Consolidation Treatment of Adult Acute Lymphoblastic Leukemia: A Prospective, Randomized Trial Comparing Allogeneic Versus Autologous Bone Marrow Transplantation and Testing the Impact of Recombinant Interleukin-2 After Autologous Bone Marrow Transplantation

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A prospective, randomized trial was initiated in adult acute lymphoblastic leukemia (ALL) to compare (1) disease-free survival (DFS) after allogeneic or autologous bone marrow transplantation (BMT) and (2) the relapse rate of patients treated with or without interleukin-2 (IL-2) after autologous BMT. A total of 135 previously untreated patients, aged under 55 years, received the Berlin-Frankfurt-Munster (BFM) induction regimen: 126 patients (93%), of which 120 were HLA-typed, achieved complete remission (CR). According to this genetic randomization, patients with (n = 43) or without an HLA-identical sibling (n = 77) were to receive allogeneic or autologous BMT, respectively. The 3-year post-CR probability of DFS was significantly higher in the HLA-identical sibling group than in the non-HLA-identical sibling group (68% vs 28%; P < .001). Eligible patients were randomized to receive (n = 30) or not to receive (n = 30) IL-2 after autologous BMT: the 3-year post-BMT probability of continuous CR was similar in both groups (29% vs 27%, respectively). We conclude that, in ALL, early allogeneic BMT after the BFM induction regimen is an effective consolidation treatment and that IL-2 does not decrease the high relapse rate observed after autologous BMT.

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Requirements for Patient Enrollment

Between February 1990 and December 1992, all patients between the ages of 15 and 55 years with a morphologic and cytochemically confirmed diagnosis of ALL (L3 French-American-British [FAB] subtype excluded) were considered eligible for this study. Exclusion criteria were as follows: (1) prior treatment for ALL, (2) another effectors. Thus, it was reasonable to speculate that an IL-2-based immunotherapy in the context of autologous BMT for ALL may eradicate the residual leukemic cells surviving after high-dose therapy through the stimulation of NK and LAK activities.

Therefore, we performed a multicentric, randomized trial in 135 adult patients aged under 55 years with de novo ALL. Patients in CR after a Berlin-Frankfurt-Munster (BFM) induction regimen were HLA-typed. Patients with an HLA-identical sibling were to receive allogeneic BMT, whereas patients without an HLA-identical sibling were to receive autologous BMT. Patients were randomized to receive or not to receive IL-2 after autologous BMT. The objectives of this study were to compare (1) disease-free survival (DFS) of patients genetically randomized to receive allogeneic or autologous BMT and (2) relapse rates of patients randomized to receive or not to receive IL-2 after autologous BMT.

Patients and Methods

During the last few years, improvement in the prognosis of adult acute lymphoblastic leukemia (ALL) has been modest. With intensive regimens similar to those used in childhood ALL complete remission (CR) rates range from 70% to 87%. However, the probability of leukemia-free survival is 35%, leading to an overall cure rate of only 25%. To decrease this relapse rate, high-dose therapy supported with allogeneic2-3 or autologous24-27 bone marrow transplantation (BMT) has been investigated as consolidation treatment of adult ALL in first CR. Allogeneic BMT was found to be associated with a low relapse rate ranging from 10% to 20%. The antileukemic effect of allogeneic BMT was considered to be dependent on the high-intensity treatment used in the preparative regimen, as well as on an adoptive immunotherapy due to donor cells and defined as the graft-versus-leukemia (GVL) reaction.28-31 This effectiveness, however, was offset by a high toxic death rate ranging from 25% to 35%. Thus, the role of allogeneic BMT remains controversial during first CR.2,13 Autologous BMT, when applied in first CR, was found to be associated with a low toxic death rate (less than 5%). However, a higher relapse rate (ranging from 40% to 70%) in comparison with allogeneic BMT has been reported, possibly due to the absence of GVL reaction.2,13,18,19,28,33

The precise mechanisms involved in the GVL reaction remain to be characterized. There is some evidence that different cytotoxic T cells as well as natural killer (NK) cells mediate the cytotoxic reactions against leukemic blasts. Interleukin-2 (IL-2) is a cytokine capable of expanding cytotoxic T cells, enhancing NK cell activity, and activating lymphokine-activated killer (LAK) effectors. Recent laboratory studies have indicated that human leukemic blasts of both myeloid and lymphoid origin may be lysed by LAK effectors. Furthermore, LAK cells, generated in vitro or in vivo after IL-2 administration, possessed cytotoxic activity toward autologous blasts.40 Recent phase I studies have demonstrated that IL-2 administration was feasible after autologous BMT, induced a restoration of the defective NK functions, and generated a high number of endogenous LAK effectors. Thus, it was reasonable to speculate that an IL-2-based immunotherapy in the context of autologous BMT for ALL may eradicate the residual leukemic cells surviving after high-dose therapy through the stimulation of NK and LAK activities.

