerebro-spinal fluid CR. Neutrophil and platelet engraftment were defined as the first of three consecutive days with a neutrophil count greater than 0.5 x 10^9/L and an unsupported platelet count greater than 50 x 10^9/L, respectively. Acute and chronic GvHD (aGvHD and cGvHD) were diagnosed and graded according to established criteria (36, 37). Children with evidence of donor engraftment surviving more than 14 days and 90 days from transplantation were evaluated for the occurrence of aGvHD and cGvHD, respectively. Relapse was defined on the basis of morphological evidence of leukemia in BM, or at other extra-medullary sites. Transplantation-related mortality (TRM) was defined as all causes of non-leukemia death occurring after HSCT. Overall survival (OS) was defined as the interval between HSCT and either death or date of last follow-up, disease-free survival was defined as the interval between HSCT and either relapse, or death, or date of last follow-up, whichever occurred first.

Minimal Residual Disease analysis
DNA of BM mononuclear cells, obtained after Ficoll–Paque centrifugation, was extracted and purified using Gentra kit (Gentra System, Minneapolis, MN, USA). PCR analysis to detect specific TCRγ, TCRδ, and VDJH, DJH, VK and IRSS gene rearrangements was performed at diagnosis. Clonal gene rearrangements, identified by homo/heteroduplex analysis, were sequenced by dye-terminator cycle sequencing kit on ABI Prism 310 (Applied Biosystems, Foster City, CA, USA) (30). Minimal residual disease (MRD) levels in follow-up samples were analyzed by real-time quantitative PCR with hydrolysis (TaqMan) probes (31-33). Real-time PCR analysis of BM samples was performed in accordance with the guidelines published by the European Study Group on MRD detection in acute lymphoblastic leukemia (ALL) (34). Only markers with a cutoff level of at least 10^-4 were considered. Besides MRD-based stratification criteria, other high risk features used in previous protocols were also considered in the most recent ALL protocol, AIEOP-BFM 2000: patients with prednisone poor response [PPR; ≥1000 leukemic blasts per microliter in peripheral blood on day 8], or not achieving remission after induction treatment (i.e. ≥5%
leukemic blasts in BM on day 33), or with BCR/ABL or MLL/AF4 fusion gene transcripts. Such patients were treated in the HR arm, or with protocols specific for Ph-positive ALL, irrespective of MRD risk group assessment (27).

**Statistical analysis**
Patient-, disease-, and transplantation-related variables were expressed as median and ranges, or as percentages, as appropriate. For statistical analysis, all continuous variables, except for age, were categorized as follows: each variable was first divided into 4 categories at the 25\(^{\text{th}}\), 50\(^{\text{th}}\) and 75\(^{\text{th}}\) percentiles. If the relative event rates (the ratio of the observed number of events to the expected number of events in the category) in two or more adjacent categories (and the median time to events) did not differ, those categories were grouped. If no clear pattern was observed for the primary outcomes, the median was taken as the cutoff point. Patients were censored at time of relapse, death or last follow-up. Death from any cause and graft rejection were competing risks to estimate the cumulative incidence of aGvHD and cGvHD. Death in remission was treated as a competing event to calculate the cumulative incidence of relapse. Relapse was considered to be the competing event for calculating TRM.

The following patient- or transplantation-related variables were analyzed for their potential impact on outcome: gender, age, white blood cells at diagnosis, immunophenotype, cytogenetics, interval between diagnosis and HSCT, first-line treatment, MRD, donor type, year of transplantation, stem cell source, use of total body irradiation, aGvHD and cGvHD occurrence.
### Supplementary table 1.

Univariate analyses of variables influencing the probability of DFS

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<th>Log rank test</th>
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### Acute GvHD

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### Chronic GvHD

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**Legend:** DFS: disease-free survival; HSCT: hematopoietic stem cell transplantation; WBC: white blood cells; MRD: minimal residual disease; IR: Intermediate Risk; HR: High Risk; MFD: matched family donor; UD: unrelated donor; BM: bone marrow; PB: peripheral blood; CB: cord blood; TBI: total body irradiation; GvHD: graft-versus-host disease.
## Supplementary table 2.
Univariate analyses of variables influencing the cumulative incidence of RI

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Univariate analyses of variables influencing the cumulative incidence of TRM

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<td>Absent</td>
<td>143</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Limited</td>
<td>25</td>
<td>2</td>
<td>8</td>
<td>(2-30)</td>
</tr>
<tr>
<td>Extensive</td>
<td>27</td>
<td>5</td>
<td>19</td>
<td>(9-42)</td>
</tr>
</tbody>
</table>

### Supplementary Table 4.
Causes of transplantation-related mortality according to the period of transplantation and the donor employed

<table>
<thead>
<tr>
<th></th>
<th>UD</th>
<th>MFD</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transplant between 1990 and 1999</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>4</td>
<td>5</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>1</td>
<td>3 (35%)</td>
</tr>
<tr>
<td>GvHD</td>
<td>0</td>
<td>3</td>
<td>3 (35%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>1</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td><strong>Transplant between 2000 and 2004</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>4</td>
<td>7</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>2</td>
<td>4 (35%)</td>
</tr>
<tr>
<td>GvHD</td>
<td>2</td>
<td>3</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>2</td>
<td>2 (20%)</td>
</tr>
<tr>
<td><strong>Transplant between 2005 and 2008</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>7</td>
<td>4</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Infections</td>
<td>3</td>
<td>2</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>GvHD</td>
<td>3</td>
<td>2</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>