Unrelated Donor or Autologous Marrow Transplantation for Treatment of Acute Leukemia


High-dose chemoradiotherapy followed by marrow transplantation from an HLA-matched sibling donor is curative for patients with acute leukemia. Autologous marrow transplantation has been used with success for some patients without such a sibling. Alternatively, the option of performing a transplant from an HLA-matched unrelated donor has been made possible by the recent development of large registries of HLA-typed volunteers. The purpose of this study was to compare the outcomes for patients with advanced leukemia treated by unrelated or autologous marrow transplantation. Forty-three patients with acute myeloid or lymphoid leukemia were transplanted from a closely HLA-matched unrelated donor. Results were compared with those of a disease-, disease-stage-, and age-matched cohort of 77 patients treated with autologous marrow transplantation at the same institution during the same period. Myeloid reconstitution with peripheral granulocyte counts greater than 10^9/L was achieved in 93% of unrelated recipients and 70% of autologous recipients at a median of 24 and 36 days after transplantation, respectively (P = .0001). The cumulative proportions of patients discharged alive (79% v 77%) and times from transplant to first hospital discharge (35 v 34 days) were not different between unrelated and autologous recipients (P = .85). For patients transplanted in complete remission, relapse occurred after transplantation in 27% of the unrelated and in 55% of the autologous recipients (P = .08). For patients transplanted in relapse, the corresponding posttransplant relapse rates were 48% and 63%, respectively (P = .72). Forty percent of unrelated recipients and 28% of autologous recipients died in remission. Leukemia-free survivals were 33% for unrelated and 25% for autologous recipients transplanted in remission (P = .45), and 12% for unrelated and 5% for autologous recipients transplanted in relapse (P = .75). Unrelated donor transplants appear no less effective than autologous transplants to achieve long-term survival and may be more effective in eradicating leukemia in patients who have failed conventional chemotherapy. Further studies are warranted to assess the relative effectiveness of unrelated and autologous transplantation performed earlier in the course of the disease.

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A LLOGENIC MARROW transplantation is a curative form of treatment for patients with severe hematologic disorders, including acute myeloid (AML) and lymphoid leukemias (ALL). Because most patients in need of marrow grafts lack a suitably HLA-matched sibling donor, alternative marrow sources have been explored. Autologous marrow transplantation after high-dose chemoradiotherapy has been widely used as consolidation for patients with AML or high-risk ALL who achieve a complete marrow remission, but the optimal timing for autologous transplantation remains controversial. Some investigators, including ourselves, use autologous transplantation primarily for treatment of patients who have recurrent leukemia after an initial remission induced by chemotherapy. Autologous transplantation cannot be undertaken unless remission is achieved and marrow is stored, and success may be limited by the possible presence of malignant progenitors in the cryopreserved marrow. For these reasons, attempts have been made to use HLA partially compatible normal allogeneic donors. Disease-free survival after transplantation from HLA-haploidentical family members who differ for one HLA-A, B, or DRB1 locus of the nonshared haplotypes is similar to results with HLA-identical sibling donors, but such closely matched relatives are available only to 3% to 5% of patients. Survival is poor after transplants from HLA-haploidentical relatives incompatible for two or three HLA antigens. With the recent establishment of large registries of HLA-typed volunteers, we have begun exploring the efficacy of marrow transplantation from unrelated volunteer donors for treatment of patients with acute leukemia. Preliminary reports have shown that long-term survival can be achieved with HLA-compatible unrelated donor transplants.

We report here the results of marrow transplantation from unrelated volunteer marrow donors for treatment of acute leukemia at our institution and compare these results with those obtained in a matched cohort of patients transplanted with autologous marrow at the same institution during the same time period. Given the retrospective design of the study and the limited number of patients treated, this analysis is meant to provide an estimate of any differences between the two approaches. These data will be useful to physicians who are concerned about the acceptability of allocating patients in prospective clinical trials evaluating these therapeutic modalities.

MATERIALS AND METHODS

Patient selection. After the first patient with acute leukemia received an unrelated donor transplant at our institution in 1979, further unrelated transplants were performed until 1984, when registries of HLA-typed volunteers became available to provide HLA-compatible marrow donors to patients in need of a marrow transplant. Between October 1, 1984 and August 31, 1990, 224 patients with AML or ALL lacking a suitably matched relative donor were treated by marrow transplantation at the Fred Hutchinson Cancer Research Center (FHCRC): 60 patients received marrow from an HLA-matched unrelated volunteer donor and 164 patients received autologous marrow.