Therefore, we performed a multicentric, randomized trial in 135 adult patients aged under 55 years with de novo ALL. Patients in CR after a Berlin-Frankfurt-Munster (BFM) induction regimen were HLA-typed. Patients with an HLA-identical sibling were to receive allogeneic BMT, whereas patients without an HLA-identical sibling were to receive autologous BMT. Patients were randomized to receive or not to receive IL-2 after autologous BMT. The objectives of this study were to compare (1) disease-free survival (DFS) of patients genetically randomized to receive allogeneic or autologous BMT and (2) relapse rates of patients randomized to receive or not to receive IL-2 after autologous BMT.

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malignancy, (3) abnormal cardiac function (systolic ejection fraction less than 50%, abnormal stress test), (4) chronic respiratory disease (vital capacity or monoxide diffusion less than 50% of normal), (5) abnormal liver function (serum bilirubin greater than 35 μmol/L or ALAT, ASAT greater than four times normal), or (6) psychiatric disease. A total of 141 patients from nine French centers were enrolled in the study. According to the criteria stated above, six patients were excluded for the following reasons: age greater than 55 years (n = 1), lymphoblastic lymphoma (n = 4), and severe violation of the therapy protocol (n = 1). Thus, 135 patients remained for the analysis. The study protocol was approved by the institutional ethics committees, and patients gave informed consent before entering the study.

Diagnostic Procedure

Morphologic diagnosis was based in all cases on May-Grunwald-Giemsa and cytochemical staining of bone marrow and blood smears. Leukemia was classified according to the FAB classification. Therapy was begun according to the diagnosis made at the individual institution, and blood and bone marrow smears were reviewed centrally.

Immunologic study of cell-surface markers was available for 129 of 135 patients (96%). Immunophenotyping was performed, usually on bone marrow cells, by indirect immunofluorescence using flow cytometry. The panel of monoclonal antibodies was selected to determine the B- or T-cell lineage of the leukemic cells and, if possible, to assign the cells to a stage of differentiation: for the B-cell lineage: B1 (CD19+, CD10-, CD20-), B2 (CD19+, CD10+, CD20-), B3 (CD19+, CD10+/-, CD20+); for the T-cell lineage: T1 (CD7+, CD2+/-), T2 (CD7+, CD2+, CD1-), T3 (CD7+, CD2+, CD5+, CD3-). Leukemic cells that expressed none of these markers were considered as undifferentiated (UD).

Cytogenetic analysis was not performed systematically. However, 95 karyotypes were obtained (70.4%), of which 87 (65%) were interpretable. Patients known to be Philadelphia (Ph) chromosome-positive were not excluded from the analysis

Treatment Protocol (Fig 1)

Induction Therapy

The BFM induction therapy was an 8-week regimen and consisted of two phases. In phase I, patients received prednisone (60 mg/m²/d, orally, days 1 to 28), vincristine (1.5 mg/m²/d, intravenously (IV), days 1, 8, 15, and 22), daunorubicin (30 mg/m²/d, IV, days 1, 8, 15, and 22), and L-asparaginase (10,000 U/m²/d, IV, days 10, 13, 16, 19, 21, and 24). In phase II, patients received cyclophosphamide (1 g/m²/d, IV, days 29 and 50), cytosine arabinoside (75 mg/m²/IV, IV, days 31 to 34, 38 to 41, and 45 to 48), and 6-mercaptopurine (30 mg/m²/d, orally, days 29 to 50). Central nervous system (CNS) prophylaxis with intrathecal methotrexate (10 mg/m²) was administered on days 1, 15, 31, and 45.

HLA Typing

During the induction therapy, patients achieving CR (after phase I or phase II) were HLA-typed. Patients with an HLA-identical sibling were to receive allogeneic BMT, whereas patients without an HLA-identical sibling were to receive autologous BMT.

