Allogeneic Bone Marrow Transplantation for Leukemia With Marrow Grafts Depleted of Lymphocytes by Counterflow Centrifugation

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Eighty consecutive patients were transplanted with human leukocyte antigen (HLA)-identical sibling marrow for acute myelogenous leukemia (AML, N = 29), acute lymphoid leukemia (ALL, N = 23), or chronic myelogenous leukemia (CML, N = 28). Donor marrow was depleted of lymphocytes using counterflow centrifugation. Median age of the recipients was 31 years. Pretransplant conditioning consisted of cyclophosphamide and fractionated total body irradiation (TBI) with a low (4.1 ± 0.3 cGy/min) or high (13.1 ± 1.6 cGy/min) midline average dose rate. In 43 patients, cytosine-arabinoside or anthracyclines were added to the conditioning regimen. Immunosuppression posttransplant consisted of methotrexate (MTX) alone, cyclosporine A (CsA) in combination with MTX, or CsA alone: two patients received no immunosuppression at all. Graft failure occurred in 4 of 77 evaluable patients (5%). The probability of acute graft-versus-host disease (GVHD) ≥ grade 2 at day 100 after transplantation was 15%. The projected 3-year estimate of extensive chronic GVHD was 12%. Only three patients died of cytomegalovirus-interstitial pneumonitis. The projected 3-year probability of relapse was 30% (95% confidence interval [CI], range 8% to 53%) in transplants for AML in complete remission (CR1), 36% (95% CI, 1% to 69%) after transplantation for ALL in CR1, and 38% (95% CI, 2% to 74%) after transplantation for CML in first chronic phase (CP1). The projected 3-year probability of leukemia-free survival (LFS) was 56% (95% CI, 35% to 77%) after transplantation for AML-CR1, 42% (95% CI, 16% to 69%) in patients transplanted for ALL-CR1, and 49% (95% CI, 18% to 80%) after transplantation for CML-CR1. After transplantation for AML-CR1, ALL-CR1, or CML-CR1, the median follow-up time for leukemia-free survivors was 31+, 30+, and 21+ months, respectively. Probabilities of relapse, survival, and LFS in AML-CR1 and ALL-CR1 transplants were comparable with those reported in recipients of untreated grafts. In patients transplanted for CML-CR1, probability of relapse was higher and probability of LFS was lower than in recipients of untreated grafts. In transplants for leukemia in CR1 and CP1, preparative regimen and immunosuppression posttransplant were not associated significantly with the probability of acute GVHD ≥ grade 2, extensive chronic GVHD, relapse, survival, or LFS. In bone marrow transplantation for leukemia, counterflow centrifugation is a useful technique for the prevention of GVHD. In transplants for leukemia in CR1 and CP1 receiving T-cell-depleted grafts using counterflow centrifugation, probability of survival and LFS can compete with that reported in studies from the literature on recipients of untreated marrow. Further efforts should be made to reduce relapse rate, particularly in CML transplants.

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patients received total body irradiation (TBI) in two equal fractions of 450 cGy each on days -2 and -1 using an 18 MV photon beam linear accelerator (Saturne, CGR, Buc, France) with a midline average dose-rate of 4.1 ± 0.3 cGy/min in 50 patients, and 13.1 ± 1.6 cGy/min in 30 patients. Lungs and eyes were shielded using individually adapted lead blocks. The corrected mean total lung dose was 790 ± 130 and 710 ± 80 cGy for the patients with the lower and higher midline average dose-rate, respectively. Donor marrow was infused 24 hours after completion of TBI.

