Equivalent Outcomes in Patients with Chronic Myelogenous Leukemia after Early Transplantation of Phenotypically Matched Bone Marrow from Related or Unrelated Donors

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PURPOSE: To determine if the favorable outcomes after transplantation of matched sibling donor bone marrow in patients with chronic myelogenous leukemia can be achieved using bone marrow from an HLA-A,B/DRB1-matched unrelated donor.

SUBJECTS AND METHODS: Between April 1983 and December 1997, 141 patients with chronic myelogenous leukemia in its first chronic phase received a bone marrow transplant from a matched sibling donor ($n = 96$) or an HLA-A,B/DRB1-matched unrelated donor ($n = 45$). The median age of matched sibling donor recipients was 38 years (range, 8 to 56 years) and of unrelated donor recipients was 35 years (range, 3 to 53 years; $P = 0.03$). The median follow-up was 6 years (range, 1 to 15 years) in matched sibling donor recipients and 5 years (range, 2 to 10 years) in unrelated donor recipients.

RESULTS: There was no significant difference in the 5-year survival rates of matched sibling donor recipients [58%; 95% confidence interval (CI), 48% to 68%] and unrelated donor

recipients (53%; 95% CI, 39% to 67%; $P = 0.4$). Among patients who underwent transplantation within 1 year after diagnosis, the 5-year survival rate of matched sibling donor recipients (76%; 95% CI, 65% to 87%) was not significantly different ($P = 0.5$) from that of unrelated donor recipients (70%; 95% CI, 52% to 88%). In multiple regression analysis, longer time from diagnosis to transplantation, T-cell depletion, and grades III or IV graft versus host disease were independently associated with poorer survival. Transplantation of unrelated donor bone marrow was not associated with mortality (relative risk, 1.1; 95% CI, 0.6 to 2.1; $P = 0.7$).

CONCLUSIONS: Transplantation of bone marrow from a matched sibling donor or an HLA-A,B/DRB1-matched unrelated donor produces equivalent outcomes in patients with chronic myelogenous leukemia, particularly if the transplant takes place within 1 year after diagnosis. *Am J Med.* 2001;110:339-346. ©2001 by Excerpta Medica, Inc.

Bone marrow transplantation is an effective treatment for chronic myelogenous leukemia. It is the preferred treatment for younger patients with an HLA-matched sibling donor (1-3). Among patients who undergo transplantation early in the chronic phase of the disease, the survival rate is approximately 70%. However, most potential bone marrow transplant recipients do not have a matched sibling donor, and the use of phenotypically matched unrelated donor bone marrow for transplantation is increasing (4,5). In initial reports, transplantation from an unrelated donor was associated with greater morbidity—including more frequent graft versus host disease, graft failure, and delayed immune reconstitution leading to late infections—and mortality than transplantation from a sibling donor (6-8).

Alternatives to bone marrow transplantation for chronic myelogenous leukemia include alkylating agents, such as busulfan and hydroxyurea, which control symptoms but generally do not prolong survival (9-13). The effectiveness of interferon-alpha in extending survival is controversial. Administered early and in sufficient doses, interferon-alpha prolongs survival only in the minority of patients who experience a major or complete cytogenetic response (14,15). However, toxicity can be dose limiting, and an extended interferon trial may adversely affect the outcome of subsequent allogeneic bone marrow transplantation. Although early reports described no adverse effect of prior interferon therapy (16), recent data suggest that such treatment worsens the outcome (17,18).

Information on the likely outcome of bone marrow transplantation is essential for appropriate counseling of patients on therapeutic options. In this study, we sought to determine whether the excellent outcomes after transplantation of matched sibling donor bone marrow can also be achieved with bone marrow from unrelated donors. Because donor lymphocyte infusions can produce durable remissions with full donor chimerism after relapse of chronic myelogenous leukemia, we analyzed both survival and disease-free survival.

