Allogeneic Bone Marrow Transplantation for Childhood Acute Lymphoblastic Leukemia in Second Remission After Intensive Primary and Relapse Therapy According to the BFM- and CoALL-Protocols: Results of the German Cooperative Study


Fifty-one children between 26 and 214 months of age (median, 100 months) with acute lymphoblastic leukemia (ALL) were grafted in second remission from HLA-identical sibling donors (except for two patients who were grafted with a marrow with 1 antigen-mismatch). Initial treatment and relapse therapy were similar in all patients according to the BFM- and CoALL-protocols (front line: 38 patients according to BFM-protocols and 13 patients according to CoALL-protocols; relapse: 12 patients in study ALL-REZ-BFM 83, 17 in ALL-REZ-BFM 85, 20 in ALL-REZ-BFM 87, and two in ALL-REZ-BFM 90). The conditioning regimens were different, consisting of cyclophosphamide (CY) total body irradiation (TBI) plus (n = 27), VP-16-TBI (n = 23), and CY-TBI and ARA-C (n = 1). Three patients had a second graft after conditioning with CY-TBI for the first transplantation. The second ablative regimen consisted of CY plus VP-16 in the first patient and CY plus busulfan in the two other patients, one of whom relapsed again. All patients but three had bone marrow (BM), either isolated or combined, relapses. Twenty-nine of the patients are in continuous complete remission (CCR), ranging from 1 to 67 months after transplantation with a median time of 30 months. One patient was lost to follow-up in continuous remission. Nine patients died from treatment-related complications (infections and graft-versus-host disease) and 12 patients suffered a leukemia relapse; three of them received a second graft and two are in CCR. Kaplan-Meier analysis yields an event-free survival (EFS) of 0.52 ± 0.08. The probability of a 7-year relapse-free interval (RFI) is 0.68 ± 0.08. EFS for patients with late relapses is 0.47 ± 0.12 and for patients with early relapses 0.58 ± 0.1. The RFI for patients with late relapses is 0.65 ± 0.12 and for patients with early relapses 0.69 ± 0.11. There is a nonsignificant trend towards superior results for patients grafted after conditioning with VP-16 plus TBI. When all patients who are not in CCR at day +125 (which is the median interval between relapse diagnosis and BM transplantation [BMT]) are excluded from the chemotherapy results, there is no significant difference between the results of BMT and chemotherapy for late relapses. On the other hand, there is a significant advantage between chemotherapy and BMT for early relapses over chemotherapy (P < .01).

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Table 1. Complete Status of the Patient

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age (yr)</th>
<th>Remission Duration (mo)</th>
<th>T</th>
<th>Conditioning Regimen</th>
<th>GVHD Prophylaxis</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
<th>Status</th>
<th>Length of Follow-up (mo)</th>
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<tbody>
<tr>
<td>12</td>
<td>15½</td>
<td>66</td>
<td>253</td>
<td>CY/TBI</td>
<td>T-Dep</td>
<td>0</td>
<td>0</td>
<td>Alive</td>
<td>70</td>
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<tr>
<td>16</td>
<td>13½</td>
<td>29</td>
<td>59</td>
<td>CY/TBI</td>
<td>MTX</td>
<td>0</td>
<td>0</td>
<td>+17 IP</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>13½</td>
<td>25</td>
<td>178</td>
<td>CY/TBI</td>
<td>CSA</td>
<td>0</td>
<td>0</td>
<td>+24 intracerebral hemorrhage</td>
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<tr>
<td>40</td>
<td>8½</td>
<td>47</td>
<td>338</td>
<td>CY/TBI</td>
<td>MTX</td>
<td>0</td>
<td>0</td>
<td>Alive</td>
<td>74</td>
</tr>
<tr>
<td>46</td>
<td>8</td>
<td>43</td>
<td>72</td>
<td>CY/TBI</td>
<td>CSA</td>
<td>0</td>
<td>0</td>
<td>Alive</td>
<td>75</td>
</tr>
<tr>
<td>51</td>
<td>6½</td>
<td>34</td>
<td>190</td>
<td>CY/TBI</td>
<td>MTX</td>
<td>0</td>
<td>0</td>
<td>+50 take failure infection</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>10½</td>
<td>13</td>
<td>111</td>
<td>CY/TBI</td>
<td>CSA/ATG</td>
<td>III E</td>
<td>+338 infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>17½</td>
<td>34</td>
<td>156</td>
<td>CY/TBI</td>
<td>CSA</td>
<td>II 0</td>
<td>+211 IP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>17½</td>
<td>20</td>
<td>156</td>
<td>CY/TBI</td>
<td>MTX</td>
<td>0</td>
<td>0</td>
<td>Lost for follow-up</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>12½</td>
<td>38</td>
<td>97</td>
<td>CY/TBI</td>
<td>Syngen</td>
<td>0</td>
<td>0</td>
<td>+1,040 relapse</td>
<td></td>
</tr>
<tr>
<td>146</td>
<td>11½</td>
<td>12</td>
<td>113</td>
<td>CY/TBI</td>
<td>Syngen</td>
<td>0</td>
<td>0</td>
<td>Alive</td>
<td>65</td>
</tr>
</tbody>
</table>

Abbreviations: CY, cyclophosphamide; BU, busulfan; E, extended; L, limited; ATG, anti-T-cell globuline; Pred, prednisolon; T-dep, T-cell-depletion; T, interval between relapse diagnosis and BMT in days; IP, interstitial pneumonitis; +, patient died.

