

Allogeneic bone marrow transplantation for chronic myelogenous leukemia: comparative analysis of unrelated versus matched sibling donor transplantation

Daniel J. Weisdorf, Claudio Anasetti, Joseph H. Antin, Nancy A. Kernan, Craig Kollman, David Snyder, Effie Petersdorf, Gene Nelson, and Philip McGlave

Allogeneic bone marrow transplantation (BMT) offers the only curative therapy for chronic myelogenous leukemia. We compared prospectively collected results of 2464 unrelated donor (URD) transplantations with 450 HLA-identical, matched sibling donor (MSD) transplantations performed at collaborating National Marrow Donor Program institutions. A total of 63% of URDs were matched at HLA-A, -B, and at -DRB1 alleles; all MSDs were genotypically identical at major histocompatibility loci. URD recipients were younger (median 36 vs 39, $P = .001$) than MSDs and underwent BMT later after diagnosis (median 17 [0-325 months] vs 7 [1-118 months], $P = .001$) and less often in chronic phase (CP) (67% vs 82%, $P = .001$). Multivar-

iate analysis demonstrated a significantly increased risk of graft failure and acute graft versus host disease after URD BMT. The risk of hematologic relapse was low after either matched URD or MSD transplantations. We observed significantly though modestly poorer survival and disease-free survival (DFS) after URD transplantations. However, for those undergoing transplantation during CP within 1 year from diagnosis, 5-year DFS was similar or only slightly inferior after matched URD versus MSD transplantation (age < 30: URD 61% \pm 8% vs MSD 68% \pm 15%, $P = .18$; 30-40: URD 57% \pm 9% vs MSD 67% \pm 10%, $P = .05$; > 40: URD 46% \pm 9% vs MSD 57% \pm 9%, $P = .02$). Delay from diagnosis to BMT in CP patients led to substantially poorer 5-year DFS after

matched URD than MSD BMT (CP 1-2 years: URD 39% \pm 6% vs MSD 63% \pm 12%; beyond 2 years: URD 33% \pm 7% vs MSD 50% \pm 20%). Outcome of matched URD BMT for early CP chronic myelogenous leukemia yields survival and DFS approaching that of MSD transplantation. However, delay may compromise URD outcomes to a greater extent. Improvements in URD and MSD transplantation are still needed, and results of newer, nontransplantation therapies should be evaluated against the established curative potential of URD and MSD marrow transplantation. (Blood. 2002;99:1971-1977)

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Introduction

Allogeneic bone marrow transplantation (BMT) is currently the only curative therapy for chronic myelogenous leukemia (CML).¹⁻⁶ Both the pretransplantation chemoradiotherapy conditioning and the allogeneic immune antitumor effect are responsible for leukemic cell eradication and extended leukemia-free survival.⁷⁻¹⁰ While matched sibling donor (MSD) and unrelated donor (URD) allografts have been well recognized as suitable and potentially curative therapeutic opportunities, the distinctive clinical course, complications, and outcomes of these 2 allograft approaches have not been directly compared.¹¹⁻¹⁶ We prospectively collected data on MSD transplantations performed at institutions participating with the National Marrow Donor Program (NMDP) to compare the results of MSD and URD BMT for CML. We herein report detailed results of this comparative analysis, including assessment of engraftment, graft versus host (GVH) disease, relapse, and leukemia-free survival.

data reported to and collected by the NMDP using prospectively designed data capture methods, auditing, centralized compilation, and data error correction at the NMDP.^{16,17}

Patients and characteristics

Characteristics of the 2914 cases are shown in Table 1. The URD transplantations occurred between 1988 and 1999. Beginning in 1991, prospective data from 34 transplantation centers reporting MSD transplantations to the NMDP were collected on similar data capture forms. Additional data were collected but excluded from this analysis on 129 URD cases because of inadequate follow-up data ($n = 89$) or the treatment being a second or subsequent transplantation ($n = 40$). Similarly, data on 296 other related donor transplantations were collected but excluded from this analysis because the donor was not a matched sibling ($n = 229$), follow-up was inadequate ($n = 44$), or the transplantation was not a first transplantation ($n = 23$).

Unrelated marrow donors were identified through the NMDP, and marrow was collected following established procedures through NMDP-approved donor and collection centers. Transplantations were performed at 127 NMDP-affiliated transplantation centers. Specifications for donor search and identification, marrow collection and transportation, and data gathering and analysis were performed according to procedures developed by the NMDP as described.^{16,17}

Patients and methods

Patients included in this analysis were those with CML who received bone marrow transplantation from MSD ($n = 450$) and URD ($n = 2464$) with

From the University of Minnesota, Minneapolis, MN; Fred Hutchinson Cancer Research Center, Seattle, WA; Dana-Farber Cancer Institute, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; City of Hope National Medical Center, Duarte, CA; and the National Marrow Donor Program, Minneapolis, MN.

Reprints: Daniel J. Weisdorf, University of Minnesota—Mayo Mail Code 480, 420 Delaware St SE, Minneapolis, MN 55455; e-mail: weisd001@tc.umn.edu.