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Table 1. Characteristics of Patients Receiving a Bone Marrow Transplant for Chronic Myelogenous Leukemia

	HLA-matched Donors			P Value
	Sibling (n = 96)	Unrelated (n = 45)	Total (n = 141)	
	Number (Percent) or Median (Range)			
Recipient age				
<18 years	4 (4)	6 (13)	10 (7)	0.07
18 to 34 years	32 (33)	18 (40)	50 (35)	
≥35 years	60 (63)	21 (47)	81 (57)	
Age (years)	38 (8 to 56)	35 (3 to 53)	37 (3 to 56)	0.03
Year of transplant				
1980 to 1984	6 (6)	0	6 (4)	0.4
1985 to 1989	28 (29)	2 (4)	30 (21)	
1990 to 1994	43 (45)	19 (42)	62 (44)	
1995 to 1997	19 (20)	24 (53)	43 (31)	
Recipient/donor sex				
Female/female	17 (18)	8 (18)	25 (18)	0.4
Female/male	32 (33)	9 (20)	41 (29)	
Male/female	20 (21)	13 (29)	33 (24)	
Male/male	27 (28)	15 (33)	42 (30)	
Recipient/donor cytomegalovirus serostatus				
Positive/positive	32 (33)	5 (12)	37 (27)	0.05
Positive/negative	20 (21)	10 (23)	30 (22)	
Negative/positive	10 (10)	8 (19)	18 (13)	
Negative/negative	34 (35)	20 (47)	54 (39)	
Missing	0	2	2	
Graft versus host disease prophylaxis				
No T-cell depletion	88 (92)	30 (67)	118 (84)	0.001
T-cell depletion	8 (8)	15 (33)	23 (16)	
Preparative regimen				
Cyclophosphamide/total body irradiation (1,320 cGy)	90 (94)	44 (98)	134 (95)	0.08
Busulfan/*cyclophosphamide	0	1 (2)	1 (2)	
*Cyclophosphamide/†VP16/total body irradiation [850 cGy (1)]	6 (6)	0	6 (4)	
Time from diagnosis to transplant				
<1 year	63 (66)	27 (60)	90 (64)	0.13
1 to 2 years	25 (26)	9 (20)	34 (24)	
>2 years	8 (8)	9 (20)	17 (12)	
Months	8 (3 to 82)	10 (5 to 66)	8 (3 to 82)	0.03
Number of marrow cells (10 ⁸ /kg)	2.0 (0.4 to 2.3)	2.0 (0.1 to 4.2)	2.0 (0.1 to 4.2)	0.09

* Cyclophosphamide 60 mg/hg/day × 2; cyclophosphamide 50 mg/hg/day × 4; cyclophosphamide 50 mg/hg/day × 3 for the three regimens, respectively.

† VP16 500 mg/m²/day × 3 (n = 4); VP16 350 mg/m²/day × 3 (n = 2).

PATIENTS AND METHODS

Between April 1983 and December 1997, 141 consecutive patients with chronic myelogenous leukemia in its first chronic phase underwent bone marrow transplantation at the University of Minnesota, 96 from HLA-matched sibling donors and 45 from a phenotypically matched unrelated donor. The median age was 38 years (range, 8 to 56 years) in recipients of sibling marrow and 35 years

(range, 3 to 56 years) in recipients of unrelated donor marrow (Table 1). The median follow-up was 6 years (range, 1 to 15 years) among matched sibling donor recipients and 5 years (range, 2 to 10 years) among unrelated donor recipients. Clinical and laboratory data were retrieved from the University of Minnesota Bone Marrow Transplant Database. Because detailed information on pretransplant therapy with interferon was not available for all patients, this information was not included in the

analysis. All patients or their guardians signed informed consent documents approved by the Committee on the Use of Human Subjects in Research at the University of Minnesota.

Unrelated Donor Selection

Unrelated donors were located through national and international bone marrow donor registries (19). HLA-A and -B typing was performed with serologic techniques that identified all specificities recognized by the World Health Organization at the time of transplant. All donor-recipient pairs were typed for DR by high-resolution DNA techniques, either prospectively or retrospectively. Unrelated donor recipients were included in the study only if they were HLA-A,B/DRB1 matched with their donors.

Pretransplant Conditioning Therapy and Graft versus Host Disease Prophylaxis

Most patients (94%) received cyclophosphamide (120 mg/kg) and total body irradiation (1,320 cGy in 8 fractions) before bone marrow infusion (Table 1). One patient who had previously undergone radiation therapy received busulfan and cyclophosphamide, and 6 patients receiving T-cell-directed immunotoxin received cyclophosphamide, VP16, and single-fraction total body irradiation. As part of experimental protocols for graft versus host disease prophylaxis, marrow was depleted of T cells by elutriation in 33% of unrelated donor recipients and by T-cell-directed immunotoxin in 8% of matched sibling donor recipients ($P = 0.001$) (20,21).

