Unrelated Donor Marrow Transplantation Therapy for Chronic Myelogenous Leukemia: Initial Experience of the National Marrow Donor Program

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In the interval from December 1987 to November 1990, 196 consecutive patients with chronic myelogenous leukemia (CML) received unrelated donor marrow transplantation using marrow procured by the National Marrow Donor Program (NMDP) at 21 NMDP-affiliated marrow transplant centers. Baseline donor and recipient data as well as follow-up data were obtained systematically in all cases by the NMDP. The median interval from the initiation of a search for an unrelated donor to bone marrow transplantation was 8.4 months (range, 1.7 to 34.6 months). Median age of the recipients was 33.3 years (4.5 to 54.5 years). Seventy-five recipients were female and 121 were male. At time of transplant, 115 patients were in chronic phase, 51 in accelerated phase, 14 in blast crisis, and 16 in a second or subsequent chronic phase. In 133 cases, donors and recipients were identical at the HLA A, B, and DR loci using standard serologic typing, and in 63 cases, there was nonidentity at one HLA locus. Patients were prepared for transplantation with a combination of high-dose chemotherapy and total body irradiation (N = 169) or with high-dose chemotherapy only (N = 27). Thirty-five patients received marrow depleted ex vivo of T lymphocytes, whereas 161 patients received non–T-depleted marrow. One hundred seventy-four of 196 patients engrafted (absolute neutrophil count ≥500/mm^3 for 3 consecutive days). The median time to engraftment was 22 days (6 to 69 days). Twenty-two patients failed to engraft, and an additional 10 patients experienced late graft failure. The incidence of grades III or IV acute graft-versus-host disease (GVHD) was 0.54 ± 0.10, and that of extensive chronic GVHD was 0.52 ± 0.12. A lower incidence of both grades III and IV acute GVHD (P = .0003) and of extensive chronic GVHD (P = .01) were independently associated with use of T-depleted marrow. The actuarial incidence of hematologic relapse at 2 years is 0.11 ± 0.06. The 2-year actuarial incidence of disease-free survival for patients transplanted in first chronic phase within 1 year of diagnosis is 0.45 ± 0.21, in chronic phase more than 1 year from diagnosis is 0.36 ± 0.11, in accelerated phase is 0.27 ± 0.12, in second or subsequent chronic phase is 0.22 ± 0.21, and in blast crisis is 0. Fifteen of 55 patients transplanted at 40 to 50 years of age survive. Proportional hazards analysis revealed that transplantation with HLA-matched donor marrow (P = .01), transplantation at younger age (P = .02), and transplantation in first chronic phase (P = .04) had independent, beneficial effects on disease-free survival. Thirty-eight (50%) of patients surviving at 1 year had normal activity levels (Karnofsky = 100%), whereas 31 recipients (41%) had mild impairment of activity (Karnofsky = 90% to 80%) and 7 recipients (9%) had severe impairment of activity (Karnofsky = 70% to 30%). Development of the NMDP has facilitated the use of HLA-matched unrelated donors for marrow transplantation. This treatment modality can result in prolonged disease-free survival in some patients with CML, especially younger patients transplanted early in their disease course using donors matched at the HLA A, B, and DR loci. A high incidence of graft failure, acute and chronic GVHD, and prolonged convalescence can complicate treatment.

AT PRESENT, the only proven curative therapy for chronic myelogenous leukemia (CML) is marrow transplantation.[1] Fewer than 35% of otherwise eligible patients have an HLA-identical sibling, and only an additional 5% have a suitable, partially HLA-matched related donor.[2,3] Unrelated donors matched or partially mismatched for HLA by serologic methods have been used successfully in marrow transplantation therapy for a variety of lethal disorders, including severe combined immunodeficiencies, aplastic anemia, acute leukemia, and, more recently, CML.[4-17] The National Marrow Donor Program (NMDP) has facilitated the unrelated donor identification process, safe procurement and transport of unrelated donor marrow, and systematic analysis of safety and efficacy of the marrow procurement[18,19] and unrelated donor transplant process.[20] Here we describe results of the first 196 consecutive unrelated donor marrow transplants performed as therapy for CML using marrow obtained by the NMDP.

