

BONE MARROW TRANSPLANTS FROM UNRELATED DONORS FOR PATIENTS WITH CHRONIC MYELOID LEUKEMIA

JOHN A. HANSEN, M.D., THEODORE A. GOOLEY, PH.D., PAUL J. MARTIN, M.D., FREDERICK APPELBAUM, M.D., THOMAS R. CHAUNCEY, M.D., REGINALD A. CLIFT, F.I.M.L.S., EFFIE W. PETERSDORF, M.D., JERALD RADICH, M.D., JEAN E. SANDERS, M.D., RAINER F. STORB, M.D., KEITH M. SULLIVAN, M.D., AND CLAUDIO ANASETTI, M.D.

ABSTRACT

Background Chronic myeloid leukemia can be cured by marrow transplantation from an HLA-identical sibling donor. The use of transplants from unrelated donors is an option for the 70 percent of patients without an HLA-identical sibling, but the morbidity and mortality associated with such transplants have been cause for concern. We analyzed the safety and efficacy of transplants from unrelated donors for the treatment of chronic myeloid leukemia and identified variables that predict a favorable outcome.

Methods Between May 1985 and December 1994, 196 patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase received marrow transplants from unrelated donors.

Results The median follow-up was 5 years (range, 1.2 to 10.1). Graft failure occurred in 5 percent of patients who could be evaluated. Acute graft-versus-host disease of grade III or IV severity was observed in 35 percent of patients who received HLA-matched transplants, and the estimated cumulative incidence of relapse at five years was 10 percent. The Kaplan-Meier estimate of survival at five years was 57 percent. Survival was adversely affected by an interval from diagnosis to transplantation of one year or more, an HLA-DRB1 mismatch, a high body-weight index, and an age of more than 50 years. Survival was improved by the prophylactic use of fluconazole and ganciclovir. The Kaplan-Meier estimate of survival at five years was 74 percent (95 percent confidence interval, 62 to 86 percent) for patients who were 50 years of age or younger who received a transplant from an HLA-matched donor within one year after diagnosis.

Conclusions Transplantation of marrow from an HLA-matched, unrelated donor is safe and effective therapy for selected patients with chronic myeloid leukemia. (N Engl J Med 1998;338:962-8.)

©1998, Massachusetts Medical Society.

CHRONIC myeloid leukemia can be cured only by hematopoietic stem-cell transplantation.^{1,2} Until recently this option was largely limited to patients with an HLA-identical sibling. The advent of national registries has made it possible to identify HLA-matched, unrelated donors for an increasing number of patients.³ Initial reports of the use of transplants from unrelated donors have shown that graft-versus-host disease (GVHD) occurs more frequently and survival rates

are lower than expected, given the rates for transplants from HLA-identical siblings.⁴⁻⁹ This report describes our experience with transplants from unrelated donors in patients with chronic myeloid leukemia in chronic phase and identifies variables affecting survival.

METHODS

Study Patients and Donors

From May 1985 through December 1994, 196 patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase received a first transplant from an unrelated donor. The diagnosis was confirmed by clinical examination and morphologic and cytogenetic analysis of bone marrow immediately before transplantation.¹ All patients who underwent transplantation according to the protocol described below were included in the analysis. The characteristics of the patients, donors, and grafts are summarized in Table 1. The protocols and consent forms used for these studies were approved by our institutional review board. All patients provided written informed consent. All evaluations were based on data available on December 1, 1997.

HLA Typing and Donor Matching

The analysis of HLA matching was based on typing for HLA-A and B antigens by serologic methods and retrospective typing for HLA-DRB1 alleles by DNA hybridization with sequence-specific oligonucleotide probes.¹¹ Donors were required to match the recipient for the serologically defined HLA-A, B, and DR antigens and demonstrate compatibility for HLA-Dw on the basis of the mixed-lymphocyte-culture assay.¹² In 1992, matching with the mixed-lymphocyte-culture assay was replaced by typing with sequence-specific oligonucleotide probes for HLA-DRB1 alleles.^{13,14} Patients who were 36 to 55 years of age were eligible for transplantation only if a donor matched for HLA-A, B, and Dw or DRB1 was available. A single minor mismatch of HLA-A, B, or DRB1 was allowed for patients under 36 years of age who lacked an HLA-matched donor.^{15,16} A pretransplantation lymphocyte cross-matching test with patient serum and donor cells was negative in all cases.