Postremission Therapy for Patients With an HLA-Identical Sibling

Interval therapy. At 10 days after the end of induction therapy, patients still in CR received two or three courses of methotrexate (3 g/m²/d, IV, days 1 and 15 ± day 30) and aracytine (4 g/m²/d, IV, days 1 and 15 ± day 30).

Autologous BMT. Autologous BMT was performed 15 to 30 days after the end of interval therapy. Patients received a non-T-depleted HLA-identical BMT (15 mg on days +1, +3, and +6) plus cyclosporine.

Postremission Therapy for Patients Without an HLA-Identical Sibling

Interval therapy. Patients received the same protocol as those with an HLA-identical sibling. The autologous bone marrow graft was collected after the second course of methotrexate and aracytine, and a third course was systematically applied before autologous BMT to verify that the number of colony-forming units-granulocyte/macrophage (CFU-GM) collected in the bone marrow graft was sufficient.

Autologous BMT. Autologous BMT was performed 15 to 30 days after the end of interval therapy. Patients received unpurged graft prepared with cyclophosphamide (120 mg/kg) and fractionated total body irradiation (TBI: 12 Gy with lung shielding above 8 Gy). Prevention of graft-versus-host disease was attempted by the administration of methotrexate (15 mg on days +1, +3, and +6) plus cyclosporine.

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was administered by continuous infusion for a total of five cycles every other week (first cycle, 5 days; the following four cycles, 2 days) at a dose of $12 \times 10^6$ U/m²/d.

Statistical Methods

This trial was a prospective, randomized, non-blinded study. Patients were registered at diagnosis by the coordinating center (Toulouse, France). The first randomization was a genetic one: all patients achieving CR were HLA-typed, and patients with an HLA-identical sibling were to receive allogeneic BMT, whereas patients without an HLA-identical sibling were to receive autologous BMT. The major objective of this first randomization was to compare disease-free survival (DFS) between the two groups. The second randomization was performed 1 week before autologous BMT: patients were randomized to receive or not to receive IL-2 after autologous BMT. The randomization sequences were generated by the Roussel UCLAF group, which issued treatment allocation by telephone after confirmation of patient eligibility. The major objective of this second randomization was to compare relapse rates between the two groups. As a relapse rate of 60% is observed after autologous BMT for adult ALL, in first CR, IL-2 was tested after autologous BMT to induce a GVU-like effect. Thus, a relapse rate of 20%, similar to the allogeneic BMT one, was expected in the IL-2 group. To ensure a significance level of 5% and a power of 95% to these assumptions, 30 patients assigned randomly to each treatment arm (IL-2+ and IL-2−) were required. The study was completed by the enrollment of 64 patients actually treated with autologous BMT. All analyses were performed on an intention-to-treat basis (HLA-identical donor: yes or no; and IL-2 randomization: + or −).

The proportions of patients with a given characteristic were compared by χ² test or Fischer’s exact test. Differences in the means of continuous measurements were tested with Student’s t test, controlled by nonparametric Mann-Whitney U test. All tests were two-sided. DFS duration was calculated for CR patients from date of CR (for the first genetic randomization) or autologous BMT (for the IL-2 randomization) until relapse, death, or date last known alive. Continuous complete remission (CCR) duration was calculated for CR patients from date of CR or autologous BMT until relapse or date last known in CR. When calculating DFS, deaths in CR were counted as adverse events when calculating CCR; deaths in CR were not. CCR and DFS curves were plotted according to the method of Kaplan-Meier and compared by the log-rank test. Prognostic factors for CCR duration and DFS were determined by the Cox proportional hazard model for covariate analysis.

RESULTS

Pretreatment Characteristics

The initial characteristics of the 135 patients included in this trial are listed in Table 1. The median age was 31 years, 65% of patients were male, and 35% had an initial white blood cell (WBC) count greater than 30,000/μL. Study of cell-surface markers was available for 129 patients (96%). Of these available phenotypes, 93 (72%) were of B-cell lineage, including 77 cases positive for CD10 (60% of the total group), 33 (26%) were of T-cell lineage, and 3 (2.3%) were UD. Cytogenetic evaluation was performed in 95 patients (70.4%) and was interpretable in 87 cases (64.4% of the entire population). The Ph chromosome was found in 20 patients (23% of the population tested).