MATERIALS AND METHODS

NMDP. The NMDP was founded in July 1986. The goals of the NMDP are to identify unrelated donors, to procure unrelated donor marrow, to assure donor and recipient safety, and to assess the efficacy of the unrelated donor procurement and transplant procedures. Donor identification through a national registry was initiated in September 1987, and the first unrelated donor marrow transplantation using a donor identified by the NMDP was performed in December 1987. Currently, donors are obtained from one of more than 100 NMDP donor centers in the United States using a national registry based in Minneapolis, MN. Marrow procurement procedures are performed at more than 100 collection centers, and transplants are performed at more than 50 transplant centers affiliated with the NMDP. Donor identification, marrow procurement and transport, marrow transplantation, baseline donor and recipient data gathering, follow-up recipient data gathering, data storage and analysis, and donor safety monitoring are coordinated and overseen by the NMDP.

Donor-recipient matching. Donor and recipient characteristics are presented in Table 1. In 133 cases, donors and recipients were

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Submitted August 4, 1992; accepted September 21, 1992.

The National Marrow Donor Program is supported by contract NO1-HB-17089.

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0006-4971/93/8102-0021$3.00/0

Table 1. Study Characteristics

Transplant interval	12/87–11/90
Transplant centers	N = 21
Collection centers	N = 36
Donor centers	N = 46
Patients	N = 196
Recipient age	Median = 33.3 yr
	Range = 4.5–54.5 yr
Donor age	Median = 37.8 yr
	Range = 19.1–55.6 yr
Recipient	
Female	N = 75
Male	N = 121
Donor	
Female	N = 98
Male	N = 98
Search duration	Median = 8.4 mo
	Range = 1.7–34.6 mo
Recipient disease stage	
CP	N = 115
AP	N = 51
BC	N = 14
>1 CP	N = 16
Donor-recipient HLA match	
Match	N = 133
Mismatch	N = 63
BMT preparation	
Chemotherapy + TBI	N = 169
Chemotherapy only	N = 27
GVHD prophylaxis	
T-lymphocyte depletion	N = 35
No T-lymphocyte depletion	N = 161

identical at the HLA A locus, HLA B locus, and HLA DR locus using serologic testing. In 63 cases, nonidentity between donor and recipient was detected at one HLA A, B, or DR locus.

Unrelated bone marrow donors. Ninety-eight females and 98 males served as unrelated donors. Median donor age was 37.8 years (range, 19.1 to 55.6 years). All donors signed informed consent approved by their local institutional review board. No deaths or serious medical complications resulted from harvests associated with this study. Anticoagulated bone marrow suspended in tissue culture media was transported by courier from the NMDP collection center to the NMDP bone marrow transplant (BMT) center. When indicated, ex vivo T-lymphocyte depletion was performed at the NMDP BMT center, as described below.