Transplantation Procedures and Supportive Care

Before transplantation all patients followed a regimen that included 60 mg of cyclophosphamide per kilogram of body weight per day for two days and 1200 or ≥ 1320 cGy of total-body irradiation, according to the HLA-matching status (Table 1). Donor marrow was not depleted of T cells. Cyclosporine and methotrexate were given for GVHD prophylaxis.¹⁷ Trimethoprim and sulfa-

From the Fred Hutchinson Cancer Research Center (J.A.H., T.A.G., P.J.M., F.A., T.R.C., R.A.C., E.W.P., J.R., J.E.S., R.F.S., K.M.S., C.A.), the Veterans Affairs Medical Center (T.R.C.), and the University of Washington School of Medicine (J.A.H., P.J.M., F.A., T.R.C., E.W.P., J.R., J.E.S., R.F.S., K.M.S., C.A.) — all in Seattle. Address reprint requests to Dr. Hansen at the Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109-1024.

TABLE 1. CHARACTERISTICS OF 196 PATIENTS WITH CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE WHO WERE RECEIVING A FIRST MARROW TRANSPLANT FROM AN UNRELATED DONOR AND THEIR DONORS.*

CHARACTERISTIC	VALUE	CHARACTERISTIC	VALUE
Age of patient — no. (%)		HLA-matching status — no. (%)	
0–10 yr	3 (2)	Matched for HLA-A, B, DRB1	152 (78)
11–20 yr	11 (6)	Minor mismatch of HLA-A	10 (5)
21–30 yr	51 (26)	Minor mismatch of HLA-B	9 (5)
31–40 yr	59 (30)	Minor mismatch of HLA-DRB1	20 (10)
41–50 yr	59 (30)	Minor mismatch of HLA-DRB1 and A or B	5 (3)
>50 yr	13 (7)		
Median age — yr (range)		No. of marrow cells transplanted — ×10⁻⁸/kg of recipient's body weight‡	
Patients	35 (6–55)	Median	3.0
Donors	38 (19–58)	Range	0.6–14.3
Sex of patient and donor — no. (%)		25th and 75th percentiles	2.5, 3.9
Male/male	57 (29)	Date of transplantation — no. (%)	
Male/female	43 (22)	1985–1988	14 (7)
Female/male	55 (28)	1989–1990	58 (30)
Female/female	41 (21)	1991–1992	64 (33)
Time from diagnosis to transplantation — no. (%)		1993–1994	60 (31)
<1 yr	65 (33)	CMV status of patient and donor — no. (%)	
1 to 2 yr	65 (33)	Seronegative/seronegative	82 (42)
>2 to 3 yr	21 (11)	Seronegative/seropositive	23 (12)
>3 to 4 yr	15 (8)	Seropositive/seronegative	53 (27)
>4 yr	30 (15)	Seropositive/seropositive	38 (19)
Median time from diagnosis to transplantation — yr (range)	1.4 (1–14.6)	CMV-seronegative patients — no. (%)	
Body-weight index of patient — no. (%)‡		No fluconazole	50 (26)
90–110	90 (46)	Fluconazole	55 (28)
111–125	59 (30)	CMV-seropositive patients — no. (%)	
126–140	27 (14)	No ganciclovir or fluconazole	33 (17)
>140	17 (9)	Ganciclovir or fluconazole	49 (25)
Unknown	3 (2)	Ganciclovir, no fluconazole	8 (4)
Donor history of pregnancy — no. (%)		Fluconazole, no ganciclovir	1 (<1)
None	26 (31)	Dose of total-body irradiation — no. (%)	
≥1	56 (67)	1200 cGy	160 (82)
Unknown	2 (2)	≥1320 cGy	36 (18)

*Because of rounding not all percentages total 100. CMV denotes cytomegalovirus.

‡Body-weight index was calculated as actual body weight divided by ideal body weight × 100 percent. Ideal body weight was defined according to the criteria of Hathaway and Foard.¹⁰

‡Values are the total numbers of nucleated cells.

methoxazole were given in standard doses for prophylaxis against *Pneumocystis carinii* pneumonia. From December 1990 through August 1994, all patients were placed in isolation in rooms with laminar air flow and received oral nonabsorbable antibiotics for the prevention of bacterial and fungal infection. After August 1994, patients were nursed in conventional private rooms supplied with positive-pressure filtered air. Systemic antibiotics were administered for the prevention of bacterial infection once the absolute neutrophil count fell below 500 per cubic millimeter.

Patients who were seronegative for cytomegalovirus received blood products from donors who were seronegative for cytomegalovirus or leukocyte-depleted blood products from seropositive donors. From November 16, 1990, through August 8, 1991, patients who were seropositive for cytomegalovirus were randomly assigned to receive ganciclovir or placebo at the time of engraftment for the prevention of cytomegalovirus disease.¹⁸ After August 8, 1991, such patients received ganciclovir as soon as the absolute neutrophil count exceeded 750 per cubic millimeter for two days or as soon as cytomegalovirus antigenemia was detected.¹⁹ From July 1, 1990, through March 1, 1992, all patients were

randomly assigned to receive fluconazole or placebo beginning before transplantation and continuing until day 75 after transplantation for the prevention of fungal infection.²⁰ After March 1, 1992, all patients received fluconazole prophylaxis.