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Table 1. Patient and donor characteristics

	MSDs (N = 450)	URDs (N = 2464)	P
Male (%)	286 (63)	1455 (59)	.08
Median age, y (range)	39 (3-59)	36 (1-62)	.001
Younger than 20 (%)	12 (3)	272 (11)	
20 to 39 (%)	205 (46)	1195 (49)	
40 and older (%)	233 (52)	997 (40)	
Disease stage at BMT			.001
Chronic phase (%)	369 (82)	1654 (67)	.10
Accelerated/remission after blast phase (%)	60 (13)	664 (27)	
Blast phase (%)	20 (4)	137 (6)	
Uncertain (%)	1 (0.2)	9 (0.4)	
Months from diagnosis to BMT, median (range)	7 (1-118)	17 (0-325)	.001
1 to 12 (%)	320 (71)	896 (36)	
13 to 24 (%)	84 (19)	713 (29)	
24 and more (%)	46 (10)	855 (35)	
Pre-BMT performance status*			.0001
90 to 100 (%)	387 (86)	2030 (83)	
Up to 80 (%)	63 (14)	421 (17)	
GVH disease prophylaxis			.02
T-cell depletion (%)	68 (15)	487 (20)	
Cyclosporine/tacrolimus (%)	373 (83)	1898 (77)	
Other (%)	9 (2)	79 (3)	
Pre-BMT conditioning			.001
TBI + cyclophosphamide + other (%)	287 (64)	2053 (83)	
Chemotherapy only (%)	163 (36)	411 (17)	
Median donor age, y (range)	38 (1-71)	37 (18-59)	.005
Female donors (%)	225 (50)	1040 (42)	.002
Interferon pre-BMT (%)	104 (23)	1355 (55)	< .001
CMV			.001
recipient – donor – (%)	117 (26)	855 (35)	
recipient – donor + (%)	67 (15)	391 (16)	
recipient + donor ± (%)	266 (59)	1218 (49)	

*Karnofsky performance status %.

Unrelated donor/recipient HLA molecular typing for DRB1^{18,19} was performed prior to transplantation or retrospectively using pretransplantation samples that had been cryopreserved. Serologic testing for HLA-A and -B as well as molecular testing for -DRB1 identified donor/recipient mismatching at A or B in 402 cases (16%). These included mismatch at HLA-A (n = 225) or HLA-B (n = 172) or both (n = 1); data on 4 were missing. These 402 were analyzed as partially matched. The remaining 2062 URD transplants matched at HLA-A and -B were also DRB1-matched at the allele level in 1559 cases (63% of URD transplants).^{18,19} Allele typing for class I loci was not available for this analysis. Sibling donor transplants were serologically matched at the HLA-A, -B and -DR regions in all 450 cases.

Pretransplantation conditioning included fractionated or single-dose total body irradiation along with cyclophosphamide, either alone or in combination with other chemotherapeutic agents in 2340 cases (287 MSD and 2053 URD transplantations). Only 574 patients received chemotherapy-only conditioning (without radiation), most often busulfan plus cyclophosphamide. In vivo GVH disease prophylaxis using cyclosporine or tacrolimus along with methotrexate or prednisone was used in 2271 patients (373 MSD and 1898 URD), while 555 received ex vivo T-cell-depleted marrow. T-cell depletion was more frequently employed for URD transplantation ($P = .02$).

Statistical analysis

As previously described, the NMDP uses prospectively designed forms and methods for data collection on all transplantations facilitated through the network.^{16,17} Baseline information and follow-up reporting were submitted

at scheduled posttransplantation intervals. Similar forms, adapted for matched sibling transplantation, were used for the prospective analysis of MSD transplantations.

Patient outcome was analyzed to the date of last reported follow-up or the date of death. Engraftment (neutrophil recovery to $0.5 \times 10^9/L$ [$500/\mu L$]) required survival to day +22, and patients without engraftment were considered graft failures.²⁰ Death before day +22 (100 URD, 8 MSD) and incomplete data (14 URD) excluded patients from analyses of engraftment. Relapse was analyzed as hematologic relapse. Cytogenetic sampling or reverse transcriptase–polymerase chain reaction analyses of the BCR-ABL molecular abnormality was not routinely performed at defined, scheduled posttransplantation intervals, resulting in potential reporting bias as well as imprecision in the assessment of the clinical outcome following such observations. Survival was calculated by the method of Kaplan and Meier.²¹ In the calculation of time-to-event for analysis of relapse, engraftment, or GVH disease where early death could alter the assessment frequency, the cumulative incidence method was used.²² In univariate analyses, the log-rank test statistic was employed to compare differences in outcome among subgroups, and the 95% confidence intervals were calculated from the SEs.

In multiple regression analyses for engraftment, acute and chronic GVH disease, hematologic relapse, survival, and disease-free survival (DFS), the logistic regression (engraftment) or proportional hazards model²³ was employed including the following covariates: donor and recipient age, gender, cytomegalovirus (CMV) serology, disease stage, interval from diagnosis to transplantation, donor/recipient HLA matching [class I matched or mismatched; DRB1 matched or mismatched; or number of loci mismatched HLA-A, -B, -DRB1 (0-3)], total body irradiation containing conditioning (yes/no), T-lymphocyte depletion (yes/no), and year of transplantation. The impact of transplantation center was assessed by a fixed effects variable. Statistical interactions of donor type (MSD or URD) with several risk factors were examined, testing if the effect of donor type varies among subgroups of patients identified by these risk factors. No such interactions were detected.

The data collection period for MSD BMT (1991-1995) differed from the extended period of URD data collection (1988-1999). For the 233 URD transplantations that preceded and 1396 URD transplantations that followed the MSD cohort, we analyzed the era of URD BMT as an added variable in Cox regression models but observed no effect of URD transplantations that preceded ($P = .41$) or followed ($P = .32$) the 1991 to 1995 MSD era on DFS following BMT (not shown).