Unrelated donor bone marrow recipients and transplant conditions. Seventy-five consecutive female and 121 male patients received unrelated donor marrow transplant therapy for CML. All patients had Philadelphia chromosome (Ph^1)–positive CML and met eligibility criteria that varied from institution to institution but conformed to general NMDP guidelines. The median age of the recipients was 33.3 years (4.5 to 54.5 years). At time of transplant, 115 patients were in first chronic phase (CP), 51 in accelerated phase (AP), 16 in second or subsequent chronic phase (>1CP), and 14 in blast crisis (BC). For purposes of this analysis, accelerated phase was defined as the presence of one or more of the following patient characteristics at time of transplantation: leukocytosis (WBC $\geq 10^5/\mu L$), thrombocytosis (platelets $\geq 10^6/\mu L$), thrombocytopenia (platelets $< 10^5/\mu L$), anemia (hemoglobin < 10 g/dL), or palpable splenomegaly uncontrolled by therapy with hydroxurea, busulfan, or interferon alpha; basophilia or eosinophilia (≥10% basophils or eosinophils in the peripheral blood or bone marrow); chromosome abnormalities other than or in addition to the single Ph^1 (deletion of the short arm of chromosome 22 associated with translocation of chromosome 9 or with other translocations); and moderate or severe myelofibrosis. Blast crisis was defined as ≥30% blasts in the bone marrow or peripheral blood. Patients were considered to be in a second or subsequent chronic phase if the morphology of their peripheral blood and bone marrow was compatible with chronic phase but they had experienced one or more blast crises. Patients with none of the above findings were considered to be in chronic phase. All recipients or their guardians signed informed consent approved by their local institutional review boards.

In 169 cases, patients were prepared for transplant with a combination of fractionated (N = 167) or single-dose (N = 2) total body irradiation (TBI) and cyclophosphamide alone or in combination with cytosine arabinoside or VP-16. In 27 cases, patients were prepared with regimens not containing TBI. Such regimens consisted of busulfan and cyclophosphamide (N = 24) or busulfan, cyclophosphamide, and VP-16 (N = 3).

In 161 cases, patients received in vivo acute graft-versus-host disease (GVHD) prophylaxis with combinations of methotrexate, cyclosporine, ATG, and prednisone or with the anti-CD-5 ricin A chain immunotoxin. In 22 cases, patients received bone marrow depleted of T lymphocytes ex vivo with anti-CD3 monoclonal antibody plus complement. In 10 cases, patients received bone marrow depleted of T lymphocytes ex vivo with soybean agglutination and E rosettes. In three cases, patients received marrow depleted ex vivo of T lymphocytes with anti-CD3 monoclonal antibody conjugated to the ricin A chain.

Data gathering and statistical analysis. All data pertaining to donors and recipients were obtained using forms designed by the NMDP for this purpose. Baseline data on all donors and information concerning the harvest procedure were obtained by NMDP donor and collection centers and forwarded to the NMDP data center for transcription, storage, and subsequent retrieval. Recipient baseline information as well as information obtained at 100 days, 6 months, 1 year, and then annually posttransplant were obtained by the NMDP transplant center and forwarded to the NMDP data center. Patient outcome was analyzed to date of last follow-up. A death form was completed in the case of each death in this series.

Disease-free survival (DFS) curves were calculated by the method of Kaplan and Meier.[21] The time to event was defined as time from first transplant to time of (1) relapse for patients who were reported free of disease after transplant, (2) day 28 posttransplant for patients who survived at least 28 days but were never free of the disease after transplant, or (3) death for patients not covered by (1) or (2). In univariate analyses, the log rank statistic was determined, and its significance probability is cited.[22] The 2-year disease-free survival rates and their 95% confidence intervals are cited.

In multivariate analyses involving the event of DFS and relapse, the proportional hazards model[23] was used with the following covariates: recipient age, recipient cytomegalovirus (CMV) status, HLA match (0 or 1 antigen disparity), ex vivo manipulation of bone marrow to deplete T lymphocytes, interval between diagnosis and transplant, disease stage (CP versus all other stages).

For nonfatal events such as engraftment, grade III/IV acute GVHD, and extensive chronic GVHD death was defined as a censored variable in the life table analyses. The censoring data point for the analyses involving nonfatal events was either the date of censoring variable, the date of contact, or the last regular follow-up visit. Both the Kaplan-Meier model[21] and proportional hazards model were used. The independent variables considered are: recipient age, recipient CMV status, HLA-matched (0 or 1 antigen disparity) ex vivo T lymphocyte depletion, and disease stage (CP versus other for late graft failure analysis only).