Engraftment

Neutrophil engraftment was considered to have occurred on the first of three consecutive days in which the absolute neutrophil count exceeded 500 per cubic millimeter. Platelet engraftment was considered to have occurred on the first of seven consecutive days in which the platelet count exceeded 20,000 per cubic millimeter without platelet transfusions. The presence of donor cells was demonstrated by the detection of informative variable-number tandem-repeat polymorphisms²¹ or by fluorescent in situ hybridization with a Y-chromosome-specific probe in cases of sex-mismatched transplants.²² The analysis of graft failure was limited to patients who survived at least 28 days without relapse of leukemia. Graft failure was defined as the failure to achieve an absolute neutrophil count of more than 500 per cubic millimeter for at least three consecutive days, a decrease in the ab-

solite neutrophil count to below 200 per cubic millimeter for at least three consecutive days after initial engraftment, or documentation of the loss of donor cells by testing with use of informative markers.

Graft-versus-Host Disease

Acute and chronic GVHD were diagnosed and graded according to standard criteria.^{23,24} The probability of clinically extensive chronic GVHD was evaluated in patients who survived for at least 80 days in clinical remission with sustained engraftment.

Relapse

Relapse was defined as clinical evidence of recurrent chronic myeloid leukemia or the detection of a Philadelphia chromosome on at least two occasions after day 50 in a patient with a normal blood-cell differential count and bone marrow morphology. Marrow cytogenetic studies were scheduled on days 28, 56, and 84 and then 6, 12, 18, and 24 months after transplantation.

Karnofsky Performance Scores

The Karnofsky Performance Scale was used to assess the functional capacity of surviving patients at one-year intervals. Scores were analyzed for all assessments made within three months before or after each yearly anniversary.

Statistical Analysis

Cox regression analysis was used to determine the effect of various variables on the end points granulocyte and platelet recovery, acute GVHD of grade III or IV, clinically extensive chronic GVHD, and survival. The variables examined for association with these end points are shown in Table 1. For the purposes of analysis, the patient's age and the interval from diagnosis to transplantation were treated as categorical variables. Categories for relevant variables were assigned before the data were analyzed but were broadened if the data suggested that the results were similar within subcategories. Values for the number of marrow cells transplanted were log-transformed to accommodate extreme upper outliers and then analyzed as a continuous variable. Fluconazole use, ganciclovir use, and cytomegalovirus status were highly correlated and were therefore combined to create a variable with four categories. Because there were relatively few patients with mismatches at the HLA-A or B locus, HLA-matching status was categorized as being identical for HLA-A, B, and DRB1, involving a minor mismatch of HLA-A or B, or involving a minor mismatch of HLA-DRB1.

Cumulative-incidence estimates²⁵ were used for GVHD and relapse, and survival was estimated according to the method of Kaplan and Meier.²⁶ Death without GVHD and relapse, respectively, was considered a competing risk factor for GVHD and relapse, as was relapse for the end points related to GVHD. Multivariable regression models included only variables for which the association with the clinical outcome was significant at the 0.05 level, and data on patients who did not reach an end point were censored at the time of either last contact or failure due to a competing risk factor. Two-sided P values from regression models were derived from the Wald test without adjustment for multiple comparisons. A P value ≤ 0.05 and ≥ 0.01 was therefore considered suggestive rather than conclusive evidence of an association.

RESULTS

Engraftment

Four patients died before day 28 after transplantation, leaving 192 patients who could be evaluated. Graft failure occurred in 10 patients (5 percent) (Table 2) and included 6 cases of primary graft failure. Three of the 10 patients with graft failure died: 2 on days 40 and 51 from complications of

TABLE 2. RATES OF SURVIVAL, GRAFT FAILURE, RELAPSE, AND DEATH WITHOUT RELAPSE IN PATIENTS WHO UNDERWENT TRANSPLANTATION FOR CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE.

VARIABLE	VALUE
Survival — % (95% CI)*	
1 yr	67 (61–74)
3 yr	61 (59–67)
5 yr	57 (49–64)
Length of follow-up among survivors — days	
Median	1828
Range	451–3690
Graft failure†	
No. of patients (%)	10 (5)
No. surviving graft failure	7
No. surviving disease-free	4
Relapse	
No. of patients (%)‡	15 (10)
Time to relapse — days	
Median	253
Range	39–1090
No. surviving in relapse	8
No. surviving disease-free	4
Death without relapse	
No. of patients (%)§	76 (44)
Time to death — days	
Median	142
Range	13–2590

*Kaplan–Meier estimates of overall survival one, three, and five years after transplantation, as of December 1, 1997, are shown. CI denotes confidence interval.

†The incidence of graft failure is shown for patients who survived at least 28 days.