Supportive Care

Patients were hospitalized in single rooms with high-efficiency particulate air filtration. Patients routinely received prophylaxis with trimethoprim-sulfamethoxazole; at the onset of fever, patients were treated empirically with broad-spectrum antibacterial and antifungal agents. Patients who were seronegative for cytomegalovirus received blood products from seronegative donors or blood products that had been filtered to remove contaminating leukocytes. Acyclovir was administered prophylactically to patients who were seropositive for cytomegalovirus (10 mg/kg intravenously every 8 hours) or herpes simplex virus (5 mg/kg intravenously every 8 hours). Patients who received a transplant after 1996 were monitored weekly for cytomegalovirus antigenemia until day 100 and treated with ganciclovir if positive results were obtained.

Analysis of Outcomes

Categorical variables were compared with Pearson's chi-squared test and continuous variables with the Wilcoxon test (22). Survival, relapse-free survival, and disease-free survival rates were estimated with the Kaplan-Meier method (23). End points were compared using the log-rank test.

The Cox proportional hazards model was used to determine the independent effects of study variables. The final model was chosen by a combination of statistical and clinical significance. Statistical considerations included the effect of each variable on the overall model chi-squared statistic and the confounding effects of donor type on each end point. Study variables included age, disease stage, interval from diagnosis to transplant, donor-recipient HLA matching, time-dependent onset of graft versus host disease, graft versus host disease prophylaxis, cytomegalovirus status, and donor-recipient gender match (24). The proportionality assumption of the model was verified. Interactions between donor type and other study variables were also investigated.

Patient follow-up was complete as of September 2000. Infusion of donor lymphocytes after posttransplant hematologic or cytogenetic relapse can lead to return to full donor chimerism without evidence of disease. Therefore, both overall survival and disease-free survival rates are reported. In analysis of disease-free survival, death or hematologic or cytogenetic relapse are scored as events, although some patients returned to full donor chimerism after infusion of donor lymphocytes.

RESULTS

Survival

The 5-year survival rate of matched sibling donor bone marrow recipients [58%; 95% confidence interval (CI), 48% to 68%] was similar to that of unrelated donor bone marrow recipients (53%; 95% CI, 39% to 67%; $P = 0.4$; Figure 1). Therefore, risk factors for survival were analyzed within the entire cohort of matched sibling donor and unrelated donor recipients.

Survival at 5 years was similar in recipients younger than 18 years (69%; 95% CI, 39% to 99%) and those 18 to 34 years old (68%; 95% CI, 50% to 86%), but was significantly lower in those 35 to 56 years old (47%; 95% CI, 35% to 59%; $P = 0.01$). Patients who received a transplant less than 1 year after diagnosis had a significantly ($P = 0.0001$) higher 5-year survival rate (74%; 95% CI, 65% to 83%) than those who received a transplant 1 to 2 years after diagnosis (38%; 95% CI, 19% to 57%) or more than 2 years after diagnosis (24%; 95% CI, 4% to 44%) (Figure 2). There was no significant difference ($P = 0.5$) in the 5-year survival rates of matched sibling donor recipients (76%; 95% CI, 65% to 87%) and those of unrelated donor recipients (70%; 95% CI, 52% to 88%) who underwent transplantation less than 1 year after diagnosis (Figure 3).

The 5-year survival rate was also higher in those receiving a higher marrow cell dose (greater than 2×10^8 /kg) (65%; 95% CI, 56% to 74% versus 48%; 95% CI, 65% to 89%; $P = 0.04$) and those who did not develop severe

Figure 1. Survival after transplantation of bone marrow from matched sibling donors ($n = 96$) and from unrelated donors ($n = 45$) in chronic myelogenous leukemia patients. At 5 years, 32 matched sibling donor recipients and 5 unrelated donor recipients are still alive.

graft versus host disease (65%; 95% CI, 56% to 74% in those with grades 0 to II versus 40%; 95% CI, 25% to 64%; $P = 0.01$) in those with grades III and IV]. Male recipients with female donors had a reduced survival rate (39%; 95% CI, 22% to 56%; $P = 0.03$), as did recipients of T-cell-depleted marrow, largely because of poor outcomes in matched sibling donor recipients participating in an experimental protocol that was terminated early.

Factors associated with increased mortality in the multiple regression analysis were age younger than 35 years old, transplantation more than 1 year after diagnosis, T-cell-depleted marrow, and grades III to IV graft versus host disease (Table 2). After adjustment for all other vari-

ables, the 5-year mortality was not higher in recipients of unrelated donor marrow than in recipients of matched sibling marrow (relative risk 1.1; 95% CI, 0.6 to 2.1; $P = 0.7$).