Immunophrophylaxis. Immunophrophylaxis posttransplant was omitted in two patients. Since GVHD grade 3 occurred in both patients, nine recipients received methotrexate (MTX) according to the Seattle regimen. As soon as cyclosporine A (CsA) became available, CsA was added: 30 consecutive patients received both CsA and MTX. CsA (3 mg/kg body weight/d) was given by continuous IV infusion on days -1 to +28, followed by CsA (9 mg/kg body weight/d) orally, with a gradual tapering off after 6 weeks and discontinuation after 12 weeks. Weekly IV injections of MTX were given from week 5 onward, starting with 2.5 mg/m² and weekly increments of 2.5 mg/m² until a dose of 10 mg/m² was reached. MTX treatment was discontinued in week 16 after BMT. Since MTX delayed engraftment, it was omitted and the next 39 consecutive recipients received CsA alone, 3 mg/kg body weight/d by continuous IV infusion from days -1 to +14, followed by 2 mg/kg body weight/d continuous IV on to day +21. From day +21 onward, CsA was given orally in a dose of 6 mg/kg body weight/d to 12 weeks after BMT, followed by a gradual tapering off and discontinuation after 16 weeks postgrafting. All patients were managed in single rooms with filtered air under positive pressure throughout the transplantation period inside the hospital, and all received oral selective gut decontamination, as well as co-trimoxazole for Pneumocystis carinii prophylaxis. Engraftment. The first day of engraftment was the first of 3 consecutive days with peripheral white blood cell (WBC) counts of ≥1.0 × 10⁹/L. Engraftment was proven by the presence of donor-type erythrocytes; from 6 months after BMT onward sustained engraftment was also documented by cytogenetic analysis and by studies of restriction fragment length polymorphisms (RFLPs).

Statistics. Analyses were performed using the Kaplan-Meier product-limit method. Actuarial curves were calculated for acute GVHD ≥ grade 2, extensive chronic GVHD, relapse, survival, and leukemia-free survival (LFS). The effect of diagnosis on the curves was compared using the log rank test and Wilcoxon test. P values < .05 were considered significant. For a particular diagnosis, effect of preparative regimen and immunophrophylaxis posttransplant on the curves could not be studied in multivariate analysis: the number of patients in the categories was too small. For all diagnoses in CR1 and CP1 together, however, effect of preparative regimen and immunophrophylaxis posttransplant on the curves for acute GVHD ≥ grade 2, extensive chronic GVHD, relapse, survival, and LFS was studied in univariate and multivariate analysis. Variables in preparative regimen conditioning and immunophrophylaxis posttransplant, evaluable in more than 10 patients, were examined. These variables were the lower or higher midline average dose rate of TBI, conditioning with or without anthracyclines, and immunophrophylaxis with MTX + CsA or CsA alone. Association of these variables with the incidence of mixed chimerism was studied in univariate and multivariate analysis using the Chi-square test. Follow-up ends on date of evaluation (February 1, 1989).

RESULTS

Primary engraftment. Three patients died within 22 days after transplantation and are not evaluable for engraftment. Two patients died at 37 and 44 days without proof of engraftment. Seventy-five patients showed WBC engraftment at 7 to 47 (median, 19) days after BMT.

Rejection of the marrow graft. Two of the seventy-five patients showing engraftment rejected their graft at 2 and 6 months after transplantation. Since the first patient, transplanted for AML-CR1, had no marker specific for donor-type red blood cells, red cell phenotyping could not be used for the demonstration of donor-type erythrocytes; cytogenetic analysis or studies with RFLPs were not performed. The patient died at day 103 after BMT. In the second recipient, transplanted for CML-CP1, donor-type red blood cells had not appeared by 6 months after BMT and could not be demonstrated at several occasions until end of evaluation, 4 years after BMT. Cytogenetic analysis of bone marrow revealed host-type cells only in determinations from 6 to 48 months after BMT onward, but repeatedly, 4% of peripheral blood lymphocytes were still of donor-type. Using RFLPs, persisting mixed chimerism of peripheral blood lymphocytes was confirmed on several occasions. Despite the reappearance of the Philadelphia chromosome, the patient never showed hematological evidence of relapse.

Graft failure. Graft failure, defined as failure of primary engraftment and early or late rejection of the graft, occurred in 4 of 77 patients (5%).