Results

Timing of BMT

As shown in Table 1, BMT using MSD occurred sooner after diagnosis than URD (median 7 vs 17 months, $P = .001$). This may be attributable to delays in decision making and donor availability that complicate URD transplantation. The average time for donor searching until transplantation was shorter for transplantations performed in first chronic phase (CP1) versus those in accelerated phase or after blast phase (mean search time 322, 419, and 418 days, respectively, $P = .004$). Even in the CP transplantations, search time was shorter to identify matched URD donors (mean 267 days) than partially matched URD (mean 377 days, $P = .0001$) though there was no statistically significant interaction between disease stage at transplantation and HLA match ($P = .14$).

Engraftment

Posttransplantation recovery to neutrophil level $0.5 \times 10^9/L$ ($500/\mu L$) was quicker and more likely after MSD versus URD transplantation. As shown in Table 2, significantly more patients undergoing URD matched or partially matched transplantations failed to

Table 2. Multivariate analysis of posttransplantation outcomes

	Odds ratio of graft failure (95% CI)*	Relative risk (95% CI)†	P
Graft failure			
MSD	1.0	—	—
URD matched	5.39 (1.92-15.1)	—	.001
URD partially matched	11.8 (4.12-33.8)	—	.0001
Chronic phase	1.0	—	—
Accelerated/remission post blast phase	1.49 (1.01-2.22)	—	.05
Blast phase	2.13 (1.10-4.10)	—	.02
Acute GVH disease (III-IV)			
MSD	—	1.0	—
URD matched	—	1.31 (1.06-1.62)	.01
URD partially matched	—	1.83 (1.44-2.32)	.0001
Chronic phase	—	1.0	—
Accelerated/remission post blast phase	—	1.12 (0.97-1.30)	.12
Blast phase	—	1.29 (0.99-1.67)	.06
Older donor age, per decade	—	1.10 (1.03-1.18)	.005
Time to transplantation more than 1 year	—	1.24 (1.08-1.43)	.002
Interferon therapy pre-BMT	—	0.85 (0.75-0.97)	.02
Chronic GVH disease			
MSD	—	1.0	—
URD matched	—	1.48 (1.26-1.74)	.0001
URD partially matched	—	1.50 (1.22-1.85)	.0001
Chronic phase	—	1.0	—
Accelerated/remission post blast phase	—	1.22 (1.06-1.41)	.006
Blast phase	—	1.47 (1.09-1.97)	.01
Female donor	—	1.21 (1.08-1.37)	.001
Hematologic relapse			
MSD	—	1.0	—
URD matched	—	1.13 (0.77-1.64)	.53
URD partially matched	—	1.48 (0.95-2.30)	.09
Chronic phase	—	1.0	—
Accelerated/remission post blast phase	—	4.37 (3.26-5.85)	.0001
Blast phase	—	12.8 (8.53-19.1)	.0001
Older recipient age	—	1.13 (1.00-1.27)	.06
Male donor	—	1.47 (1.11-1.92)	.006

*Multivariate logistic regression analysis of graft failure in patients surviving to day +22 (n = 2801). The odds ratio ± 95% confidence interval (CI) is shown.
 †Cox multivariate regression analyses showing the relative risk ± 95% CI of acute GVH disease, chronic GVH disease, and hematologic relapse.

achieve engraftment. Additionally, transplantations for CML beyond CP1 were associated with a lower likelihood of successful engraftment. As shown in Figure 1, for CP1 patients, graft failure occurred by day +100 in 1% ± 1% (95% confidence limits) of MSD, 4% ± 1% of matched URD, and 8% ± 2% of partially matched URD transplantations (*P* < .0001).

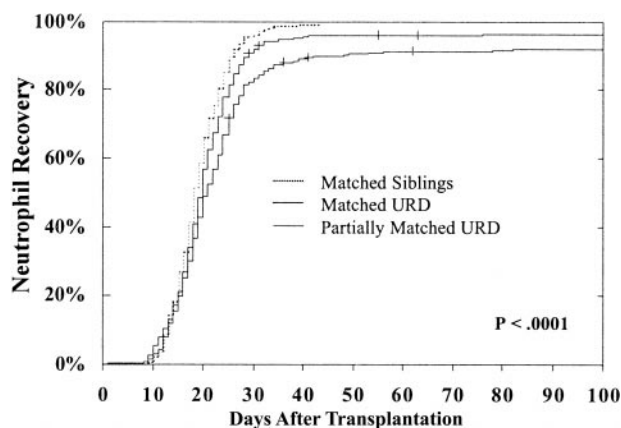


Figure 1. Engraftment. Engraftment (recovery to neutrophils > 0.5 × 10⁹/L [500/μL]) following BMT for CP CML using MSD (n = 364), matched URD (n = 1209), or partially matched URD (n = 386) BMT. Graft failure occurred in 1% ± 1% MSD, 4% ± 1% matched URD, and 8% ± 2% partially matched URD recipients (*P* < .0001).

Acute and chronic GVH disease

Advanced acute GVH disease (grade III-IV) occurred significantly more frequently after URD transplantation. As shown in Table 2, for BMT during CP, compared with MSD transplantations, matched URD transplantations were 1.31 times more likely (*P* = .01) to

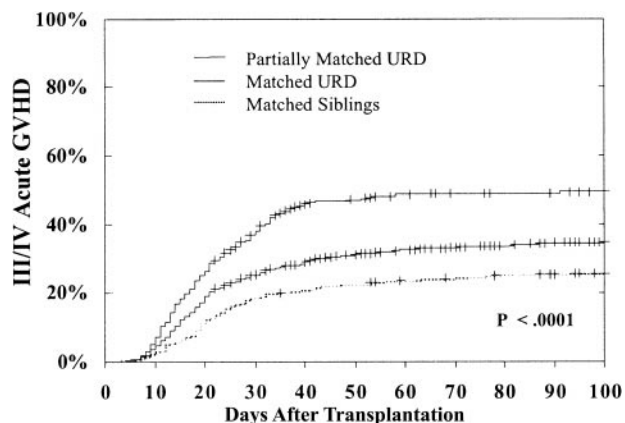


Figure 2. Cumulative 100-day incidence of grade III/IV acute GVH disease. Incidence after MSD (26% ± 5%), matched (35% ± 3%), or partially matched (49% ± 5%) URD BMT for CP CML (*P* < .0001).