Relapse

Cytogenetic or hematologic relapse occurred in 21 matched sibling donor recipients (Kaplan-Meier estimate, 29% at 5 years; 95% CI, 9% to 50%) and 6 unrelated donor recipients (Kaplan-Meier estimate, 31%; 95% CI, 19% to 44%; $P = 0.9$). Twelve of 27 patients who had a relapse received a transfusion of donor lymphocytes; 9 are in a further complete remission, 2 are in com-

Figure 2. Survival in patients who received a transplant less than 1 year after diagnosis ($n = 90$), 1 to 2 years after diagnosis ($n = 34$), and more than 2 years after diagnosis ($n = 17$). At 5 years, 26 patients who received a transplant less than 1 year after diagnosis, 7 who received a transplant within 1 to 2 years, and 4 who received a transplant more than 2 years after diagnosis are still alive.

Figure 3. Survival after matched sibling donor ($n = 63$) or unrelated donor ($n = 27$) bone marrow transplant for chronic myelogenous leukemia in patients who received a transplant less than 1 year after diagnosis. At 5 years, 23 matched sibling donor recipients and 4 unrelated donor recipients are still alive.

plete remission after a second bone marrow transplant, and one died without remission. Fifteen patients did not receive transfusion of donor lymphocytes; 5 are in a further complete remission after a second bone marrow transplant, 2 are in complete remission after interferon therapy, 2 have chronic myelogenous leukemia, and 6 died of their disease.

Disease-free Survival

In univariate analyses, T-cell depletion, transplantation more than 1 year after diagnosis, low cell dose, and grades III and IV graft versus host disease were associated with poorer disease-free survival. The disease-free survival rates were similar after transplantation from an unrelated donor (44%; 95% CI, 34% to 54%) or a matched sibling donor (42%; 95% CI, 28% to 58%; $P = 0.6$). Delay in transplantation strongly influenced the 5-year disease-free survival rate, which was 53% in those who received a transplant in less than 1 year, 30% in those who received a transplant in 1 to 2 years, and 6% in those who received

a transplant more than 2 years after diagnosis ($P = 0.0001$). Among patients who underwent transplantation within 1 year after diagnosis, the disease-free survival rates were similar in recipients of matched sibling and unrelated donor bone marrow (Figure 4). Multiple regression analysis confirmed the adverse effects of delay in bone marrow transplantation and T-cell depletion on disease-free survival (Table 3).

DISCUSSION

This study shows that equivalent survival can be achieved in patients with chronic myelogenous leukemia who receive matched sibling donor marrow and those receiving unrelated donor marrow. However, we analyzed recipients of marrow that was serologically matched at HLA-A and -B and molecularly matched at DRB1. Outcomes might not be as favorable in recipients of less well-matched marrow. Molecular typing at the HLA-A and -B alleles might further improve outcomes.

In early reports of unrelated donor bone marrow transplantation, graft versus host disease, graft failure, and late infections were frequent, and treatment-related mortality was common (6–8). Our findings in this study are consistent with recent reports of improved outcomes in patients who receive unrelated donor marrow (25,26). Hansen et al (25) reported a 5-year survival rate of 57% in patients with early-phase chronic myelogenous leukemia; survival was reduced in those who underwent transplantation more than 1 year after diagnosis, received DRB1-mismatched marrow, had a high body-weight index, or were older than 50 years. As in our study, these results were similar to those obtained with matched sib-

Table 2. Association between Selected Characteristics and 5-Year Mortality: Multivariate Proportional Hazards Model

Factor	Relative Risk (95% Confidence Interval)	<i>P</i> Value
Unrelated donor	1.1 (0.6–2.1)	0.7
Age ≥ 35 years	3.3 (0.9–11)	0.06
T-cell depletion	2.5 (1.3–4.8)	0.009
Time to transplant 1–2 years*	2.1 (1.2–4.0)	0.01
Time to transplant > 2 years*	5.8 (2.8–12)	0.0001
Graft versus host disease	2.2 (1.2–4.1)	0.01

* Compared with < 1 year.