‡The value in parentheses is the cumulative-incidence estimate of relapse five years after transplantation among all 196 patients.

§Death was not related to leukemia. The value in parentheses is the cumulative-incidence estimate of death without relapse three years after transplantation.

pancytopenia, and 1 on day 1736 with recurrent leukemia. Of the seven patients who survived despite failure of engraftment, two had recovery of autologous hematopoiesis, with recurrent chronic myeloid leukemia, and five underwent a second transplantation. In four of these five patients the second transplant engrafted, and at the most recent follow-up visit, they remained in remission 971, 1196, 1230, and 2168 days after the first transplantation. A logistic-regression analysis suggested that patients who received fewer marrow cells were more likely to have graft failure than those who received a large number of marrow cells (modeled as a continuous variable and adjusted for the recipient's body weight) ($P=0.03$; relative risk, 4.9 for each decrement of $\log_{10} [1.0 \times 10^8 \text{ cells per kilogram}]$).

The median time to neutrophil recovery was 22 days (range, 14 to 51). Neutrophil recovery occurred earlier in patients who received a larger num-

ber of marrow cells ($P=0.05$; relative risk, 1.5 for each increment of \log_{10} [1.0×10^8 cells per kilogram]). The median time to platelet recovery was 22 days (range, 5 to 170). The time to platelet recovery was longer in patients who received HLA-DRB1-mismatched transplants than in those who received fully matched transplants (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.8; $P=0.007$), and patients who received a larger number of marrow cells were more likely to have platelet recovery ($P=0.002$; relative risk, 1.9 for each increment of \log_{10} [1.0×10^8 cells per kilogram]).

Graft-versus-Host Disease

The incidence of acute GVHD of grade II to IV was 77 percent among patients who received transplants matched for HLA-A, B, and DRB1; 89 percent among those with a minor mismatch of HLA-A or B; and 95 percent among those with a minor mismatch of HLA-DRB1. The respective incidence of severe acute GVHD of grade III or IV was 35, 37, and 50 percent in these groups. The cause-specific risk of acute GVHD was not significantly associated with the patient's age, the donor's age, the time from diagnosis to transplantation, or the number of marrow cells transplanted. The association of the sex of patient-donor pairs with the risk of acute GVHD differed according to the extent of the HLA matching ($P=0.003$). Among fully matched pairs, male patients who received a marrow graft from a female donor had a higher risk than all other patient-donor pairs (relative risk, 2.5; 95 percent confidence interval, 1.4 to 4.5; $P=0.003$). Among pairs with HLA mismatches, GVHD was less likely to develop among male patients than among female patients regardless of the sex of the donor (relative risk, 0.3; 95 percent confidence interval, 0.1 to 0.7; $P=0.01$).

The cumulative-incidence estimate of clinically extensive chronic GVHD was 67 percent among the 161 patients who survived without relapse for at least 80 days. The extent of the HLA matching had no detectable association with the cause-specific risk of clinically extensive chronic GVHD. Grafts from women with a history of pregnancy were associated with an increased risk of chronic GVHD as compared with grafts from men (relative risk, 2.0; 95 percent confidence interval, 1.3 to 3.0; $P=0.002$). Among 54 patients with clinically extensive chronic GVHD who were still alive with complete follow-up at three years, 19 (35 percent) had discontinued immunosuppressive therapy, and among 25 patients who were still alive at five years, 14 (56 percent) had discontinued immunosuppressive therapy.

Relapse

Clinical or cytogenetic relapse was detected between 39 and 1090 days (median, 253) after transplantation in 15 patients, yielding a cumulative-incidence estimate of 10 percent at 5 years (Table 2).

At the most recent follow-up visit, 8 of the 15 patients (53 percent) were alive 315 to 1558 days after transplantation, and 4 were in cytogenetic remission after discontinuing immunosuppressive therapy (1 patient), receiving treatment with interferon (2), or undergoing a second transplantation (1).

Cause of Death

Three patients (2 percent) died from complications of graft failure, and seven patients (4 percent) died from complications of recurrent chronic myeloid leukemia between 53 and 1736 days after transplantation (median, 244). Seventy-six patients (39 percent) died without recurrent chronic myeloid leukemia between 13 and 2590 days after transplantation (median, 142). Death was associated most frequently with treatment-resistant GVHD. Bacterial infection contributed to 19 deaths, and fungal infection (especially aspergillus) to 13. Cytomegalovirus disease contributed to 10 deaths, but only 1 of these occurred after 1992. Death was associated with a lymphoproliferative syndrome in one patient.