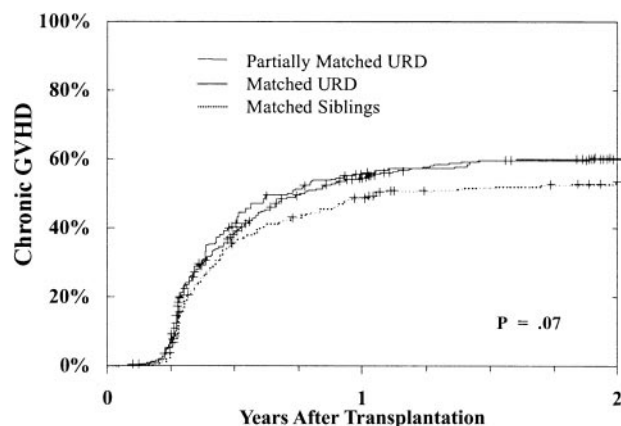


Figure 3. Cumulative incidence of chronic GVHD. Incidence in day +80 survivors after MSD ($n = 343$), matched ($n = 992$), or partially matched ($n = 241$) URD BMT for CP CML. By 2 years, MSD $53\% \pm 5\%$, $60\% \pm 3\%$ matched, and $60\% \pm 6\%$ partially matched URD developed chronic GVHD disease, $P = .07$.

result in acute GVHD and partially matched URD had a 1.83 times greater likelihood of acute GVHD disease ($P = .0001$). Transplantations beyond CP1 (especially in blast phase) were associated with more frequent acute GVHD disease. In addition, GVHD disease was significantly more frequent in transplantations from older donors and in transplantations performed beyond 1 year from diagnosis. Interferon therapy prior to BMT was associated with a lower risk of acute GVHD disease. As shown in Figure 2, in CP patients the 100-day cumulative incidence of grade III-IV GVHD disease was only $26\% \pm 5\%$ in MSD, $35\% \pm 3\%$ in URD matched, and $49\% \pm 5\%$ in URD partially matched transplantations ($P < .0001$).

Chronic GVHD disease occurred more frequently after URD transplantation as well. Table 2 shows that there was a nearly 1.5-fold greater risk of chronic GVHD disease after URD transplantation when compared with MSD BMT. This increased risk was similar following matched and partially matched URD BMT. In addition, chronic GVHD disease was more frequent in transplantations performed beyond the CP and using a female donor. Figure 3 shows the cumulative incidence of chronic GVHD disease in patients undergoing transplantation in CP1. As shown, at 2 years $53\% \pm 5\%$ of MSD recipients, $60\% \pm 3\%$ of URD matched recipients, and $60\% \pm 6\%$ of URD partially matched recipients developed chronic GVHD disease ($P = .07$).

Hematologic relapse

Hematologic relapse was uncommon and occurred with similar frequency in recipients of MSD ($n = 42$, 9.3%) or URD ($n = 199$, 8.1%) transplants ($P = .39$). As shown (Table 2), the donor type had only modest impact on hematologic relapse after transplantation. However, relapse was significantly more frequent in transplantations beyond the CP1, in older patients, and in patients receiving marrow from a male donor. Hematologic relapse was infrequent when performed in CP1: 5% to 8% for all 3 donor types (Figure 4A) ($P = .24$). As shown in Figure 4B, while the risk of relapse was higher for those undergoing transplantation beyond the CP (17%-20%), it was still similar after MSD or URD transplantation ($P = .54$).

Donor lymphocyte infusions

Donor lymphocyte infusions (DLIs) were given to only 68 (2.8%) patients after URD BMT. DLIs were given to 32 URD patients following CML relapse; of the 32, 17 had received a T-depleted graft. Two received DLIs for prevention of hematologic relapse (1 had received T-depleted BM). Fourteen others, 12 with T-depleted BM, received DLIs for management of B-cell lymphoproliferative disease, 4 for graft failure, 3 for management of viral infection, and 13 for unspecified reasons. DLIs were given to 17 (3.8%) MSD recipients, 16 for treatment of relapse (3 recipients of T-depleted marrow). Thus, of 555 recipients of T-depleted BM, 52 received DLI treatments compared with 33 DLIs in 2359 recipients of unmanipulated grafts ($P = .001$).

Survival and DFS

Patients in this series had a median follow-up of 2.1 years (range 0-11) in the URD recipients and 4.8 years (range 0.3-6.1) in the MSD recipients, although 233 (24%) of URD survivors have been followed for more than 5 years after BMT. A total of 988 (40.1%) URD and 268 (59.6%) MSD recipients are alive. Multivariate analysis showed better survival after MSD versus URD transplantations and significantly better survival for transplantations performed in CP (Table 3). Superior survival was seen in younger patients, in CMV-seronegative recipients, following transplantation (in CP) within 1 year of diagnosis, and in transplantations using younger donors. Even for transplantations performed during CP1, 5-year survival was superior for MSD ($63\% \pm 5\%$) compared with matched URD ($45\% \pm 3\%$) or partially matched URD