GVHD. Eleven of seventy-five patients at risk had acute GVHD ≥ grade 2 (seven recipients had grade 2; three patients, grade 3; and one recipient, grade 4). Among them were the two patients who did not receive immunophrophylaxis posttransplant. The probability of acute GVHD ≥ grade 2 at day 100 after BMT was 15% (95% confidence interval [CI], range 7% to 23%). Sixteen of sixty-three evaluable patients developed chronic GVHD with an extensive manifestation in seven. The 3-year probability of extensive GVHD was 12% (95% CI, 4% to 21%). For acute and extensive chronic GVHD, no significant differences were found in patients transplanted for AML-CR1, ALL-CR1, or CML-CP1. In two cases, extensive chronic GVHD was preceded by acute GVHD ≥ grade 2.

Causes of death. Thirty-five of the eighty patients (44%) died at 8 to 1,360 (median, 114) days after BMT. The principal causes of death are shown in Table 1. Three patients died from cytomegalovirus-interstitial pneumonitis.

Relapse. Seven patients transplanted for AML (N = 29) relapsed at 3 to 15 (median, 6) months after BMT. After transplantation for ALL (N = 23), five patients relapsed at 1 to 32 (median, 5) months after BMT. Seven patients relapsed after transplantation for CML (N = 28): relapse occurred at 6 to 32 (median, 19) months after BMT. The projected 3-year probability of relapse for the different diagnoses and for the patients transplanted in CR1 or CP1 is shown in Table 2. Actuarial relapse curves for AML-CR1, ALL-CR1, and CML-CP1 are depicted in Fig 1. No significant differences were found for the probability of
relapse in patients transplanted for AML-CR1, ALL-CR1, or CML-CP1.

Probability of survival. Sixteen patients transplanted for AML survived for 4+ to 84+ (median, 31+) months; 12 transplants for ALL survived for 7+ to 61+ (median, 26+) months; and 17 patients transplanted for CML survived for 14+ to 59+ (median, 23+) months after BMT. The projected 3-year probability of survival for the different diagnoses and for the patients transplanted in CR1 or CP1 is shown in Table 2; survival curves for AML-CR1, ALL-CR1, and CML-CP1 are given in Fig 2. No significant differences were found for the probability of survival in patients transplanted for AML-CR1, ALL-CR1, or CML-CP1.

Probability of LFS. All 12 patients who relapsed after transplantation for AML or ALL died at 33 to 464 (median, 43) days after relapse occurred, respectively. Four of seven patients with a relapse after transplantation for CML died at 103 to 591 (median, 306) days after diagnosis of relapse. Three are alive at 49 to 663 (median, 638) days after relapse occurred. The projected 3-year probability of LFS for the different diagnoses and for the patients transplanted in CR1 or CP1 is shown in Table 2; survival curves for AML-CR1, ALL-CR1, and CML-CP1 are depicted in Fig 3. No significant differences were found for the probability of LFS in patients transplanted for AML-CR1, ALL-CR1, or CML-CP1.

Table 2. Projected 3-Year Probability of Relapse, Survival, and LFS in Patients Transplanted for AML, ALL, and CML

<table>
<thead>
<tr>
<th>Indication/N</th>
<th>% Probability (Range)*</th>
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<tbody>
<tr>
<td></td>
<td>Relapse</td>
</tr>
<tr>
<td>AML All cases/29</td>
<td>36 (14-59)</td>
</tr>
<tr>
<td>CR1/26</td>
<td>30 (8-53)</td>
</tr>
<tr>
<td>ALL All cases/23</td>
<td>36 (7-64)</td>
</tr>
<tr>
<td>CR1/17</td>
<td>35 (1-69)</td>
</tr>
<tr>
<td>CML All cases/28</td>
<td>57 (24-90)</td>
</tr>
<tr>
<td>CP1/19</td>
<td>38 (2-74)</td>
</tr>
</tbody>
</table>

*95% confidence interval.