From the Division of Clinical Research, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA. Submitted August 16, 1993; accepted January 19, 1994. Supported by National Institutes of Health Grants No. CA 18029 and CA 18221.

Address reprint requests to Claudio Anasetti, MD, Fred Hutchinson Cancer Research Center, 1124 Columbia St, Seattle, WA 98104.

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Standard-risk patients referred in first marrow remission had autologous marrow stored for use in the event of leukemic relapse. First remission patients considered to be at high risk for marrow relapse because of a high blast count at diagnosis, Ph-positive disease, or extramedullary disease, and patients referred is second or subsequent marrow remission had marrow stored and were counseled to be transplanted immediately. At the discretion of the referring physician, some patients had an unrelated donor search started at the time of the autologous marrow storage with the intent of using the unrelated donor if a suitable donor was found by the time the patient needed the transplant. Patients with primary refractory disease, leukemia secondary to myelodysplasia, or chemotherapy-resistant leukemia at the time of referral were considered not to be candidates for autologous transplantation, and an unrelated donor search was initiated. The clinical characteristics of patients treated by unrelated or autologous marrow transplantation were not identical. The current study used a retrospective matched cohort design to minimize differences between patients selected for either unrelated or autologous transplantation. For each unrelated recipient we attempted to identify two autologous recipients as controls who were similar with respect to age (± 5 years), diagnosis of AML or ALL, and disease stage. Matching for disease stage was made within one of three categories: (1) first complete remission, (2) first relapse or second remission, or (3) second or third relapse or third remission. Three unrelated recipients treated for leukemia after primary induction failure or myelodysplasia were excluded from the analysis. The 2:1 matching for all three characteristics was successful for 34 unrelated recipients. Only one matched autologous control was identified for 9 unrelated recipients. We were unable to identify suitably matched controls for 14 unrelated recipients among the remaining 87 autologous patients. Two unrelated recipients had no matched autologous controls with respect to the age at transplant, and 12 unrelated recipients beyond second remission had no matched autologous controls with respect to diagnosis and disease stage. Thus, 43 patients transplanted from an unrelated volunteer donor were compared to a disease-, disease-stage-, and age-matched cohort of 77 patients transplanted with autologous marrow. Characteristics of the two groups did not differ significantly (Table 1). Relapse and survival at the date of the last contact were analyzed as of December 15, 1992. Median follow-up of surviving patients was 1,099 days in unrelated recipients (range, 721 to 2,516 days) and 1,131 days in autologous recipients (range, 741 to 2,588 days).

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Disease diagnosis</th>
<th>Unrelated Donor Transplant (n = 43)</th>
<th>Autologous Transplant (n = 77)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>25/18</td>
<td>52/25</td>
<td>.33</td>
</tr>
<tr>
<td><strong>Median age in years (range)</strong></td>
<td>19 (1-49)</td>
<td>20 (3-51)</td>
<td>.4</td>
</tr>
<tr>
<td><strong>Disease stage at transplant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st CR</td>
<td>2</td>
<td>2</td>
<td>.66</td>
</tr>
<tr>
<td>1st REL</td>
<td>4</td>
<td>9</td>
<td>.26</td>
</tr>
<tr>
<td>2nd CR</td>
<td>5</td>
<td>6</td>
<td>.41</td>
</tr>
<tr>
<td>2nd REL</td>
<td>5</td>
<td>3</td>
<td>.73</td>
</tr>
<tr>
<td>3rd CR</td>
<td>2</td>
<td>3</td>
<td>.56</td>
</tr>
<tr>
<td>3rd REL</td>
<td>2</td>
<td>2</td>
<td>.46</td>
</tr>
<tr>
<td><strong>Median day from last marrow CR to transplant</strong></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>for patients in CR (range)</td>
<td>160 (9-690)</td>
<td>98 (35-3,213)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete marrow remission; REL, relapse.