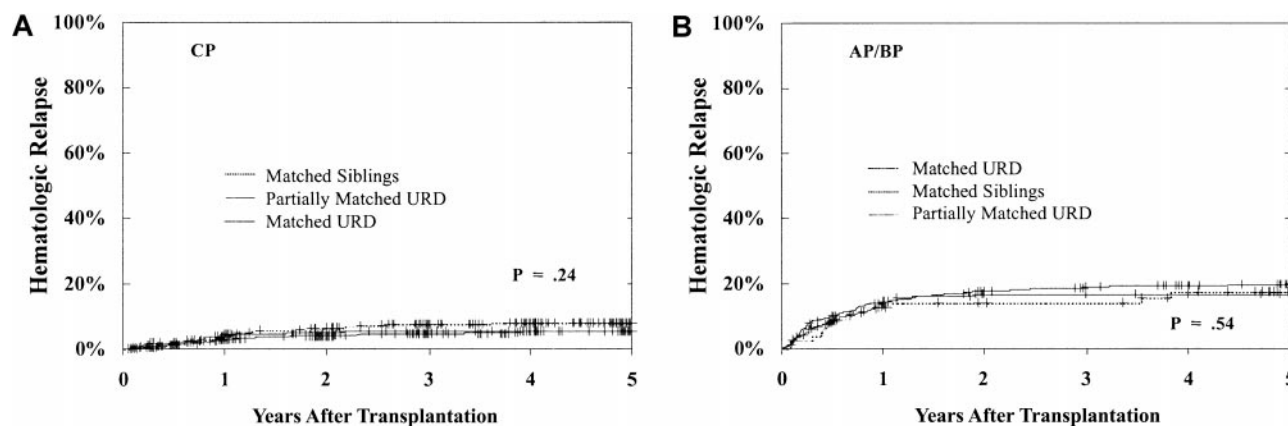


Figure 4. Hematologic relapse. Hematologic relapse of CML after BMT using MSD, matched, or partially matched URD in CP1 ([A] $n = 369$, 1244, 401, respectively; $P = .24$) and beyond CP (accelerated phase/blast phase; [B] $n = 80$, 536, 262, respectively; $P = .54$).

Table 3. Survival and DFS after BMT for CML: multivariate analyses

	Relative risk (95% CI)	P
Survival*		
MSD	1.0	—
URD matched	1.89 (1.59-2.25)	.0001
URD partially matched	2.74 (2.25-3.35)	.0001
Chronic phase	1.0	—
Accelerated phase/remission postblast phase	1.52 (1.35-1.70)	.0001
Blast phase	2.47 (2.04-2.99)	.0001
Older recipient age, per decade	1.17 (1.11-1.23)	.0001
Older donor age, per decade	1.08 (1.02-1.14)	.009
Recipient CMV-seropositive	1.17 (1.06-1.30)	.002
Time to BMT more than 1 year	1.34 (1.20-1.51)	.0001
DFS†		
MSD	1.0	—
URD matched	1.82 (1.53-2.16)	.0001
URD partially matched	2.66 (2.18-3.25)	.0001
Chronic phase	1.0	—
Accelerated phase/remission postblast phase	1.58 (1.41-1.78)	.0001
Blast phase	2.67 (2.20-3.24)	.0001
Older recipient age, per decade	1.18 (1.12-1.24)	.0001
Older donor age, per decade	1.05 (0.99-1.11)	.09
Recipient CMV-seropositive	1.17 (1.05-1.30)	.004
Time to BMT more than 1 year	1.33 (1.18-1.49)	.0001

*RR of death.
†RR of death or relapse.

(31% ± 5%) transplantation (Figure 5A, $P = .0001$). These differences were still apparent, with substantially poorer 5-year survival for transplantations performed beyond CP1 (Figure 5B, MSD 31% ± 11%; matched URD 20% ± 4%; partially matched URD 16% ± 6%, $P = .002$).

Prolonged survival without leukemia relapse is, of course, the desired outcome following allogeneic transplantation. As shown in Table 3, DFS was best after MSD versus URD transplantation, best when performed in CP, and significantly better for younger patients (and a trend with younger donors), for CMV-seronegative recipients and, importantly, for patients undergoing transplantation within 1 year of diagnosis. These prognostic indicators (donor type, disease phase, recipient age, and time from diagnosis to transplantation) had a major impact on both individual cohort outcome and on the comparison between URD and MSD BMT. As shown in Figure 6, for patients undergoing transplantation within 1 year of diagnosis, still within the CP1, patients aged less than 30 years, 30 to 40 years, and more than 40 years have superior 5-year DFS with

MSD versus matched URD BMT, though the differences are modest (age < 30: MSD 68% ± 15% vs matched URD 61% ± 8%, $P = .18$; 30-40: MSD 67% ± 10% vs matched URD 57% ± 9%, $P = .05$; > 40: MSD 57% ± 9% vs matched URD 46% ± 9%, $P = .02$).

As shown in Figure 7, 5-year DFS for patients in CP is best with a less than 1-year interval from diagnosis to BMT. Delay until BMT had a greater adverse impact on URD transplantation. There is little decrement in DFS for MSD recipients undergoing transplantation more than 1 year from diagnosis when compared with those undergoing transplantation within the first year ($P = .41$). However, while DFS after matched URD BMT is similar to MSD in the early (< 1 year) CP patients, DFS in the URD cohort is substantially worse after a delay of more than 1 year from diagnosis (Figure 7B, $P = .0001$). Similar falloff in DFS with longer diagnosis to BMT interval is observed with partially matched URD as well (Figure 7C, $P = .02$). Therefore, the outcome for transplantation in CP within 1 year from diagnosis is comparable in matched URD and MSD recipients, but for BMT delayed beyond 1 and 2 years the outcome for the URD recipients is notably worse.