Survival

The Kaplan-Meier estimate of survival at five years was 57 percent (95 percent confidence interval, 49 to 64 percent) (Table 2). The median duration of follow-up was 5 years (range, 1.2 to 10.1). A multivariable analysis identified six factors associated with a risk of death: extent of HLA matching, time from diagnosis to transplantation, body-weight index, use of prophylaxis against cytomegalovirus, use of prophylaxis against fungal infections, and age (Table 3). Patients who were over 50 years of age had a significantly higher risk of death than patients who were 21 to 50 years of age (relative risk, 3.4; 95 percent confidence interval, 1.6 to 7.4) (Fig. 1 and Table 3).

Patients who were 50 years of age or younger who received transplants matched for HLA-A, B, and DRB1 within one year after diagnosis had a particularly good prognosis. In this subgroup of 51 patients, the probability of surviving five years was 74 percent (95 percent confidence interval, 62 to 86 percent) (Fig. 2). The administration of fluconazole for fungal prophylaxis and the administration of ganciclovir to cytomegalovirus-seropositive patients at the time of engraftment or antigenemia increased the probability of survival. After the institution of routine prophylaxis with fluconazole and ganciclovir, estimated survival in this group was 87 percent at three years (30 patients; 95 percent confidence interval, 74 to 99 percent).

Karnofsky Performance Scores

One year after transplantation, 36 percent of 119 patients who could be evaluated had a Karnofsky

TABLE 3. MULTIVARIABLE ANALYSIS OF MORTALITY AMONG PATIENTS WHO RECEIVED A TRANSPLANT FROM AN UNRELATED DONOR FOR CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE.

VARIABLE	RELATIVE RISK (95% CONFIDENCE INTERVAL)	P VALUE
Patient's age		
0–20 yr	0.9 (0.3–2.6)	0.84
21–50 yr*	1.0	
>50 yr	3.4 (1.6–7.4)	0.002
HLA-matching status		
Matched for HLA-A, B, DRB1*	1.0	
Minor mismatch of HLA-A or B	1.2 (0.6–2.5)	0.61
Minor mismatch of HLA-DR	2.7 (1.4–5.2)	0.002
Time from diagnosis of disease to transplantation		
<1 yr*	1.0	
1–3 yr	1.2 (0.7–2.0)	0.57
>3 yr	2.0 (1.1–3.8)	0.03
Body-weight index†		
	1.6 (1.2–2.2)	0.001
Seronegative for CMV‡		
Fluconazole prophylaxis*	1.0	
No fluconazole prophylaxis	2.2 (1.2–4.0)	0.02
Seropositive for CMV‡		
Ganciclovir prophylaxis§	0.7 (0.4–1.4)	0.36
No ganciclovir prophylaxis¶	2.2 (1.2–4.3)	0.02

*This is the reference group.

†Body-weight index was modeled as a continuous variable, with increments of 25 percent.

‡CMV denotes cytomegalovirus.

§Patients in this category received ganciclovir at the time of initial engraftment or had ganciclovir available in the event of cytomegalovirus antigenemia detected by weekly monitoring. Forty-nine of the 57 seropositive patients in this category (86 percent) also received fluconazole as prophylaxis against fungal infection.

¶Patients in this category did not receive ganciclovir at the time of initial engraftment and did not have ganciclovir available in the event of cytomegalovirus antigenemia. Only 1 of the 34 seropositive patients in this category (3 percent) received fluconazole as prophylaxis against fungal infection.

performance score of 100, 70 percent had a score of 90 or more, and 86 percent a score of 80 or more. At three years, 50 percent of 46 patients who could be evaluated had a Karnofsky performance score of 100, 76 percent a score of 90 or more, and 98 percent a score of 80 or more.

DISCUSSION

This study, like others before it, demonstrates that marrow transplantation from an HLA-matched unrelated donor can cure patients with chronic myeloid leukemia in chronic phase. Previous studies, however, have reported that this approach has less favorable results than transplantation from an HLA-identical sibling, most likely because of the higher incidence of severe GVHD among recipients of marrow from unrelated donors.^{4,9} Nevertheless, we iden-

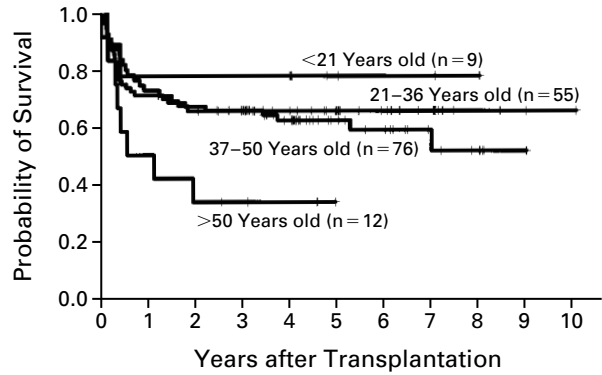


Figure 1. Probability of Survival in 152 Patients with Chronic Myeloid Leukemia in Chronic Phase Who Received a Transplant Matched for HLA-A, B, and DRB1 from an Unrelated Donor, According to Age.