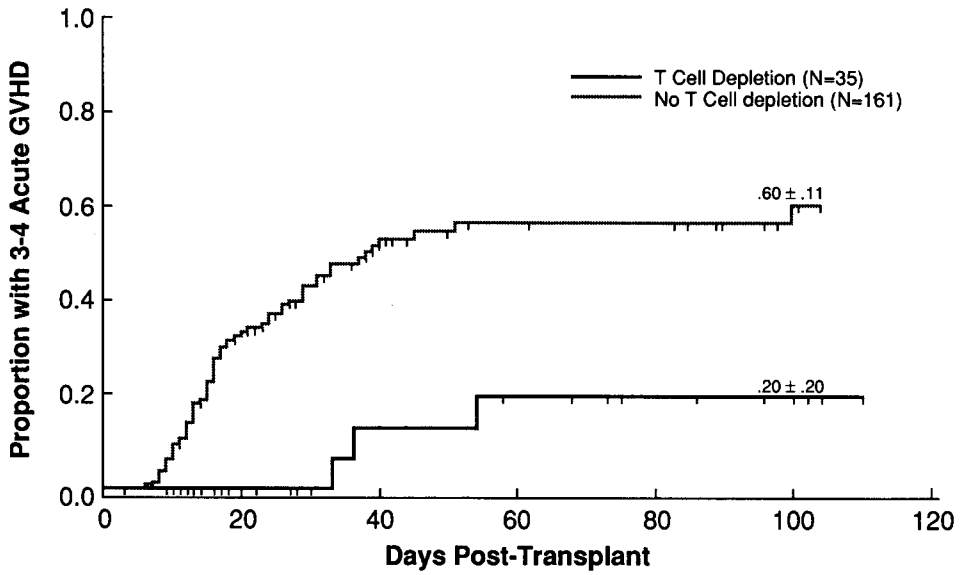

Fig 1. The incidence of grade III or IV acute GVHD at 100 days observed in recipients of T lymphocyte–depleted bone marrow (0.20 ± 0.20) is significantly less than that observed in recipients of bone marrow not depleted of T lymphocytes (0.60 ± 0.11) (*P* = .0003).

RESULTS

Engraftment. Engraftment was defined as the achievement of a peripheral blood absolute neutrophil count greater than 500/μL for 3 consecutive days. Formal studies of donor/recipient chimerism were not reported in all cases. Engraftment occurred in 174 of 196 patients. The actuarial incidence of initial engraftment before day +100 was 0.94 ± 0.04, and the median time to engraftment was 22 days (range, 6 to 69 days). Two of 35 patients receiving T-lymphocyte–depleted marrow and 20 of 161 patients receiving non–T-depleted marrow failed to engraft. Late graft failure was defined as the development of pancytopenia in patients who had previously engrafted. Late graft failure occurred in 10 patients at a range of 14 to 147 days after engraftment. In proportional hazards analysis, no independent association of late graft failure with T-lymphocyte depletion, donor/recipient matching, recipient age, disease stage, or recipient CMV status was identified.

Acute GVHD. The incidence of grades II to IV acute GVHD was 0.82 ± 0.07. The 0.20 ± 0.20 incidence of grade III or IV seen in recipients of T-lymphocyte–depleted bone marrow was significantly lower than the incidence of 0.60 ± 0.11 observed in recipients of bone marrow that was not T depleted (*P* = 0.003) (Fig 1). Analysis by proportional hazards model showed a significant, independent association of T depletion (*P* = 0.002; RR = 0.15 [0.05 to 0.49]) but not of donor/recipient matching, recipient age, disease stage, or recipient CMV status with a reduced incidence of grades III to IV acute GVHD.