Figure 4. Disease-free survival in patients who received bone marrow from a matched sibling donor ($n = 63$) or unrelated donor ($n = 27$) within 1 year of diagnosis. At 5 years, 18 matched sibling donor and 3 unrelated donor recipients are still alive.

ling donors. Dini et al (26) reported survival of 64% at 4 years in 30 patients with chronic myelogenous leukemia who received a transplant after 1993; survival was reduced in patients who received HLA-mismatched marrow, did not receive radiation therapy, or were treated with cyclosporine before transplantation. Transplantation within 1 year after diagnosis did not influence survival, perhaps, as the authors suggested, because most of the transplants were performed more than 1 year after diagnosis. In our study and in others, transplantation more than 1 year after diagnosis strongly influenced survival in recipients of unrelated donor marrow as well as in recipients of matched sibling donor marrow (2,27,28). As in the study of Hansen et al, older recipient age adversely affected outcome in the present study.

Severe graft versus host disease was associated with reduced survival in our patients. Previous studies of unrelated donor and matched sibling donor transplants for chronic myelogenous leukemia have shown reduced relapse rates in patients with graft versus host disease and in

unrelated donor recipients compared with matched sibling donor recipients, likely because of a graft versus leukemia effect (27,29). Despite any potential graft versus leukemia effect, severe graft versus host disease markedly increased mortality in our patients, indicating the need for improved prophylaxis. T-cell depletion also reduced survival, largely reflecting the excessive mortality in a small cohort of matched sibling donor recipients of T-cell-depleted marrow. An ongoing national randomized study of T-cell depletion in unrelated donor bone marrow transplantation will more clearly address the role of graft versus host disease prophylaxis in recipients of unrelated donor bone marrow, including those with early chronic myelogenous leukemia.

Transplantation of phenotypically matched marrow yielded excellent results. Studies from our center and others have demonstrated the adverse effect of HLA mismatch on outcome. The availability of over 6 million potential bone marrow donors through a web-based bone marrow search tool (Bone Marrow Donors Worldwide, 1998) increases the likelihood of identifying a well-matched donor. The likelihood of identifying at least one 6-antigen-matched potential donor in a preliminary search of the National Marrow Donor Program is greater than 75% (National Marrow Donor Program, personal communication, 1998). This still leaves many patients, especially those from minority ethnic and racial groups, without a potential donor. Continuing efforts to diversify the HLA phenotypes in bone marrow registries are important for increasing the availability of suitable bone marrow donors. An alternative strategy for increasing donor availability is to use umbilical cord blood. Although cord blood can be an excellent source of stem cells for young recipients, the small number of stem cells and the

Table 3. Associations between Selected Characteristics and Disease-free Survival: Multivariate Proportional Hazards Model

Factor	Relative Risk (95% Confidence Interval)	P Value
Unrelated donor	0.8 (0.5–1.5)	0.5
Age ≥ 35 years	1.6 (0.9–2.6)	0.06
T-cell depletion	3.3 (1.7–6.2)	0.0003
Time to transplant 1–2 years*	2.1 (1.2–3.5)	0.005
Time to transplant >2 years*	5.3 (2.9–9.7)	0.0001

* Compared with <1 year.

reduced rates of engraftment limit the immediate applicability of this approach in adults with chronic myelogenous leukemia (30). Ex vivo expansion of stem cells may improve engraftment in these patients.

Patients with chronic myelogenous leukemia can enjoy excellent quality of life, sometimes for years after diagnosis, and the decision to proceed to unrelated donor bone marrow transplantation can be difficult for both patients and physicians. A decision analysis based on data from the National Marrow Donor Program and International Bone Marrow Transplant Registry, including patient age, quality of life, risk aversion, and competing risks of disease progression and transplant toxicity, supports the use of early unrelated donor bone marrow transplantation for most patients with chronic myelogenous leukemia (31). However, these analyses were performed before the tyrosine kinase inhibitor STI 571 became available. The role of this important new agent in the treatment of chronic myelogenous leukemia is currently unknown (32).

STI 571 is an oral agent designed to inhibit the Bcr-Abl transcript produced by the Philadelphia chromosome that is characteristic of chronic myelogenous leukemia. Treatment with STI 571 has led to complete cytogenetic responses in some patients with chronic myelogenous leukemia in the chronic or accelerated phase and in some patients with resistant or refractory disease, with little toxicity (32–34). However, the frequency of responses is modest in some groups of patients (9% in the accelerated phase and 13% in the resistant disease), and the duration of response is unknown (33,34). Because chronic myelogenous leukemia progresses slowly, it will be some years before it is apparent whether any patients treated with STI 571 are cured of their disease. We recommend that patients with newly diagnosed chronic myelogenous leukemia search aggressively for an unrelated donor and, if a donor is identified, undergo bone marrow transplantation without delay.

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