Tick marks represent patients alive at the last follow-up.

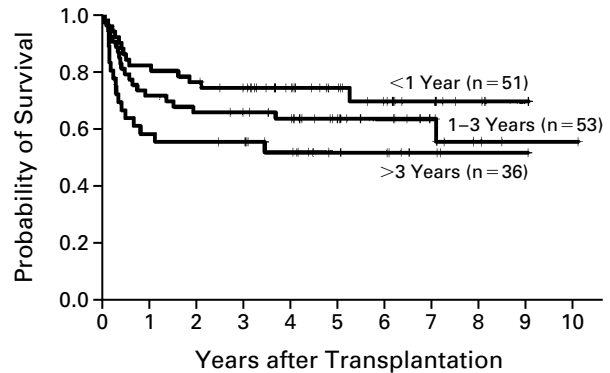


Figure 2. Probability of Survival in 140 Patients with Chronic Myeloid Leukemia in Chronic Phase Who Were ≤50 Years Old and Received a Transplant Matched for HLA-A, B, and DRB1 from an Unrelated Donor, According to the Time from Diagnosis to Transplantation.

Tick marks represent patients alive at the last follow-up.

tified a group of patients whose survival compares well with the results in patients who received a transplant from an HLA-identical sibling. Among patients 50 years old or younger who received a graft from an unrelated donor matched for HLA-A, B, and DRB1 within one year after diagnosis, the estimated survival was 74 percent at five years. The probability of survival among patients with chronic myeloid leukemia in chronic phase who receive marrow from an HLA-identical sibling at our center is 77 percent at five years if the transplantation is performed within one year after diagnosis.²⁷

Results of transplantation with marrow from unrelated donors for the treatment of chronic myeloid leukemia have been analyzed in previous studies. Direct comparisons are difficult for several reasons. Selection bias can be introduced by center-specific

eligibility criteria, and definitions of end points other than survival have not been standardized. Clinical results might be affected by differences in treatment, especially with regard to the pretransplantation conditioning regimen, T-cell depletion of the marrow, immunosuppression after transplantation, prophylaxis against infection, and other types of supportive care. Moreover, the cumulative-incidence estimates used in this study and the Kaplan–Meier estimates used in previous studies to report outcomes such as graft failure, GVHD, and relapse can yield numerically different results.

In our series, the incidence of graft failure was higher than expected for patients with chronic myeloid leukemia in chronic phase who received a transplant from an HLA-identical sibling.²⁷ Graft failure after marrow transplantation from an unrelated donor has been more frequent among patients with chronic myeloid leukemia than among patients with acute leukemia.²⁸ A previous study has shown that incompatibility for class I HLA alleles, especially HLA-C, increases the risk of graft failure.²⁸

The 10 percent cumulative-incidence estimate of clinical or cytogenetic relapse in this study may be lower than the cumulative incidence of 15 to 20 percent observed after transplantation from an HLA-identical sibling.²⁷ In the current analysis, there was no detectable association between the donor's sex or the extent of HLA mismatching and the cause-specific risk of relapse, although the ability to detect such an association was limited by the small number of relapses.

The sex of the donor and the recipient and a history of pregnancy in donors were identified as risk factors for acute and chronic GVHD in patients who received transplants matched for HLA-A, B, and DRB1 from unrelated donors. These same risk factors have also been reported for transplants from HLA-identical siblings.²⁹ The absence of any detectably increased risk of GVHD in association with a mismatch of HLA-A or B was unexpected in the light of previous results showing that a single disparity in class I HLA alleles increased the risk of GVHD after transplantation from HLA-haploidentical relatives.^{30,31} We allowed a disparity of HLA-A or B only within serologically cross-reactive groups of antigens, a selection factor that could have limited the risk of GVHD. The findings that recipients of transplants mismatched for HLA-DRB1 are at increased risk for acute GVHD and death are consistent with those of a previous study.¹¹

The age of the recipient appeared to be a significant variable only for patients over 50 years of age, although the number of patients in this group was small. The overall survival of patients 21 to 36 years of age and 37 to 50 years of age was very similar. This finding argues that eligibility for transplantation should not be routinely limited to patients un-

der 35 or 40 years of age, as is the current practice in some centers.