Hematopoietic chimerism. In the present study, hematopoietic chimerism was assessed at 6 months after BMT using red blood cell phenotyping, cytogenetic analysis, and RFLPs as described previously.20 Fifty-one patients with a follow-up of 6 months or more did not relapse within 6 months after transplantation. At 6 months after BMT, 31 (61%) had mixed chimeras and 20 (39%) were complete donor chimeras (Table 3). Follow-up of the 31 mixed chimeras was 6+ to 61+ (median, 24+) months; 5 (16%) relapsed at 12 to 32 (median, 24) months after BMT. Follow-up of the 20 complete donor chimeras was 6+ to 84+ (median, 20+) months; six (30%) relapsed at 6 to 32 (median, 9) months posttransplant. Similar to our previous analysis on mixed chimerism, no relationship between mixed chimerism and relapse after BMT was observed.20 In univariate and multivariate analysis, pretransplant conditioning and immunoprophylaxis posttransplant were not associated significantly with the incidences of mixed chimerism (data not shown).

Variables examined for association with acute GVHD ≥ grade 2, extensive chronic GVHD, relapse, survival, and LFS in patients transplanted for leukemia in CR1 and CP1. Although not significant in univariate analysis, the probabilities of GVHD ≥ grade 2, extensive chronic GVHD, survival, and LFS were higher in patients irradiated with the higher midline average dose rate, in patients prepared with anthracyclines, and in patients who received CsA alone as immunoprophylaxis posttransplant (Tables 4 and 5). In multivariate analysis, the lowest probabilities of relapse and the highest probabilities of acute GVHD ≥ grade 2, extensive chronic GVHD, survival, and LFS were found in patients conditioned with both the higher midline average dose rate and anthracyclines and who received CsA alone as immunoprophylaxis posttransplant (data not shown). However, differences were not significant.

DISCUSSION

Acute GVHD is one of the major complications of allogeneic bone marrow transplantation. The incidence and severity of acute GVHD is decreased when the graft is depleted of lymphocytes before BMT. Several techniques have been developed for ex vivo elimination of T lymphocytes. These include antibody-mediated elimination,10,23-30 and physical like counterflow centrifugation.12 In the present study, the probability of acute GVHD ≥ grade 2 at day 100 after BMT was 15%. This compares favorably with the (actuarial) incidence of 39% to 82% in recipients of HLA-identical, unmanipulated grafts.22,25,27,31 In studies on HLA-identical, T cell-depleted transplants, (actuarial) incidence of acute GVHD ≥ grade 2 varied from 0 to 50%,22,29,31,32 The patients in the different studies, however, are not comparable with regard to risk factors for acute GVHD, such as pretransplant diagnosis,33 older age of the recipient,26,33,34 sex-mismatch,33,34 and immunoprophylaxis posttransplant.34 Furthermore, in recipients of T cell-depleted grafts, the number of T cells infused can be factors of risk.26,32,35-39

In the present study, the 2-year probability of chronic GVHD and its extensive manifestation was 25% and 12%, respectively.
BMT WITH LYMPHOCYTE-DEPLETED GRAFTS

Fig 1. Probability of relapse in patients transplanted for AML-CR1, ALL-CR1, and CML-CP1. Tick marks in the relapse curves denote leukemia-free survivors.

respectively. Chronic GVHD occurred in 39% to 62% of recipients of HLA-identical, unmanipulated grafts, with an extensive manifestation in 35% to 54% of cases. In HLA-identical, T cell-depleted transplants, these percentages varied from 0 to 30% and from 0 to 11%, respectively.