Extramedullary relapse. The remission number was defined by events in the marrow, and extramedullary relapses were not counted as separate relapses. The time interval from the last marrow remission to transplant did not consider intercurrent extramedullary relapses (Table 1). One unrelated recipient in first marrow remission and two in second remission each had a single central nervous system (CNS) relapse. Of 4 patients who received an autologous graft in first marrow remission, 2 patients had had CNS relapse and 2 patients had an extramedullary relapse involving CNS, testis, skin, and muscle. Six autologous recipients transplanted in second remission and 1 transplanted in third remission had experienced concurrent marrow and extramedullary involvement.

**Histocompatibility studies.** Testing for all patients and donors was performed by the Clinical Immunogenetics Laboratory at the FHCR. Typing for HLA-A and B antigens was performed according to the standard National Institutes of Health (NIH) two-stage microcytotoxicity assay. Antigens were assigned according to the standard World Health Organization (WHO) nomenclature. HLA-DR typing was performed using nylon-wool–purified B cells in a modified microcytotoxicity crossmatch assay. HLA-D region compatibility was defined by testing with HLA-D homozygous typing cells (HTC) in a standard HLA-D typing assay. Beginning in 1990, HLA-D specificities were assigned by DRB1 typing using sequence-specific oligonucleotide probe hybridization. Donor selection was based on HLA-A, B, and D matching. For patients less than 36 years of age, incompatibility for a single HLA locus was allowed if there was HLA-A or B disparity within a crossreactive group (eg, HLA-A23 and A24 or HLA-B7 and B27) or if there was HLA Dw or DRB1 disparity within the same DR type (eg, Dw4(DR4) v Dw14 (DR4), or DRB1*0401 (DR4) v DRB1*0402 (DR4)).

**Transplant procedure.** Patients were prepared for transplantation with regimens that varied according to the primary disease, the source of marrow, and the year of transplantation (Table 2). Allogeneic recipients who were incompatible for the donor for a major blood group (ABO) were treated by plasma exchange or immunoadsorption to decrease the titer of anti-A or anti-B antibody. Children received red blood cell-depleted bone marrow. Acute graft-versus-host disease (GVHD) prophylaxis for 41 of 43 allogeneic recipients was a combination of methotrexate (15 mg/m² administered on day 1, and 10 mg/m² on days 3, 6, and 11) plus cyclosporine (administered intravenously at 3 mg/kg/d, starting on day −1). When tolerated, oral cyclosporine (12.5 mg/kg/d) was substituted and was tapered by 5% per week after day 50 and discontinued on day 180 after transplantation, unless acute or chronic GVHD developed. T-cell depletion of the donor marrow was not used for GVHD prophylaxis in unrelated recipients. Autologous marrow was treated with 4-hydroperoxycyclophosphamide for patients (54%) with AML. Marrow was treated with B- or T-lymphocyte–specific monoclonal antibodies and complement in 16 patients (44%) with ALL.
ENGLISH

UNRELATED DONOR OR AUTOLOGOUS MARROW TRANSPLANTS

Table 2. Transplant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Unrelated Donor Transplant (n = 43)</th>
<th>Autologous Transplant (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median donor age in years (range)</td>
<td>39 (25-54)</td>
<td>—</td>
</tr>
<tr>
<td>Donor sex (M/F)</td>
<td>28/15</td>
<td>—</td>
</tr>
<tr>
<td>Donor HLA Matching</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HLA-A, B, D identical (%)</td>
<td>26 (61)</td>
<td>—</td>
</tr>
<tr>
<td>1 locus minor mismatch (%)</td>
<td>17 (39)</td>
<td>—</td>
</tr>
<tr>
<td>Purged marrow (%)</td>
<td>0</td>
<td>38 (49)</td>
</tr>
<tr>
<td>Disease status at the time of marrow harvest</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1st CR</td>
<td>—</td>
<td>37 (48)</td>
</tr>
<tr>
<td>2nd CR</td>
<td>—</td>
<td>37 (48)</td>
</tr>
<tr>
<td>3rd CR</td>
<td>—</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cy (120 mg/kg) + HF-TBI (13.2-14.4 Gy)</td>
<td>35 (83)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>VP16 (36-52 mg/kg) + Cy (67-104 mg/kg) + FTBI (12 Gy)</td>
<td>0</td>
<td>12 (15)</td>
</tr>
<tr>
<td>VP16 (80 mg/kg) + BCNU (600 mg/m²) + Cy (200 mg/kg)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Bu (6.9-8.8 mg/kg) + Cy (60-100 mg/kg) + FTBI (12 Gy)</td>
<td>0</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Bu (16 mg/kg) + Cy (200 mg/kg)</td>
<td>1 (2)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Bu (16 mg/kg) + Cy (120 mg/kg)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Cy (120 mg/kg) + TBI (10 Gy)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Cy (120 mg/kg) + FTBI (12 Gy)</td>
<td>2 (4)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Cy (120 mg/kg) + FTBI (15.75 Gy)</td>
<td>4 (9)</td>
<td>16 (22)</td>
</tr>
<tr>
<td>Cy (120 mg/kg/2d) + FTBI (16 Gy)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>GVHD prophylaxis</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MTX + CSP</td>
<td>41 (96)</td>
<td>—</td>
</tr>
<tr>
<td>MTX</td>
<td>1 (2)</td>
<td>—</td>
</tr>
<tr>
<td>CSP + prednisone</td>
<td>1 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Median no. of marrow cells transplanted × 10⁶/kg prior to purging (range)</td>
<td>4.07 (1.7-46.1)</td>
<td>3.08 (0.2-10.5)</td>
</tr>
</tbody>
</table>