Chronic GVHD. The 1-year actuarial incidence of extensive chronic GVHD was 0.22 ± 0.20 in recipients of T-

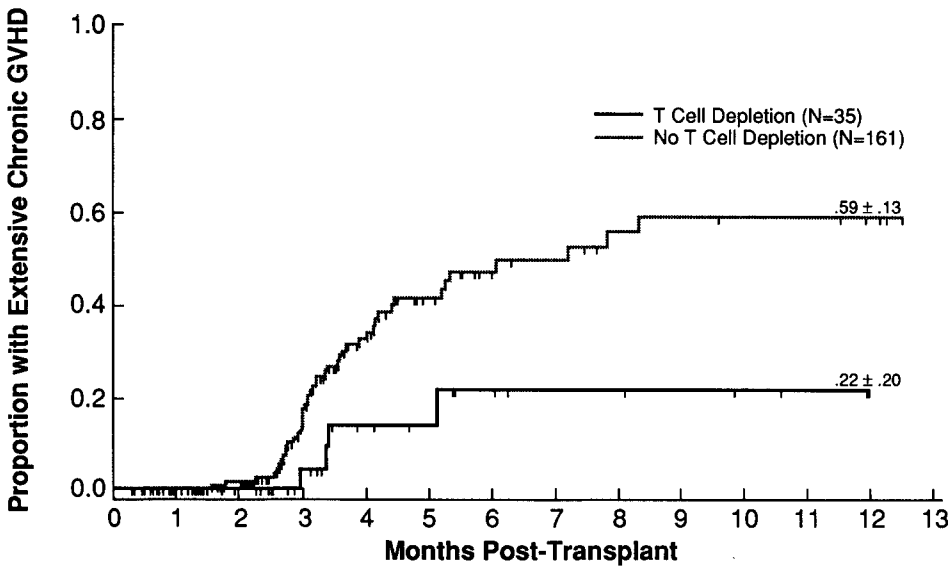

Fig 2. The incidence of extensive chronic GVHD at 1 year observed in recipients of T lymphocyte–depleted bone marrow (0.22 ± 0.20) is significantly less than that observed in recipients of bone marrow not depleted of T lymphocytes (0.59 ± 0.13) (*P* = .01).

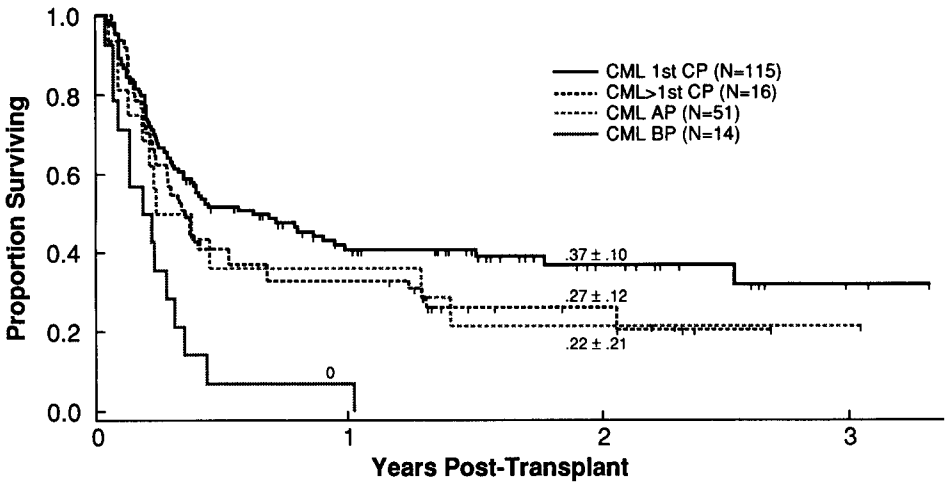

Fig 3. The 2-year DFS figures and their 95% confidence intervals for patients transplanted in various stages of disease are presented.

lymphocyte–depleted bone marrow, significantly lower than that of 0.59 ± 0.13 observed in recipients of marrow not depleted of T lymphocytes (P = 0.01) (Fig 2). Proportional hazards analysis demonstrated that use of T-lymphocyte–depleted bone marrow (P = 0.03; RR = 0.33 [0.12 to 0.91]), but not donor/recipient matching, recipient age, or recipient CMV status was independently associated with a diminished incidence of extensive chronic GVHD.