*One antigen-mismatch.
discontinuation of maintenance treatment; late relapse, more than 6 months after discontinuation of maintenance treatment). Immunologic investigations of relapse leukemia showed that 35 patients had c-ALL, three patients had pre-T-/T-ALL, four patients had O-ALL, one patient had pre-B-ALL, one patient had c-ALL with Ph", and in seven patients immunologic data were not documented.

Informed consent was obtained from the patients or their parents for participating in each study. Statistical evaluation of outcome after relapse and BMT was performed by actuarial life-table analysis according to the Kaplan-Meier method. Log-rank tests were used for comparison of subgroups. On the basis of a multicenter study, selection for BMT was mainly in the hands of the chemotherapy centers and the decision of the parents. Therefore, some selection of patients cannot be excluded but cannot be prevented.

RESULTS

All but two patients engrafted, as shown by increasing peripheral cell counts. Thirty-one of the 51 patients are in continuous complete remission (CCR), ranging from 1 to 67 months after transplantation, two of them after a second graft. Nineteen patients died from relapsing leukemia after transplantation and from treatment-induced complications including infections and GVHD; one patient was lost to follow-up. It has to be mentioned that there is a decreasing incidence of transplantation-associated complications over the years, reflecting the increasing experience with BMT. Of 12 patients grafted in study ALL-REZ 83, five died from treatment-associated complications; in study ALL-REZ 85, two of 17 children died; and in study ALL-REZ 87, the death rate was two of 14. The actuarial event-free survival (EFS) for the 51 patients is shown in Fig 1 separated into late and early relapses. The 7-year EFS (median observation time, 3.4 years) is 52% for the total group, 56% for early relapses, and 47% for late relapses. The probability of a 7-year relapse-free interval (RFI) is 68% for the total group, with 69% for early and 65% for late relapses (Fig 2). Hence, the relapse rate is low in these patients. In comparing the relapse rates obtained with different conditioning regimens, we saw a trend in favor of VP-16 plus TBI (Fig 3). This has to be interpreted with caution because patients treated with VP-16/TBI are those transplanted most recently with shorter follow-up (Fig 4).

The median time between the diagnosis of relapse and BMT is 125 days. To compare the results obtained with chemotherapy and BMT, all events occurring before day 125 were censored for the Kaplan-Meier plot as shown in Fig 5. For children with late relapses there is no significant difference between the results of BMT and chemotherapy. However, there is a significant difference between both treatment modalities for early relapses.

Eight patients had an extended chronic GVHD, two of them died of subsequent relapse, two of GVHD-related infections, and one is alive in a very bad clinical condition with joint contractures and repeated infections, mainly of the skin.

DISCUSSION

There are several reports in the literature suggesting no difference in survival rates after BMT or chemotherapy for children with ALL in second remission. Sanders et al showed an actuarial survival of 40% with intervals extending from 2.5 to 10.4 years for the group of patients treated with BMT. The best results for transplantation in second CR have been reported in 1987 from the Memorial Sloan Kettering Institute with a disease-free survival rate of 60%.
ALLOGENEIC BMT FOR CHILDHOOD ALL

Fig 4. EFS after different conditioning regimens. n.s., not significant.

Update of this study is lacking, however, and data of the initial chemotherapy in this group are not known, in contrast to our group of patients who have been treated according to very aggressive protocols. For this reason, these groups are not comparable. Most reports in the literature lack sufficient numbers of patients for significant statistical conclusions as to the survival of the different groups. The BFM-ALL relapse study showed that patients with BM relapses before 18 months of first CCR and any relapse of T-ALL have only a minimal chance of surviving with chemotherapy alone, with survival rates being below 5%. With BMT, the results are not different between late and early relapses, indicating that the latter group clearly benefits from BMT. As patients with late relapses currently have an EFS of 41% with chemotherapy, BMT appears not to be indicated for these children.

Despite the different conditioning regimens, the overall EFS for the total group of 51 patients is 52%. We suppose that this result is in part due to the reinduction chemotherapy according to the ALL-BFM relapse protocols, particularly because of the relatively low relapse rate after BMT. Even lower relapse rates during the more recent years may be attributed to improvements of reinduction chemotherapy and perhaps better prevention of relapses after introduction of the conditioning regimen with TBI and VP-16.

In the early years of BMT some patients died of transplantation-related complications. More recently the experience with this treatment modality has increased, leading to a reduction of the transplantation-related death rate. A lower rate of therapy-associated complications would increase the survival of patients after BMT and the procedure could be considered in all patients with ALL in second remission. In our experience, however, patients with late relapses and patients with extramedullary relapses more than 18 months after initial diagnosis have a similar prognosis with chemotherapy alone, and BMT seems not to be indicated. If these results remain stable over the next several years, BMT in second remission will be indicated in patients who relapse early in the BM or have T-cell disease or relapse in extramedullary compartments after a very short-lasting first CR (18 months).

For the first time it has been possible to define in children with ALL in second remission a group of patients that clearly benefits from BMT; ie, the children who relapse in the BM earlier than 6 months after discontinuation of maintenance therapy. For this group of patients, the results of chemotherapy alone are significantly worse than those of BMT. This is especially true for those patients with T-ALL and those who relapse within 18 months of front-line treatment, for whom the prognosis is below 5%. On the other hand, the reported data also give evidence that in children with late relapses BMT transplantation does probably not increase the chances of cure significantly, making TBI dispensable for them. It has to be emphasized again, however, that these results have to be regarded in the context of the chemotherapy protocols used here.

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Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-protocols: results of the German Cooperative Study

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