Lymphocyte depletion of the marrow graft is associated with a higher incidence of graft failure: graft failure occurred in 0 to 35% of HLA-identical, T cell-depleted transplants and in 0 to 1% of recipients of HLA-identical, unmanipulated marrow. In recipients of T cell-depleted grafts, an immunologic advantage is created for the host resulting in a higher risk of graft failure. In order to prevent this, additional pretransplant immunosuppression of the host is required. This can be achieved by in vivo application of monoclonal antibodies directed against conditioning regimen surviving host-immunocompetent cells, by application of a higher total dose of fractionated TBI, or by TBI in a single dose. Certain donor derived T cells or their products can facilitate engraftment by suppressing residual host cells and/or by promoting hematopoietic stem cell growth. This can be accomplished by infusion of irradiated donor buffy coat after BMT. In the present study, graft failure occurred in 5% of patients. Two mechanisms may be responsible for this low incidence: the number of T cells left in the graft and the relatively high midline average dose rate in 50 patients.

Lymphocyte depletion of the marrow graft is associated with a higher relapse rate: after transplantation for leukemia in CR1 or CP1, probability of relapse varied from 17% to

Fig 2. Probability of survival in transplants for AML-CR1, ALL-CR1, and CML-CP1. Tick marks in the survival curves denote patients who are alive. Arrows identify the three CML patients who are alive with a relapse after BMT.
60% in recipients of HLA-identical, T cell-depleted grafts. In the present study, the projected 3-year probability of relapse after transplantation for AML-CR1, ALL-CR1, or CML-CP1 was 30%, 35%, and 38%, respectively. Differences in relapse rate between transplants with and without GVHD, suggest that GVHD is associated with an antileukemic effect. Butturini and Gale reported on a novel antileukemic mechanism after transplantation for CML in chronic phase: recipients of T cell-depleted, HLA-identical transplants had a higher incidence of relapse than syngeneic transplants, suggesting that the removal of immune cells, probably T cells, is responsible for a higher relapse rate. Slavin et al observed a severe suppression of the generation of interleukin-2-induced cytotoxic lymphocytes against natural killer (NK)-resistant and NK-sensitive target cells after pretreatment of human bone marrow cells with Campath-1M. An analysis of the International Bone Marrow Transplant Registry (IBMTR) showed that recipients of T cell-depleted marrow without GVHD had a 2-year probability of relapse of 54%, which was higher than the 22% observed in patients receiving unmanipulated grafts without GVHD. Simultaneously with T cell-depletion, cells with antileukemic activity producing antileukemic factors may be eliminated.

Attempts to decrease leukemic relapse after T cell-depletion include intensification of the pretransplant regimen, infusion of irradiated donor buffy coat after BMT, omission of immunosuppressive drugs posttransplant, and the enhancement of donor- or host-derived NK and lymphokine-activated killer (LAK) function. In our patients, preliminary data suggest that intensification of the conditioning regimen with anthracyclines may reduce leukemia relapse.

In transplants for leukemia in CR1 or CP1, the probability of LFS varied from 29% to 74% in recipients of HLA-identical, unmanipulated grafts and from 37% to 74% in recipients of HLA-identical, T cell-depleted grafts. In the present study, the projected 3-year probability of relapse after transplantation for AML-CR1, ALL-CR1, or CML-CP1 was 30%, 35%, and 38%, respectively.

### Table 3. Number of Mixed Chimeras and Complete Donor Chimeras at 6 Months Posttransplant. Number and Occurrence of Relapses and Follow-up of Patients in Continuous Complete Remission

<table>
<thead>
<tr>
<th></th>
<th>Mixed Chimera</th>
<th>Complete Donor Chimera</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (%)</td>
<td>31 (61)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Relapses (%)</td>
<td>5 (16)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Occurrence of relapse: range (median)*</td>
<td>12-32 (24)</td>
<td>6-32 (9)</td>
</tr>
<tr>
<td>Follow-up patients in CCR: range (median)*</td>
<td>6-61 (24)</td>
<td>6-84 (20)</td>
</tr>
</tbody>
</table>