Numbers in the columns refer to the number (percentage in parentheses) of patients in each group, unless otherwise specified.

Abbreviations: Cy, cytoxan; TBI, total body irradiation; FTBI, fractionated TBI; HFTBI, hyper-fractionated TBI; Bu, busulfan; VP16, etoposide; MTX, methotrexate; CSP, cyclosporine.

Evaluation of GVHD. Diagnosis and grading of acute and chronic GVHD followed conventional criteria. Patients who engrafted and survived longer than 100 days after transplantation were evaluated for occurrence of chronic GVHD.

Statistical methods. Comparisons of patient characteristics were based on χ², Fisher’s exact, or Wilcoxon rank-sum tests. Time to engraftment and disease-free survival were estimated using the method of Kaplan and Meier and comparisons were based on log-rank statistics. Allogeneic recipients were evaluated for the development of acute GVHD, with incidence estimated according to Kaplan and Meier. In evaluating the relapse rate, deaths from causes not directly associated with relapse were considered competing risk events. Similarly, for time to discharge from hospital, death before discharge was considered a competing risk. To account for these competing risks, cumulative incidence curves were used to describe these rates. P values were based on the method proposed by Pepe. In addition to comparing patients in the two matched cohorts, Cox proportional hazard models were used to further evaluate each event time endpoint occurring in the entire population of 224 patients to control for any potential effects of the incomplete matching. These results were entirely consistent with the primary analysis and are not shown here for brevity. Analyses were performed using the statistical package SAS/ULTRIX Version 6.07 (SAS Institute, Cary, NC). All P values presented are two-sided.

RESULTS

Engraftment. Forty of 43 unrelated recipients (93%) achieved a sustained granulocyte count greater than 10⁹/L at a median of 24 days after transplantation, and 54 of 77 autologous recipients (70%) did so at a median of 36 days (P = .0001, Fig 1). Autologous recipients with ALL exceeded 10⁶ granulocytes/L at a median 30 days after transplantation, whereas autologous recipients with AML did so at a median greater than 100 days. Three unrelated donor recipients (7%) died without achieving a granulocyte count of 10⁹/L, 10, 11, and 14 days, respectively, after transplantation. Twenty-three autologous recipients (30%) died without achieving a granulocyte count of 10⁹/L, 8 to 280 days (median, 38 days) after transplantation, 9 with leukemia in relapse and 14 in remission. Three additional autologous recipients who had initially achieved engraftment died after the granulocyte count had decreased to less than 10⁹/L. Marrow had been purged in 49% of autologous recipients who achieved a granulocyte count of ≥10⁹/L and in 48% of those who died with less than 10⁹ granulocytes/L.

Two unrelated recipients and 4 autologous recipients were treated with granulocyte-macrophage colony-stimulating factor (GM-CSF) from day 0 to 20, according to protocols designed to stimulate early recovery of granocytes. Two unrelated and 11 autologous recipients were treated with one to three courses of GM-CSF because of absolute neutrophil counts lower than 0.5 × 10⁹/L beyond day 21 after transplant. Improvement in the granulocyte count occurred for both unrelated and for 7 of the 11 autologous recipients. No unrelated recipient rejected the first graft or received a second marrow infusion. In contrast, 4 patients received a back-up autologous marrow infusion 32, 33, 38, and 69 days after the first, but none had subsequent improvement in counts.