Remission Induction

The results of induction therapy are listed in Table 2. A total of 126 patients (93%) achieved CR. In 114 patients, the CR was recorded within 4 weeks, i.e., after phase I of the induction regimen; and in 12 patients, CR occurred only

<table>
<thead>
<tr>
<th>Variable</th>
<th>Induction (%)</th>
<th>HLA-identical Sibling (%)</th>
<th>BMT Performed (%)</th>
<th>IL-2 Post-Auto-BMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>135</td>
<td>77</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>82 (61)</td>
<td>47 (61)</td>
<td>30 (70)</td>
<td>37 (62)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>53 (39)</td>
<td>30 (39)</td>
<td>13 (30)</td>
<td>23 (38)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>88 (65)</td>
<td>50 (65)</td>
<td>31 (72)</td>
<td>43 (67)</td>
</tr>
<tr>
<td>F</td>
<td>47 (35)</td>
<td>27 (35)</td>
<td>12 (28)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>Leukocyte count/L</td>
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<td></td>
</tr>
<tr>
<td>&lt;30 × 10⁹</td>
<td>88 (65)</td>
<td>50 (65)</td>
<td>31 (72)</td>
<td>41 (64)</td>
</tr>
<tr>
<td>≥30 × 10⁹</td>
<td>47 (35)</td>
<td>27 (35)</td>
<td>12 (28)</td>
<td>23 (36)</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-ALL</td>
<td>93 (72)</td>
<td>56 (76)</td>
<td>23 (63)</td>
<td>46 (75)</td>
</tr>
<tr>
<td>CD10−</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>CD10+</td>
<td>77</td>
<td>47</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>T-ALL</td>
<td>33 (26)</td>
<td>18 (24)</td>
<td>14 (37)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>UD</td>
<td>3 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ph1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>67 (77)</td>
<td>40 (82)</td>
<td>23 (88)</td>
<td>35 (65)</td>
</tr>
<tr>
<td>Y</td>
<td>20 (23)</td>
<td>9 (18)</td>
<td>3 (12)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>No. of courses to CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>114 (90)</td>
<td>69 (90)</td>
<td>39 (91)</td>
<td>59 (92)</td>
</tr>
<tr>
<td>2</td>
<td>12 (10)</td>
<td>8 (10)</td>
<td>4 (9)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

None of the initial factors significantly differed between treatment groups.

Abbreviations: Auto, autologous; Allo, allogeneic.
were considered as nonresponders and died of disease. Four patients (3%) died of early toxicity (infections, three cases; hemorrhage, one case). None of the various factors tested (age, sex, leukocyte count, immunology, Ph chromosome) was found to have a statistically significant influence on the CR rate.

Six patients did not have an HLA-identical sibling (36% of patients assessable for the first genetic randomization and 32% of all enrolled patients), while 77 of 364 patients did not receive allogeneic BMT because of early relapse. Forty-one patients were actually transplanted during first CR. The median time between CR and allogeneic BMT was 3.1 months (SD, 1.1). Five transplant-related deaths (12%) occurred during the procedure (graft-versus-host disease, four cases; aspergillosis, one case). The incidence of severe acute graft-versus-host disease (grade 2 to 4) was 37% (15 of 41 patients), and 6 of 36 (17%) patients developed an extensive chronic graft-versus-host disease. With a median follow-up of survivors of 27 months from allogeneic BMT, five (12%) relapses occurred. The 3-year post-allogeneic BMT probabilities of CCR and DFS were 87% (95% CI, 71% to 95%) and 71% (95% CI, 54% to 83%), respectively.

In the no HLA-identical sibling group (n = 77), with a median follow-up of survivors of 29.1 months from CR, the 3-year probabilities of CCR and DFS were 28% (95% CI, 17% to 39%) and 26% (95% CI, 16% to 37%), respectively, which appeared significantly lower than in the HLA-identical sibling group (P < .001; Table 2 and Fig 3). In this group, 13 of 77 (17%) patients did not receive autologous BMT (early relapse, 11 cases; toxic death, one case; and patient refusal, one case). Sixty-four patients were actually transplanted during first CR. The median time between diagnosis and autologous BMT was 4.1 months (SD, 1.1). This interval appeared significantly longer than in the allogeneic BMT group (P < .05). This difference was related to the duration of phase II of the induction therapy. Five patients (4%) were considered as nonresponders and died of disease. Four patients (3%) died of early toxicity (infections, three cases; hemorrhage, one case). None of the various factors tested (age, sex, leukocyte count, immunology, Ph chromosome) was found to have a statistically significant influence on the CR rate.