Table 4. Variables Examined for Association With the Probability of Acute GVHD ≥ Grade 2 and Extensive Chronic GVHD in Univariate Analysis of Patients Transplanted for Leukemia in CR1 and CP1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute GVHD ≥ Grade 2</th>
<th>Extensive Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td>12 (1-24)</td>
<td>12 (0-24)</td>
</tr>
<tr>
<td>HDR (N = 25)</td>
<td>24 (7-41)</td>
<td>21 (2-40)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without (N = 32)</td>
<td>14 (1-27)</td>
<td>13 (0-27)</td>
</tr>
<tr>
<td>With (N = 30)</td>
<td>21 (6-35)</td>
<td>18 (2-34)</td>
</tr>
<tr>
<td>Immunophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX + CsA (N = 21)</td>
<td>10 (0-24)</td>
<td>11 (0-26)</td>
</tr>
<tr>
<td>CsA alone (N = 31)</td>
<td>20 (6-34)</td>
<td>17 (1-33)</td>
</tr>
</tbody>
</table>

No significant associations were found. Probability for acute GVHD ≥ grade 2 was calculated at 100 days; for extensive chronic GVHD, projected at 3 years after BMT (corrected for patients at risk).

Abbreviations: LDR, TBI with the lower midline average dose rate; HDR, with the higher midline average dose rate. *95% CI.
BMT WITH LYMPHOCYTE-DEPLETED GRAFTS

In a recent study from the IBMTR on marrow grafts, Blood 19:2600, 1987, a preliminary report from the International Bone Marrow Transplant Registry. Transplant Proc 67:1302, 1986.

Table 5. Variables Examined for Association With the Projected 3-Year Probability of Relapse, Survival, and LFS in Univariate Analysis of Patients Transplanted for Leukemia in CR1 or CP1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Relapse</th>
<th>Survival</th>
<th>LFS</th>
<th>% Probability (Range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDR (N = 37)</td>
<td>35 (17-54)</td>
<td>51 (34-67)</td>
<td>45 (29-62)</td>
<td></td>
</tr>
<tr>
<td>HDR (N = 25)</td>
<td>36 (0-88)</td>
<td>78 (61-96)</td>
<td>52 (9-98)</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without (N = 32)</td>
<td>39 (19-59)</td>
<td>50 (32-67)</td>
<td>44 (27-61)</td>
<td></td>
</tr>
<tr>
<td>With (N = 30)</td>
<td>20 (0-49)</td>
<td>75 (59-91)</td>
<td>63 (37-89)</td>
<td></td>
</tr>
<tr>
<td>Immunophrophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX + CsA (N = 21)</td>
<td>33 (12-55)</td>
<td>62 (41-83)</td>
<td>57 (36-78)</td>
<td></td>
</tr>
<tr>
<td>CsA alone (N = 31)</td>
<td>24 (0-53)</td>
<td>76 (61-92)</td>
<td>60 (34-86)</td>
<td></td>
</tr>
</tbody>
</table>

No significant associations were found.
Abbreviations: LDR, TBI with the lower midline average dose rate; HDR, with the higher midline average dose rate.

*95% CI.

58% after transplantation with HLA-identical, T cell-depleted grafts. In a recent study from the IBMTR on HLA-identical BMT, 5-year probability of LFS after BMT for AML-CR1, ALL-CR1, or CML-CP1 was 48%, 43%, and 41%, respectively. The majority of these patients received unmanipulated marrow. In the present study, the 3-year projected LFS for AML-CR1, ALL-CR1, or CML-CP1 was 56%, 42%, and 49%, respectively. Median follow-up time for leukemia-free survivors after transplantation for AML-CR1, ALL-CR1, and CML-CP1 was 31+, 30+, and 21+ months, respectively.

In comparison with studies from the literature on recipients of untreated marrow, patients receiving T cell-depleted grafts using counterflow centrifugation have a lower incidence and severity of GVHD. The lower GVHD-related mortality is counterbalanced by an increase of graft failure and relapse. In the present study, the probability of survival and LFS after transplantation for leukemia in CR1 and CP1 can compete with that reported in studies from the literature on recipients of untreated grafts. Further efforts should be made to reduce relapse rate, particularly in CML transplants.

ACKNOWLEDGMENT

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