GVHD. Five unrelated recipients, including 3 patients who died before day 14, had no acute GVHD. Four patients...
unrelated recipients currently alive show active chronic GVHD with Kamofsky scores of 70% and 90%, respectively, and both required immunosuppressive therapy for 23 ent between the two groups syndrome requiring immunosuppressive therapy.

discharged and the lengths of hospitalization were  not differ-

of these 

of 43 patients (67%) survived more than 100 days and 12 days after transplantation (median, 13 days). Twenty-nine transplant and all have died; 45 autologous recipients (57%) lapsed at a median of 407 days (range, 21 to 602) after transplant to discharge from the marrow transplant unit were

GVHD was 104 days (range, 90 to 322 days). Two of 9 received with autologous marrow developed a GVHD-like syndrome requiring immunosuppressive therapy.

Duration of first hospitalization. The median times from transplant to discharge from the marrow transplant unit were 35 days (range, 20 to 89 days) for unrelated recipients and 34 days (range, 18 to 101 days) for autologous recipients. Figure 2 shows that the cumulative proportions of patients discharged and the lengths of hospitalization were not different between the two groups (P = .65). Nine unrelated recipients (21%) and 18 autologous recipients (23%) died in the hospital.

Relapse. Seventeen unrelated recipients (40%) have relapsed at a median of 407 days (range, 21 to 602) after transplant and all have died; 45 autologous recipients (57%) have relapsed at a median of 126 days (range, 15 to 829) after transplantation and 1 is alive. The probability of relapse after unrelated or autologous transplant was not different for ALL or AML (P = .3), but depended on the state of leukemia at the time of transplant. The cumulative incidence of relapse at 3 years after transplantation for patients in complete marrow remission was 27% for unrelated recipients and 55% for autologous recipients (Fig 3; P = .08). The cumulative incidence of relapse at 3 years was not significantly different between unrelated and autologous recipients who underwent transplantation in relapse, ie, 48% versus 65%, respectively (Fig 4; P = .72).

Causes of death. During the first 100 days, transplant-related complications accounted for 10 of 14 deaths (71%) in unrelated recipients and 19 of 29 deaths (65%) in autologous recipients. After 100 days, relapse was the predominant factor leading to death, with 13 of 20 unrelated recipients (65%) and 34 of 36 autologous recipients (95%) dying with recurrent malignancy. Causes of death are listed in Table 3. Failure to recover a granulocyte count of 10^9/L was a contributing factor in 17 of 21 autologous recipients (81%) who died because of causes other than relapse. One patient with ALL who received an unrelated transplant developed an Epstein-Barr virus (EBV)-related malignant lymphoma 5 months after the transplant, whereas no second malignancies occurred among autologous recipients.

Disease-free survival. Disease-free survival at 3 years after transplantation was 33% for the unrelated recipients and 25% for the autologous recipients transplanted in complete remission (Fig 5; P = .45). Three of 9 unrelated recipients with ALL in remission and 3 of 9 unrelated recipients with AML in remission are alive and free of leukemia. Five of 19 autologous recipients with ALL in remission and 3 of 12 autologous recipients with AML in remission are alive and
UNRELATED DONOR OR AUTOLOGOUS MARROW TRANSPLANTS

Table 3. Survival

<table>
<thead>
<tr>
<th></th>
<th>Unrelated Donor Transplant (n = 43)</th>
<th>Autologous Transplant (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients alive in remission</td>
<td>9 (20%)</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>No. of patients alive after relapse</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Relapse-related</td>
<td>17 (40%)</td>
<td>44 (57%)</td>
</tr>
<tr>
<td>Non-relapse-related</td>
<td>17 (40%)</td>
<td>21 (28%)</td>
</tr>
</tbody>
</table>

Infection:
- Fungal: 2/7
- CMV: 3/1
- EBV: 1/−
- Bacterial: −/3
- P. carinii: 1/−
- Mixed: 1/2
- Idiopathic pneumonia: 2/4
- Liver failure: 1/2
- CNS accident: 2/−
- Hemorrhage: 2/2
- Chronic GVHD: 2/−

Abbreviations: CMV, cytomegalovirus; P. carinii, Pneumocystis carinii pneumonia.