Relapse. Relapse was defined as the recurrence of morphologic evidence of leukemia in the peripheral blood or bone marrow. Relapse has been identified in 15 patients at a range of 28 to 752 days following transplant. The 2-year actuarial incidence of relapse is 0.16 ± 0.14 in recipients of T lymphocyte–depleted bone marrow, not significantly different from the 0.10 ± 0.07 incidence seen in recipients of marrow that had not been T depleted (P = 0.28). Transplant at prolonged interval from diagnosis was independently associated with increased risk of relapse in proportional hazards analysis (P = 0.03; RR = 1.22 [1.02 to 1.46]). Other characteristics studied, including T lymphocyte depletion, disease stage (chronic versus other), donor/recipient matching, recipient age, or recipient CMV status, were not independently associated with relapse.

DFS. DFS was defined as survival without evidence of hematologic relapse in peripheral blood or marrow. The incidence of DFS for patients in various disease stages is represented in Fig 3. The 0.45 ± 0.21 2-year actuarial incidence of DFS observed in patients in chronic phase transplanted within 1 year of diagnosis is significantly higher than the 0.36 ± 0.11 incidence seen in patients in chronic phase transplanted at more than 1 year from diagnosis (P = 0.03) (Fig 4). When patients were grouped by age and donor/recipient matching status, older recipients of mismatched marrow fared poorly (DFS, 0.14 ± 0.13) compared with other patient subsets (Fig 5). Analysis by proportional hazards model indicated that transplant with an HLA-matched donor, transplant at a younger age, and transplant in first chronic phase compared with transplant in any other disease stage were independently associated with better DFS (Table 2). Use of marrow depleted of T lymphocytes was associated with a trend for better DFS; however, this association did not reach statistical significance (P = 0.10).

Causes of death. In the majority of cases, a single cause of death was difficult to identify. Investigators were asked to list in order of importance clinical conditions contributing to death. The number and percentage of cases in which com-

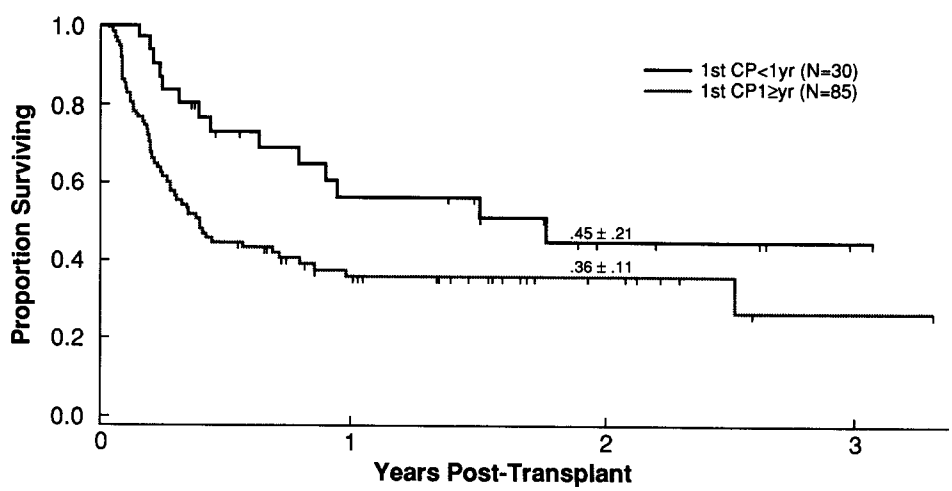

Fig 4. The incidence of DFS at 2 years for chronic phase patients transplanted within 1 year of diagnosis (0.45 ± 0.22) is significantly higher than that observed in chronic phase patients transplanted more than 1 year from diagnosis (0.36 ± 0.11) (P = .03).