**Table 2. Response, CCR, and DFS by Initial Factors**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>CR (%)</th>
<th>3-Year CCR (95% CI)</th>
<th>3-Year DFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>135</td>
<td>126 (93)</td>
<td>44 (35-54)</td>
<td>36 (28-45)</td>
</tr>
<tr>
<td>HLA-identical sibling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>77</td>
<td>28 (17-39)</td>
<td>26 (18-37)</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>43</td>
<td>63 (67-92)*</td>
<td>68 (51-80)*</td>
<td></td>
</tr>
<tr>
<td>Age (yr) &lt; 35</td>
<td>82</td>
<td>77 (94)</td>
<td>45 (33-57)</td>
<td>38 (28-50)</td>
</tr>
<tr>
<td>≥35</td>
<td>53</td>
<td>49 (92)</td>
<td>44 (28-60)</td>
<td>32 (20-47)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>98</td>
<td>82 (93)</td>
<td>44 (32-57)</td>
<td>36 (26-47)</td>
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<tr>
<td>F</td>
<td>47</td>
<td>44 (94)</td>
<td>44 (28-60)</td>
<td>36 (23-51)</td>
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<td>Leukocyte count/L</td>
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<td>&lt;3 x 10^9</td>
<td>88</td>
<td>83 (94)</td>
<td>50 (38-62)</td>
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<td>≥3 x 10^9</td>
<td>47</td>
<td>43 (92)</td>
<td>33 (19-52)</td>
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<td>Immunology</td>
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<tr>
<td>B-ALL</td>
<td>93</td>
<td>85 (91)</td>
<td>33 (23-45)</td>
<td>28 (19-39)</td>
</tr>
<tr>
<td>T-ALL</td>
<td>33</td>
<td>32 (97)</td>
<td>68 (48-84)*</td>
<td>54 (35-71)*</td>
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<tr>
<td>Ph+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>67</td>
<td>63 (94)</td>
<td>52 (38-66)</td>
<td>43 (30-56)</td>
</tr>
<tr>
<td>Y</td>
<td>20</td>
<td>17 (85)</td>
<td>8 (0-44)*</td>
<td>6 (0-27)*</td>
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<td>No. of courses to CR</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>114</td>
<td>45 (35-55)</td>
<td>40 (31-60)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>37 (11-70)</td>
<td>25 (7-57)</td>
<td></td>
</tr>
</tbody>
</table>

* P < .001.
† P < .01.
‡ P < .05.

After phase II of the induction therapy, five patients (4%) were considered as nonresponders and died of disease. Four patients (3%) died of early toxicity (infections, three cases; hemorrhage, one case). None of the various factors tested (age, sex, leukocyte count, immunology, Ph chromosome) was found to have a statistically significant influence on the CR rate.

**HLA Typing**

The flow chart of the 135 enrolled patients is shown in Fig 2. An HLA typing was scheduled during the induction phase (after phase I or at the end of phase II) for all patients in CR. Six patients (5% of CR patients) were not typed for the following reasons: toxic death, two cases; early relapse, three cases; patient refusal, one case. Thus, of the 120 patients (90% of all enrolled patients) assessable for the first genetic randomization, 43 were found to have an HLA-identical sibling (36% of patients assessable for the first genetic randomization and 32% of all enrolled patients), while 77 patients did not have an HLA-identical sibling (64% of patients assessable for the first genetic randomization and 57% of all enrolled patients).

**HLA-Identical Sibling Group Versus No HLA Identical Sibling Group**

As shown in Table 1, initial patient characteristics of each group were similar, and no significant differences were found with regard to age, sex, leukocyte count, immunology, or Ph chromosome. The proportion of patients achieving CR within 4 weeks was also similar between the two groups.

In the HLA-identical sibling group (n = 43), with a median follow-up of survivors of 30.3 months from CR, the 3-year probabilities of CCR and DFS were 83% (95% confidence interval [CI], 67% to 92%) and 68% (95% CI, 51% to 80%), respectively (Table 2 and Fig 3). In this group, 2 of 43 patients did not receive allogeneic BMT because of early relapse. Forty-one patients were actually transplanted during first CR (n = 39) or early untreated relapse (n = 2). The median time between CR and allogeneic BMT was 3.1 months (SD, 1.1). Five transplant-related deaths (12%) occurred during the procedure (graft-versus-host disease, four cases; aspergillosis, one case). The incidence of severe acute graft-versus-host disease (grade 2 to 4) was 37% (15 of 41 patients), and 6 of 36 (17%) patients developed an extensive chronic graft-versus-host disease. With a median follow-up of survivors of 27 months from allogeneic BMT, five (12%) relapses occurred. The 3-year post-allogeneic BMT probabilities of CCR and DFS were 87% (95% CI, 71% to 95%) and 71% (95% CI, 54% to 83%), respectively.