In some institutions, standard treatment of patients with AML or high-risk ALL who lack an HLA-identical sibling is to harvest and cryopreserve autologous marrow at the time of first remission and to proceed to transplantation in the event of recurrent leukemia. In these instances, the approach is based on the observations that conventional chemotherapy can cure 20% to 50% of newly diagnosed patients but cure becomes much more difficult after leukemia recurrence. The morbidity and mortality caused by marrow transplantation remains too high for many patients who are curable by less toxic treatment. On the other hand, marrow transplantation can cure some patients who would otherwise have a negligible chance of disease-free survival with conventional treatment. The current study was performed between 1984 and 1990, when transplant centers accepted patients with leukemia at stages more advanced than would be considered optimal or appropriate today. The study assessed whether transplantation from an unrelated donor might be as effective as transplantation of autologous marrow in patients with leukemia at or after a first relapse. The results indicated that disease-free survival is similar with either treatment modality. The lower probability of relapse after unrelated transplantation might result from an antileukemic effect of the unrelated marrow and also from malignant progenitors in the autologous marrow. The length of first hospitalization was identical for either unrelated or autologous donor marrow transplants and survival by day 100 was also similar. Early mortality was closely associated with acute GVHD in unrelated recipients and with prolonged granulocytopenia in autologous recipients. Quality of life was compromised by chronic GVHD in 40% of the unrelated recipients but not in autologous recipients.

DISCUSSION

In some institutions, standard treatment of patients with AML or high-risk ALL who lack an HLA-identical sibling is to harvest and cryopreserve autologous marrow at the time of first remission and to proceed to transplantation in the event of recurrent leukemia. In these instances, the approach is based on the observations that conventional chemotherapy can cure 20% to 50% of newly diagnosed patients but cure becomes much more difficult after leukemia recurrence. The morbidity and mortality caused by marrow transplantation remains too high for many patients who are curable by less toxic treatment. On the other hand, marrow transplantation can cure some patients who would otherwise have a negligible chance of disease-free survival with conventional treatment. The current study was performed between 1984 and 1990, when transplant centers accepted patients with leukemia at stages more advanced than would be considered optimal or appropriate today. The study assessed whether transplantation from an unrelated donor might be as effective as transplantation of autologous marrow in patients with leukemia at or after a first relapse. The results indicated that disease-free survival is similar with either treatment modality. The lower probability of relapse after unrelated transplantation might result from an antileukemic effect of the unrelated marrow and also from malignant progenitors in the autologous marrow. The length of first hospitalization was identical for either unrelated or autologous donor marrow transplants and survival by day 100 was also similar. Early mortality was closely associated with acute GVHD in unrelated recipients and with prolonged granulocytopenia in autologous recipients. Quality of life was compromised by chronic GVHD in 40% of the unrelated recipients but not in autologous recipients.

Matched cohorts were used to compare results of the two procedures and adjust for the three major factors known to influence transplant outcome, ie, patient age, disease, and disease stage. Because relatively more unrelated transplants were performed in patients beyond second remission, 14 had to be excluded from the analysis because of the lack of matched autologous controls. Certain factors may select pa-
tients for one or the other transplant procedure. Candidates for autologous grafts must achieve at least one complete marrow remission to have marrow harvested and stored. Candidates for unrelated grafts must survive long enough to complete a donor search. Differences between the groups were minimized but could not be abolished entirely by cohort matching. For example, relatively more autologous transplants were performed with patients in second remission and more unrelated transplants were performed with patients in third remission. The time interval between marrow remission and transplant was similar but not identical in the two cohorts transplanted in remission ($P = .19$). Even a prospective trial might not be able to eliminate such differences. Results of the matched-cohort analysis were supported by a multivariate proportional hazard regression analysis of survival that included all 244 patients treated during the study period. The multivariate analysis also failed to detect a difference in leukemia-free survival between unrelated and autologous graft recipients. The number of patients studied was too small to determine whether unrelated or autologous transplantation could be advantageous in a certain subgroup of patients. It would be of particular interest to compare patients with ALL and AML separately in future studies.