Discussion

While only 20 years ago no curative therapy existed for CML, now allotransplantation can cure a sizable fraction of patients.^{1-6,11-16} Other advances have shown that α -interferon, with or without cytarabine, can extend time in CP and prolong survival.²⁴⁻²⁶ More recently, tyrosine kinase inhibitors can reverse the clinical manifestations of Philadelphia-positive CML with even less toxicity, although their impact on time to blast crisis and survival is as yet unknown.^{27,28} These promising alternatives, however, must be judged in the context of the defined value of allogeneic marrow transplantation with its well-established curative potential despite its initial toxicity and mortality.

In this report, we show the comparative value of MSD and URD allografts for treatment of CML in the largest cohort of allotransplantation recipients to be studied. Although the outcome overall is superior in the MSD cohort, certain populations of patients have remarkably similar outcomes after matched URD and MSD transplantations. Patients in CP receiving transplants within 1 year from diagnosis enjoy more than 60% DFS after MSD transplantations and 55% DFS at 5 years following matched URD transplantation. Both delay beyond 1 year and delay until clinical acceleration of the leukemia markedly compromises outcome, especially for

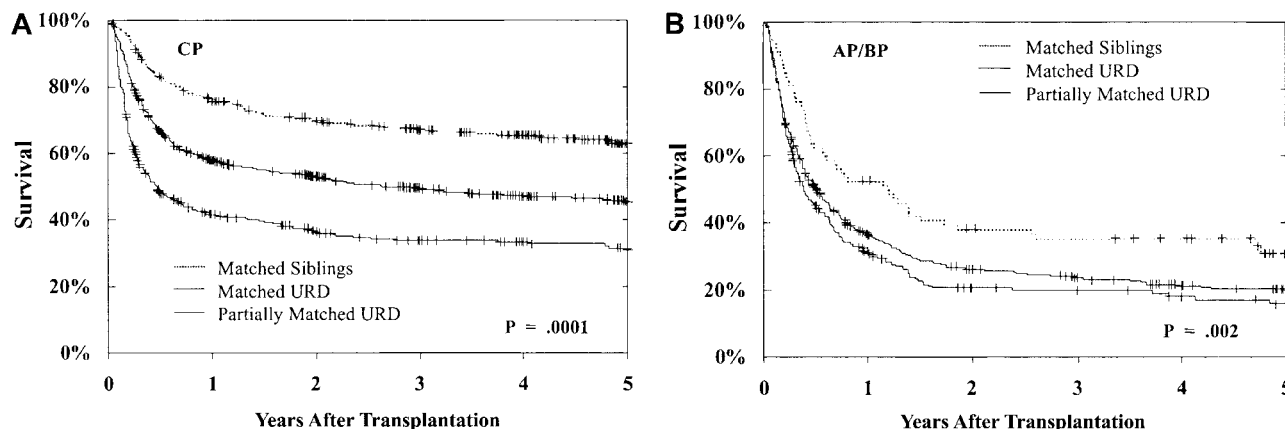


Figure 5. Survival. Survival following BMT during CP1 ([A] $P = .0001$) and beyond CP ([B] $P = .002$).

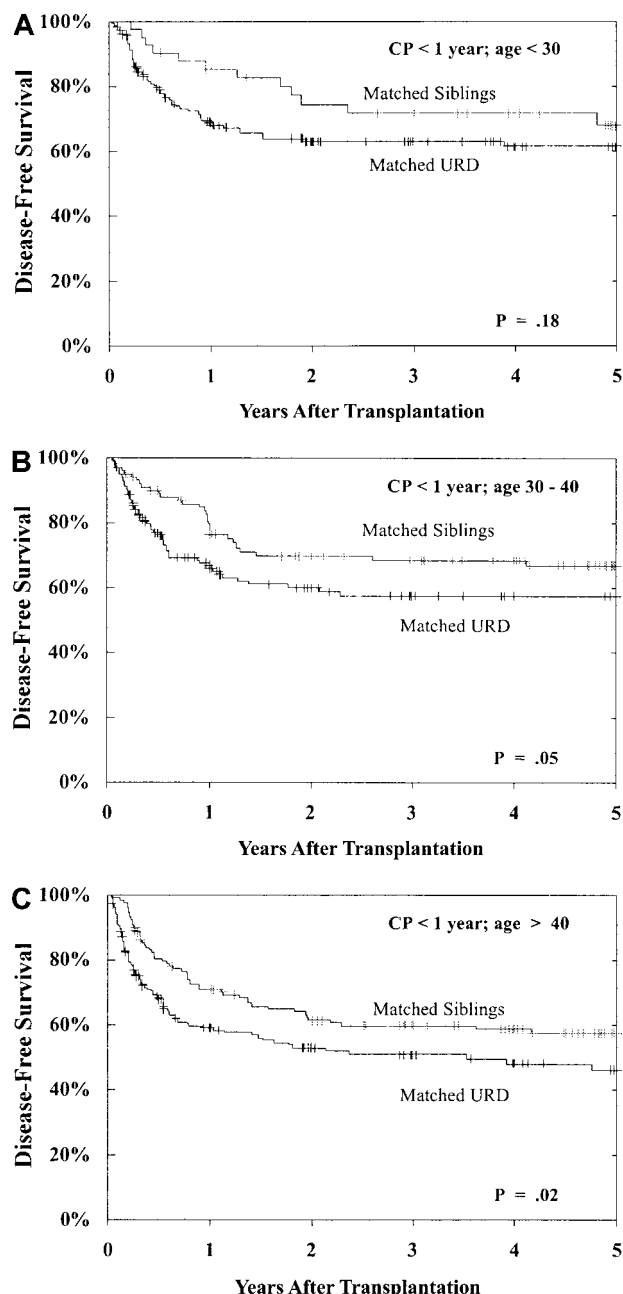


Figure 6. DFS following BMT during CP within 1 year from diagnosis: effect of patient age.