In the no HLA-identical sibling group (n = 77), with a median follow-up of survivors of 29.1 months from CR, the 3-year probabilities of CCR and DFS were 28% (95% CI, 17% to 39%) and 26% (95% CI, 16% to 37%), respectively, which appeared significantly lower than in the HLA-identical sibling group (P < .001; Table 2 and Fig 3). In this group, 13 of 77 (17%) patients did not receive autologous BMT (early relapse, 11 cases; toxic death, one case; and patient refusal, one case). Sixty-four patients were actually transplanted during first CR. The median time between diagnosis and autologous BMT was 4.1 months (SD, 1.1). This interval appeared significantly longer than in the allogeneic BMT group (P < .05). This difference was related to the duration of the induction therapy. Five patients (4%) were considered as nonresponders and died of disease. Four patients (3%) died of early toxicity (infections, three cases; hemorrhage, one case). None of the various factors tested (age, sex, leukocyte count, immunology, Ph chromosome) was found to have a statistically significant influence on the CR rate.

**Fig 2. Flow chart of enrolled patients (pts).**
Fig 3. DFS was significantly superior \( (P < .001) \) for patients with an HLA-identical sibling \( (---) \) than for patients without an HLA-identical sibling \( (-) \).

of interval therapy: a median of two courses of methotrexate and aracytine were administered before allogeneic BMT versus three before autologous BMT (see Patients and Methods). One transplant-related death (2\%) occurred during this procedure. With a median follow up of survivors of 25 months from autologous BMT, 40 (62\%) relapses occurred. The 3-year post-autologous BMT probabilities of CCR and DFS were similar, 30\% (95\% CI, 19\% to 44\%), and significantly lower than after allogeneic BMT \( (P < .001) \).

IL-2 After Autologous BMT

Sixty-four patients were actually treated with autologous BMT. Four of them were excluded from the IL-2 randomization before BMT for the following reasons: patient refusal, two cases, bilirubin greater than 1.5 N, one case; and history of cardiac rhythm disturbance during induction phase, one case. Thus, 60 patients were randomized to receive \( (n = 30) \) or not to receive \( (n = 30) \) IL-2 after autologous BMT.

As shown in Table 1, patient characteristics of each group were similar, and no significant differences were found with regard to age, sex, initial leukocyte count, immunology, Ph chromosome, and proportion of patients achieving CR within 4 weeks. The median interval between CR and autologous BMT was also similar: 4.3 months in the IL-2+ group (SD, 1), versus 4.1 months in the IL-2− group (SD, 0.6). The median numbers of nucleated cells in the grafts were comparable: \( 3.2 \times 10^8/kg \) (SD, 1.3) in the IL-2+ group versus \( 3.4 \times 10^8/kg \) (SD, 1.4) in the IL-2− group.

When considering the 30 patients randomized in the IL-2+ group versus the 30 patients randomized in the IL-2− group (intention-to-treat analysis), no significant difference was observed with regard to median CR duration (7 months \( \pm \) 10 months, respectively), 3-year post-autologous BMT probability of CCR (29\% [95\% CI, 15\% to 49\%] \( v \) 27\% [95\% CI, 10\% to 71\%], respectively; Fig 4), and 3-year post-autologous BMT probability of survival (28\% [95\% CI, 13\% to 50\%] \( v \) 36\% [95\% CI, 10\% to 71\%, respectively).

Only 22 of 30 patients (73\%) randomized in the IL-2+ group were actually treated with IL-2. The reasons for exclusion were early relapse (four cases), delay in hematologic reconstitution (two cases), abnormal hepatic function (one case), and patient refusal (one case). The median time between autologous BMT and IL-2 administration was 2.6 months (SD, 1). The mean number of days on IL-2 was 11 (range, 7 to 13 days): 15 patients received IL-2 for the total planned duration of 13 days (cycles 1 through 5), four patients received IL-2 for 9 days (cycles 1 through 3), and three patients received IL-2 for 7 days (cycles 1 and 2; see Patients and Methods). When considering the 22 patients actually treated with IL-2 versus the 28 patients of the IL-2− group remaining in CR 2 months after autologous BMT, no significant differences were observed with regard to 3-year post-autologous BMT probability of CCR (38\% [95\% CI, 19\% to 62\%] \( v \) 30\% [95\% CI, 12\% to 54\%], respectively) and 3-year post-autologous BMT probability of survival (37\% [95\% CI, 16\% to 64\%] \( v \) 38\% [95\% CI, 11\% to 74\%], respectively).
Overall Results