The use of autologous marrow as a source of hematopoietic stem cells has great appeal because it can be used for any patient who achieves a clinical remission. Consistent with our previous reports, the present study indicates that the limitations of autologous transplantation in patients with advanced disease are a high rate of relapse after transplantation and poor engraftment leading to fatal infections. Because marrow had been purged in similar fractions of patients who did or did not achieve sustained granulocyte counts greater than $10^9/L$, it appears that purging was not the sole explanation for impaired recovery of myeloid function. Normal stem cells might be severely depleted in patients pretreated with multiple courses of chemotherapy before marrow harvest. In addition, marrow purging, freezing, and thawing may damage normal hematopoietic precursors. Relapse after transplantation must be caused predominantly by regrowth of leukemic cells resistant to the conditioning chemoradiotherapy administered to the patients because it occurred in $40\%$ of the recipients of marrow from a healthy donor and in $58\%$ of the recipients of autologous marrow. In addition, marrow harvested from patients with leukemia may be contaminated with leukemic cells not detectable by routine morphologic examination of marrow smears. Whereas purging techniques have been advocated by certain investigators, definitive evidence that any technique can significantly decrease the rate of relapse after transplantation is lacking.

In studies of patients with less advanced leukemia, the low morbidity of autologous transplantation has been attributed to the lack of GVHD and the lack of need for postgrafting immunosuppression. Disease-free survival at 3 to 5 years after autologous marrow transplantation depends on the underlying disease, disease stage, and remission or relapse status at transplant. For patients transplanted in first or second remission or in first untreated relapse, our results are similar to those reported by others. Disease-free survival has been $41\%$ to $43\%$ in patients transplanted for first remission AML, $36\%$ for first untreated relapse, and $25\%$ to $35\%$ in second remission. Disease-free survival has been $42\%$ to $50\%$ for patients with ALL in first remission and $22\%$ to $31\%$ in second remission.

With the development of large registries of HLA-typed volunteers, the probability of identifying an HLA-matched marrow donor for patients in need of a transplant has grown substantially. One major limitation of unrelated donor transplantation for treatment of acute leukemia is the heterogeneity of HLA types and the fact that a match cannot be found for some patients. The probability of finding an HLA-A, B, and DR serologically matched donor for a patient in the NMDP file is now estimated at $52\%$ (NMDP data, as of June 1993). For the period studied in this report, $19.5\%$ of the patients with acute leukemia who had a donor search initiated were transplanted an average of 5 months after initiation of the search (Anasetti et al, manuscript in preparation). During that time, $35\%$ of patients with leukemia beyond first remission died. Shortening the time needed to identify an HLA-matched unrelated donor may decrease the number of patients who die while waiting for a transplant. Another limitation of unrelated transplantation is the high rate of acute and chronic GVHD, which predisposes to opportunistic infections and contributes to the high mortality rate.

Analyses of transplants facilitated by the NMDP showed disease survivals of $15\%$ to $45\%$ for patients with acute leukemia, depending on patient age, disease stage, and degree of HLA matching of the donor. Marrow transplantation from HLA-unrelated volunteers has proven feasible and effective for treatment of patients with relapsed acute leukemia. Despite morbidity associated with GVHD, unrelated recipients have a long-term survival similar to patients who were treated with autologous transplantation. The lower risk of relapse remains a theoretical advantage for patients with acute leukemia receiving allogeneic marrow compared with those receiving autologous marrow. As shown for transplants from HLA-matched siblings, results of unrelated or autologous transplants may improve by treating patients earlier in the course of the disease before leukemia becomes resistant to chemotherapy. A donor search should be initiated as soon as possible, and certainly at initial diagnosis in high-risk patients. If an unrelated donor is found, it may be possible to rescue some patients whose disease does not respond to primary induction treatment. Patients who achieve a first remission and do not have a suitably matched unrelated donor should have autologous marrow stored. Patients with a high risk of relapse could be transplanted early during first remission before disease recurs, and patients with standard risk disease could be transplanted after first relapse or early in second remission. Unrelated transplants are not yet feasible in first untreated relapse because of the time required to arrange for the procedure. The relative effectiveness of unrelated and autologous transplantation performed at first remission or early after a first relapse remains to be addressed in future prospective trials.

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A Busca, C Anasetti, G Anderson, FR Appelbaum, CD Buckner, K Doney, PJ Martin, E Petersdorf, JE Sanders and JA Hansen