During the past decade, the results of marrow transplantation have been improved by better supportive care. For patients with chronic myeloid leukemia, this improvement has in turn encouraged transplantation earlier in the course of the disease. Before the advent of ganciclovir as prophylaxis against cytomegalovirus, seropositive patients had a high risk of cytomegalovirus disease, which was frequently fatal. The use of ganciclovir at the time of initial antigenemia early in the course of infection has dramatically diminished the incidence of cytomegalovirus disease and interstitial pneumonia.^{18,19} A randomized study likewise showed that prophylaxis with fluconazole decreases the risk of fungal infection and improves survival.²⁰

The duration of disease before transplantation was identified as a predictor of survival in this study. The importance of the time from diagnosis to transplantation was initially recognized in patients with chronic myeloid leukemia who received a transplant from an HLA-identical sibling.^{1,32,33} This finding underscores the overall importance of planning treatment and the need to conduct an efficient and timely search for unrelated donors for patients who lack an HLA-identical sibling. Although successful hematopoietic stem-cell transplantation remains the only known cure for patients with chronic myeloid leukemia, the use of interferon has produced clinical and sometimes cytogenetic remission, which can delay the progression of the disease and prolong survival.³⁴⁻³⁷ The choice between interferon therapy and allogeneic stem-cell transplantation can be problematic. Lee et al.³⁸ used decision analytic techniques to compare these options. Their results, based on quality-adjusted life-expectancy data, support the use of early transplantation from unrelated donors for most patients with chronic myeloid leukemia.

Our data on survival and relapse demonstrate that the results of marrow transplantation from HLA-matched, unrelated donors can be similar to those for transplantation from HLA-identical siblings for patients with chronic myeloid leukemia in chronic phase. In the case of transplantation from unrelated donors, the risk of acute GVHD can be minimized in male patients by the use of an HLA-matched male donor, and the risk of chronic GVHD can be minimized in both male and female patients by the use of male donors or female donors who have not been pregnant. Survival can be optimized by performing transplantation early in the course of disease, by matching for HLA-DRB1 alleles, and by the use of fluconazole and ganciclovir for the prevention of fungal and cytomegalovirus infection.

Supported by grants (AI33484, CA15704, CA18029, and CA18221) from the National Institutes of Health.

We are indebted to the physicians and investigators at the Fred Hutchinson Cancer Research Center who participated in this trial: William I. Bensinger, M.D., Eileen M. Bryant, Ph.D., H. Joachim Deeg, M.D., Kris C. Doney, M.D., Mary Flowers, M.D., Richard A. Nash, M.D., Patricia Stewart, M.D., Robert P. Witherspoon, M.D., and Ann Woolfrey, M.D.; and to Jennie Lorenz and Alison Sell for their assistance in the collection of data and preparation of the manuscript.