Patients have now been observed for 13 to 47 months after diagnosis (median, 32 months). During follow up, 77 of 135 patients died. The median survival time was 22 months, and the probability of being alive at 3 years from diagnosis was 39% (95% CI, 30% to 49%). At the time of analysis, 63 of the 126 patients who reached CR had relapsed. The 3-year probabilities of CCR and DFS for patients achieving CR were 44% (95% CI, 35% to 54%) and 38% (95% CI, 30% to 48%), respectively. Table 2 summarizes the variables tested as prognostic factors for DFS. In univariate analysis, three factors were found to be significantly associated with a longer DFS: T-ALL (v non-T-ALL; P < .05), no Ph chromosome (v Ph+; P < .001), and HLA-identical sibling (v no HLA-identical sibling; P < .001). In multivariate analysis, two variables were found to enter the regression model at a significant level: no Ph chromosome (P < .01) and HLA-identical sibling (P < .01).

DISCUSSION

The combination of vincristine and prednisone has been demonstrated to produce a CR rate of approximately 60% in adult ALL. Several pilot studies have suggested that the addition of an anthracycline to the vincristine-prednisone regimen may increase the CR rate to 80%, which was definitively demonstrated in a randomized trial. Many attempts have been made to intensify induction regimens by adding other agents to this standard vincristine-prednisone-anthracycline regimen, such as cyclophosphamide, asparaginase, aracytine, and 6-mercaptopurine. The actual benefit of such intensive induction chemotherapy has not been established, but the German BFM group using such an approach reported one of the most favorable CR rates and remission duration in a large cohort of unselected adult ALL. Our trial using the BFM regimen confirmed these results, as 93% of enrolled patients achieved CR. In our study, patients aged over 55 years were excluded. Whether the high CR rate we observed, was related to multidrug combination induction or to age selection remains to be answered.

Experience in allogeneic BMT for adult ALL is extensive. Experience in allogeneic BMT for adult ALL is extensive. However, there is some evidence that fractionated TBI is associated with a reduction in transplant-related mortality as compared with single-dose TBI, which led to the use of a fractionated TBI in this study. We also applied a strategy of early BMT after CR (median, 3 months) to avoid pre-BMT organ injury due to prolonged exposure to antileukemic agents, which is potentially responsible for increased toxicity after BMT. We found a low mortality rate of 12% associated with a relapse rate of 12%, resulting in a 3-year post-allogeneic BMT probability of leukemia-free survival of 71% (95 CI, 54% to 83%). These results compare favorably with previous reports and strongly suggest that allogeneic BMT prepared with the standard cyclophosphamide-TBI regimen and applied early after a BFM induction regimen should be evaluated in future prospective trials.