URD recipients. Therefore, the clinical choice of transplantation versus other therapies in the early CP becomes even more vexing for those lacking an available related donor. Delay from diagnosis until MSD or URD transplantation has been previously reported to compromise clinical outcome.^{1-3,14-16} Although subclinical disease acceleration (even without basophilia, fibrosis, rising blast percentage, or cytogenetic evolution) may contribute to the poorer results accompanying later transplantations, other mechanisms may be operative. These may include immune compromise due to replacement of normal dendritic cells or natural killer cells with BCR-Abl-positive effectors. Inconsistent findings have been reported regarding the adverse effect of prolonged (> 6 or 12 months) interferon therapy preceding allogeneic URD transplantation.

Few earlier reports have contrasted the outcomes of MSD

versus URD transplantations for leukemia, primarily in children.²⁹⁻³¹ Similar, though more complex, clinical courses followed the URD allografts. The immediate or early hazards of graft failure, infection, GVH disease, and death would certainly give pause to all patients facing the choice of pharmacologic versus transplantation therapy soon after diagnosis. However, formal decision analyses (prepared before the era of tyrosine kinase inhibitors) that have weighed these results support the choice of early transplantation for patients with an available donor. However, the post-BMT survival advantage is not seen until 4 or more years following transplantation.³² Even with the encouraging results reported

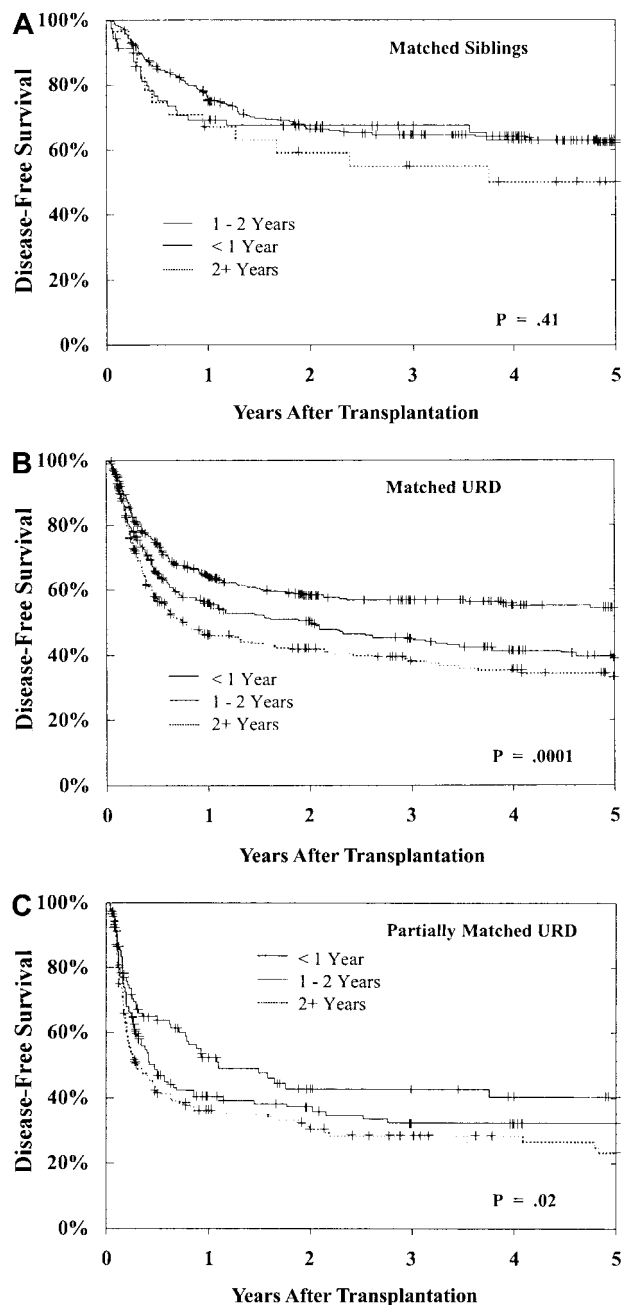


Figure 7. DFS after BMT during CP1 of CML based upon time from diagnosis to BMT. (A) Results of MSD BMT within 1 year (n = 270), 1 to 2 years (n = 70), and beyond 2 years (n = 29) from diagnosis (P = .41). (B) Results of matched URD BMT within 1 year (n = 556), 1 to 2 years (n = 394), and beyond 2 years (n = 294) from diagnosis (P = .0001). (C) Results of partially matched URD BMT within 1 year (n = 104), 1 to 2 years (n = 143), and beyond 2 years (n = 154) from diagnosis (P = .02).

herein, this survival advantage might not be realized until even later following URD transplantation. Recent reports suggest that outcomes after URD BMT may be further improved by allele matching of class I and II histocompatibility between donors and recipients.^{33,34} Despite these data, however, treatment guidelines have weighed heavily against early transplantation in favor of hoped-for improvements in medical therapy without loss of curative potential of early allotransplantation.^{35,36} In view of the current results showing quite good outcomes for younger, early CP transplantations using either MSD or matched

URD donors and the substantive survival penalty for delay, the strategies of deferred BMT may be questioned.