REFERENCES

1. Thomas ED, Clift RA, Fefer A, et al. Marrow transplantation for the treatment of chronic myelogenous leukemia. *Ann Intern Med* 1986;104:155-63.
2. Goldman JM, Apperley JF, Jones L, et al. Bone marrow transplantation for patients with chronic myeloid leukemia. *N Engl J Med* 1986;314:202-7.
3. McCullough J, Hansen J, Perkins H, Stronck D, Bartsch G. The National Marrow Donor Program: how it works, accomplishments to date. *Oncology* 1989;3:63-74.
4. Beatty PG, Ash R, Hows JM, McGlave PB. The use of unrelated bone marrow donors in the treatment of patients with chronic myelogenous leukemia: experience of four marrow transplant centers. *Bone Marrow Transplant* 1989;4:287-90.
5. McGlave PB, Beatty P, Ash R, Hows JM. Therapy for chronic myelogenous leukemia with unrelated donor bone marrow transplantation: results in 102 cases. *Blood* 1990;75:1728-32. [Erratum, *Blood* 1990;76:654.]
6. Mackinnon S, Hows JM, Goldman JM, et al. Bone marrow transplantation for chronic myeloid leukemia: the use of histocompatible unrelated volunteer donors. *Exp Hematol* 1990;18:421-5.
7. McGlave P, Bartsch G, Anasetti C, et al. Unrelated donor marrow transplantation therapy for chronic myelogenous leukemia: initial experience of the National Marrow Donor Program. *Blood* 1993;81:543-50.
8. Marks DI, Cullis JO, Ward KN, et al. Allogeneic bone marrow transplantation for chronic myeloid leukemia using sibling and volunteer unrelated donors: a comparison of complications in the first 2 years. *Ann Intern Med* 1993;119:207-14.
9. Spencer A, Szydlo RM, Brookes PA, et al. Bone marrow transplantation for chronic myeloid leukemia with volunteer unrelated donors using ex vivo or in vivo T-cell depletion: major prognostic impact of HLA class I identity between donor and recipient. *Blood* 1995;86:3590-7.
10. Hathaway ML, Foard ED. Heights and weights of adults in the U.S. Home Economics Research Report no. 10. Washington, D.C.: Department of Agriculture, 1960:111.
11. Petersdorf EW, Longton GM, Anasetti C, et al. The significance of HLA-DRB1 matching on clinical outcome after HLA-A, B, DR identical unrelated donor marrow transplantation. *Blood* 1995;86:1606-13.
12. Hansen JA, Mickelson EM, Choo SY, et al. Clinical bone marrow transplantation: donor selection and recipient monitoring. In: Rose NR, de Macario EC, Fahey JL, Friedman H, Penn GM, eds. *Manual of clinical laboratory immunology*. 4th ed. Washington, D.C.: American Society for Microbiology, 1992:850-66.
13. Mickelson EM, Guthrie LA, Etzioni R, Anasetti C, Martin PJ, Hansen JA. Role of the mixed lymphocyte culture (MLC) reaction in marrow donor selection: matching for transplants from related haploidentical donors. *Tissue Antigens* 1994;44:83-92.
14. Mickelson EM, Longton G, Anasetti C, et al. Evaluation of the mixed lymphocyte culture (MLC) assay as a method for selecting unrelated donors for marrow transplantation. *Tissue Antigens* 1996;47:27-36.
15. Beatty PG, Hansen JA, Longton GM, et al. Marrow transplantation from HLA-matched unrelated donors for treatment of hematologic malignancies. *Transplantation* 1991;51:443-7.
16. Anasetti C, Petersdorf EW, Martin PJ, Hansen JA. Marrow transplantation from unrelated volunteer donors. In: Buckner CD, Clift RA, eds. *Technical and biological components of marrow transplantation. Cancer treatment and research no. 76*. Boston: Kluwer Academic, 1995:137-68.
17. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N Engl J Med* 1986;314:729-35.
18. Goodrich JM, Bowden RA, Fisher L, Keller C, Schoch G, Meyers JD. Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. *Ann Intern Med* 1993;118:173-8.
19. Goodrich JM, Bocckh M, Bowden R. Strategies for the prevention of cytomegalovirus disease after marrow transplantation. *Clin Infect Dis* 1994;19:287-98.
20. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation — a prospective, randomized, double-blind study. *J Infect Dis* 1995;171:1545-52.
21. Blazar BR, Orr HT, Arthur DC, Kersey JH, Filipovich AH. Restriction fragment length polymorphisms as markers of engraftment in allogeneic marrow transplantation. *Blood* 1985;66:1436-44.
22. Durnam DM, Anders KR, Fisher L, O'Quigley J, Bryant EM, Thomas ED. Analysis of the origin of marrow cells in bone marrow transplant recipients using a Y-chromosome-specific in situ hybridization assay. *Blood* 1989;74:2220-6.
23. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995;15:825-8.
24. Sullivan KM, Agura E, Anasetti C, et al. Chronic graft-versus-host disease and other late complications of bone marrow transplantation. *Semin Hematol* 1991;28:250-9.
25. Pepe MS, Longton G, Pettinger M, Mori M, Fisher LD, Storb R. Summarizing data on survival, relapse, and chronic graft-versus-host disease after bone marrow transplantation: motivation for and description of new methods. *Br J Haematol* 1993;83:602-7.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
27. Clift RA, Buckner CD, Thomas ED, et al. Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. *Blood* 1994;84:2036-43.
28. Petersdorf EW, Longton GM, Anasetti C, et al. Association of HLA-C disparity with graft failure after marrow transplantation from unrelated donors. *Blood* 1997;89:1818-23.
29. Nash RA, Pepe MS, Storb R, et al. Acute graft-versus-host disease: analysis of risk factors after allogeneic marrow transplantation and prophylaxis with cyclosporine and methotrexate. *Blood* 1992;80:1838-45.
30. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med* 1985;313:765-71.
31. Anasetti C, Hansen JA. Effect of HLA incompatibility in marrow transplantation from unrelated and HLA-mismatched related donors. *Transfus Sci* 1994;15:221-30.
32. Goldman JM, Szydlo R, Horowitz MM, et al. Choice of pretransplant treatment and timing of transplants for chronic myelogenous leukemia in chronic phase. *Blood* 1993;82:2235-8.
33. Buckner CD, Clift RA. Timing of allogeneic marrow transplants for patients with chronic myeloid leukemia. *Bone Marrow Transplant* 1995;15:Suppl 1:S203-S206.
34. Talpaz M, Kantarjian HM, McCredie K, Trujillo JM, Keating MJ, Gutterman JU. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha₂ in chronic myelogenous leukemia. *N Engl J Med* 1986;314:1065-9.
35. Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of interferon- α with busulfan and hydroxyurea in chronic myelogenous leukemia. *Blood* 1994;84:4064-77.
36. The Italian Cooperative Study Group on Chronic Myeloid Leukemia. Interferon alfa-2a as compared with conventional chemotherapy for the treatment of chronic myeloid leukemia. *N Engl J Med* 1994;330:820-5.
37. Allan NC, Richards SM, Shepherd PC. UK Medical Research Council randomised, multicentre trial of interferon-alpha n1 for chronic myeloid leukemia: improved survival irrespective of cytogenetic response. *Lancet* 1995;345:1392-7.
38. Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myeloid leukemia: a decision analysis. *Ann Intern Med* 1997;127:1080-8.