An important objective of this trial was to compare DFS of patients treated with allogeneic or autologous BMT as consolidation treatment of first CR. Different investigators have reported impressive results obtained by autologous BMT in first CR for adult ALL, with a 3-year DFS of greater than 50%. A multicentric retrospective study of 233 patients autografted in first CR reported similar results, with a 5-year DFS probability of 40%. These results suggested that the probabilities of DFS observed after allogeneic and autologous BMT were overlapping. However, direct comparison of different transplant series is unsatisfactory, as patient selection for BMT is subject to considerable bias, including differences in age selection and risk factors of relapse. An additional source of bias is the proportion of patients achieving CR but finally excluded from BMT for poor performance status, organ failure, severe infection, or early relapse. Indeed, a high exclusion rate might lead to apparently increased survival after BMT. Our trial was designed to avoid these sources of bias in comparing allogeneic and autologous BMT. Only patients aged less than 55 years with de novo ALL in first CR after the same induction regimen were included in this trial. All patients were HLA-typed, and according to the results of this genetic randomization, were intended to receive allogeneic or autologous BMT, with the results being analyzed on an intention-to-treat basis to avoid the time-to-treatment bias. Our study demonstrates that patients with an HLA-identical sibling have a significantly higher 3-year DFS than patients without an HLA-identical sibling (68% v 26%; P < .01). However, in our trial, the results of the autologous BMT arm appear disappointing as compared with those previously reported.
The reasons for this discrepancy remain unclear. Differences in patient selection is a possible explanation. In most previously reported series, the exclusion rate for autologous BMT of patients achieving CR is unknown, as only results of patients actually transplanted were reported. In an M.D. Anderson Cancer Institute study, autologous BMT was intended to be systematically performed 8 months into CR. Of 79 patients achieving CR, only 26 (33%) underwent autologous BMT, and the 3-year CCR rate was 60%. Fiere et al reported the results of a French multicentric, randomized trial comparing autologous BMT versus conventional chemotherapy. Among 262 patients aged less than 50 years and achieving CR, 191 (73%) patients were randomized. Of the 95 patients randomized to receive autologous BMT, only 63 (66%) were actually transplanted. Thus, the total exclusion rate was 32% for patients achieving CR, and the 3-year DFS was 51% after autologous BMT. In our trial, all patients in CR without an HLA-identical sibling were analyzed on an intention-to-treat basis. This absence of exclusion might be responsible for the poor results we observed in the non-HLA-identical sibling group. Another possible explanation for these results was the use of an unpurged graft in our autologous BMT procedure. Graft contamination with leukemic cells may be a contributive source of relapse after autologous BMT. Several studies have evaluated bone marrow purging and reported encouraging results in ALL. None, however, clearly demonstrates the superiority of ex vivo treatment of bone marrow. Also, the purging strategies shown to eliminate most mature leukemic cells may not affect the progenitor leukemic cells. Using a purged graft, Fiere et al recorded 35 (56%) relapses among the 63 patients autografted in first CR. Using the same conditioning regimen but an unpurged graft, we reported 40 (62%) relapses among the 64 patients actually grafted in first CR. These results suggest that the impact of bone marrow purging, if any, is only marginal in prevention of relapse after autologous BMT.

Our results demonstrate that allogeneic BMT is superior to autologous BMT as consolidation treatment of adult ALL. This study also suggests that unpurged autologous BMT is of limited interest in first CR and confirms the results of the French multicentric trial, demonstrating that patients randomized to receive conventional chemotherapy or autologous BMT have a comparable DFS. One major objective of this study was to estimate the impact of IL-2 on the post-autologous BMT CCR rate. Clinical and biologic observations have supported the use of IL-2 in the post-BMT setting. In relapsed acute leukemia, it has been suggested that IL-2 was all the more effective when the tumor mass was relatively small. Furthermore, in acute leukemia patients treated with IL-2, the degree of endogenous LAK cell generation appeared greater after autologous BMT than in nongrafted patients. Thus, the maximal reduction of blast cells induced by high-dose therapy, together with the relatively high numbers of circulating LAK precursors after BMT, could enhance the efficacy of IL-2. In a previous phase I study, we reported that an IL-2 dose of $12 \times 10^6$ IU/m$^2$/d (delivered by constant infusion, every other week, for a total of five cycles) was feasible without major toxicities and induced an intense stimulation of the immune system. Several pilot studies using various schedules of IL-2 administration confirmed these results. Thus, randomized trials were required to evaluate the efficacy of IL-2 in preventing relapse after autologous BMT for ALL. In our randomized trial, we did not observe a beneficial effect of IL-2. Indeed, the 3-year post-autologous BMT probability of CR was 29% (95% CI, 15% to 49%) in the IL-2 group versus 27% (95% CI, 11% to 50%) in the control group. In our trial, IL-2 was administered after hematologic recovery, at a median time of 2.6 months after BMT. The high early relapse rate we observed may suggest that earlier administration of IL-2 should be evaluated. This is further supported by evidence that, in mice, delay in IL-2 administration after syngeneic BMT was found to be associated with a decreased GVL effect. In our trial, a high dose of IL-2 was used over a period of 2 months. A recent study demonstrated that prolonged low-dose intravenous infusion was associated with minimal toxicity and marked immune activation. The role of such early administration of prolonged low-dose IL-2 should be evaluated in future prospective trials.

Finally, our study demonstrates that early allogeneic BMT after a BFM induction regimen is a highly effective consolidation treatment of adult ALL in first CR. We also report that, in this indication, IL-2 does not decrease the high relapse rate observed after autologous BMT. Previous reports suggested that acute myeloblastic leukemia (AML) patients could be more responsive to IL-2 therapy, both after chemotherapy and after autologous transplant.

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