Our results strongly document the importance of early URD transplantation. We recognize need for improvements in survival following URD transplantation, especially when performed beyond CP and beyond the first year after diagnosis. For the most favorable group, however, including early CP patients up to age 40, new nontransplantation approaches must be tested as rigorously in prospective fashion to best help patients and their physicians make the optimal clinical choice.

References

1. Thomas ED, Clift RA, Fefer A, et al. Marrow transplantation for the treatment of chronic myelogenous leukemia. *Ann Intern Med.* 1986;104:155-163.
2. Goldman JM, Apperley JF, Jones L, et al. Bone marrow transplantation for patients with chronic myeloid leukemia. *N Engl J Med.* 1986;314:202-207.
3. 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;82:2235-2238.
4. 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;84:2036-2043.
5. Gale RP, Hehlmann R, Zhang M-J, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. *Blood.* 1998;91:1810-1819.
6. van Rhee F, Szydlo RM, Hermans J, et al. Long term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1997;20:553-560.
7. Apperley JF, Mauro FR, Goldman JM, et al. Bone marrow transplantation for chronic myelogenous leukemia in chronic phase: importance of a graft-versus-leukemia effect. *Br J Haematol.* 1988;69:239-245.
8. Devergie A, Reiffers J, Vermant JP, et al. Long-term follow-up after bone marrow transplantation for chronic myelogenous leukemia: factors associated with relapse. *Bone Marrow Transplant.* 1990;5:379-386.
9. Kolb HJ, Mittermueller J, Clemm C, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. *Blood.* 1990;76:2462-2465.
10. Collins RH Jr, Rogers ZR, Bennet M, Kumar V, Nikein A, Fay JW. Hematologic relapse of chronic myelogenous leukemia following allogeneic bone marrow transplantation: apparent graft-versus-leukemia effect following abrupt discontinuation of immunosuppression. *Bone Marrow Transplant.* 1992;10:391-395.
11. 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;75:1728-1732.
12. Drobyski WR, Ash RC, Casper JT, et al. Effect of T-cell depletion as graft-versus-host disease prophylaxis on engraftment, relapse, and disease-free survival in unrelated marrow transplantation for chronic myelogenous leukemia. *Blood.* 1994;83:1980-1987.
13. 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;86:3590-3597.
14. Devergie A, Apperley JF, Labopin M, et al. European results of matched unrelated donor bone marrow transplantation for chronic myeloid leukemia. Impact of HLA class II matching. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1997;20:11-19.
15. Hansen JA, Gooley TA, Martin PJ, et al. Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med.* 1998;338:962-968.
16. McGlave PB, Shu XO, Wen W, et al. Unrelated donor marrow transplantation for chronic myelogenous leukemia: nine years' experience of the National Marrow Donor Program. *Blood.* 2000;95:2219-2225.
17. Standards of the National Marrow Donor Program. NMDP Standards Committee. *Transfusion.* 1993;33:172-180.
18. 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;86:1606-1613.
19. Petersdorf EW, Hurley C, Dupont B, et al. Analysis of 328 marrow transplants for the treatment of chronic myeloid leukemia from unrelated donors facilitated by the US National Marrow Donor Program (NMDP): effect of HLA-DRB1 allele disparity on clinical outcome [abstract]. *Blood.* 1996;88(suppl):268a.
20. Davies SM, Kollman C, Anasetti C, et al. Engraftment and survival after unrelated donor bone marrow transplantation: a report from the National Marrow Donor Program (NMDP). *Blood.* 2000;96:4096-4102.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
22. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representation of old estimators. *Stat Med.* 1999;18:695-706.
23. Cox DR. Regression models and life tables. *J Royal Stat Soc.* 1972;34:187-220.
24. Kantarjian HM, Smith TL, O'Brien S, Beran M, Pierce S, Talpaz M. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon- α therapy. *Ann Intern Med.* 1995;122:254-261.
25. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. *N Engl J Med.* 1997;337:223-229.
26. Interferon alfa versus chemotherapy for chronic myeloid leukemia: a meta-analysis of seven randomized trials: Chronic Myeloid Leukemia Trialists' Collaborative Group. *J Natl Cancer Inst.* 1997;89:1616-1620.
27. Druker BJ, Talpaz M, Resta D, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031-1037.
28. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med.* 2001;344:1038-1042.
29. Locatelli F, Pession A, Comoli, et al. Role of allogeneic bone marrow transplantation from an HLA-identical sibling or a matched unrelated donor in treatment of children with juvenile chronic myeloid leukemia. *Br J Haematol.* 1996;92:49-54.
30. Hongeng S, Krance R, Bowman L, et al. Outcomes of transplantation with matched sibling and unrelated donor marrow in children with leukemia. *Lancet.* 1997;350:767-771.
31. Gustafsson A, Remberger M, Winiarski J, Ringdén O. Unrelated bone marrow transplantation in children: outcome and a comparison with sibling donor grafting. *Bone Marrow Transplant.* 2000;25:1059-1065.
32. Lee SJ, Kuntz KM, Horowitz MM, et al. Unrelated donor bone marrow transplantation for chronic myeloid leukemia: a decision analysis. *Ann Intern Med.* 1997;127:1080-1088.
33. Sasazuki T, Uji T, Morishima Y, et al. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor. Japan Marrow Donor Program. *N Engl J Med.* 1998;339:1177-1185.
34. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. *Blood.* 1998;92:3515-3520.
35. Gratwohl A, Hermans J, Goldman JM, et al. Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Lancet.* 1998;352:1087-1092.
36. Silver RT, Woolf SH, Hehlmann R, et al. An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood.* 1999;94:1517-1536.