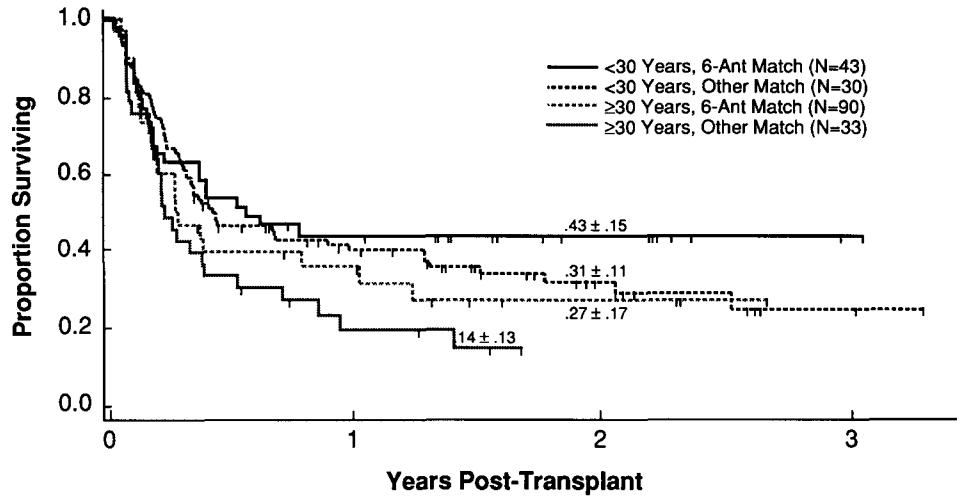

Fig 5. The 2-year DFS figures and their 95% confidence interval for patients grouped by HLA donor/recipient matching status and by age are presented.

mon clinical problems were considered a primary or a secondary cause of death are listed in Table 3. As expected, GVHD, infection, pneumonitis, and graft failure are important clinical problems associated with the death of CML patients after unrelated donor bone marrow transplantation.

Assessment of survivors. The level of activity observed in patients surviving at 1 year (N = 76) was measured using the Karnofsky activity score. Results are presented in Table 4. Fifty percent of patients had impairment of activity when assessed at 1 year, and in 10% of cases overall, this impairment resulted in significant debility. No association between impaired activity levels at 1 year and either use of mismatched donor marrow or transplant at an older age could be demonstrated (data not presented).

DISCUSSION

The development of the NMDP has facilitated the identification of unrelated donors and the procurement of unrelated donor marrow. Because the NMDP also gathers and stores data concerning both the donor and the recipient, it has become possible to assess the efficacy of unrelated donor transplantation therapy for CML in a large number of cases.

In this study, unrelated donor marrow transplant therapy for CML is associated with a high incidence of engraftment problems. Twenty-two patients failed to engraft, and an additional 10 patients experienced late graft failure. Failure to engraft was observed in recipients of both phenotypically matched and phenotypically mismatched unrelated donor marrow. This incidence of failure to engraft is strikingly higher than expected in the case of matched sibling donor transplantation therapy for leukemia and raises the possibility that nonidentity between donor and recipient for transplantation antigens, either HLA or non-HLA, contributes to graft failure as has been observed in the related donor setting.[2,24] Indeed, recent reports demonstrate that in some cases, failure of unrelated donor marrow to engraft may be associated with important structural polymorphisms not recognized by current serologic HLA typing methods.[25] T-lymphocyte depletion has also been associated with failure to engraft in the related donor setting.[26] In this series, however, only 2 of 35 patients receiving T-lymphocyte–depleted marrow failed to engraft. An additional 10 patients experienced late graft failure after initial engraftment. No independent association of late graft failure with donor/recipient match, T-lymphocyte depletion, or other marrow transplant characteristics, however, could be identified. Engraftment problems were considered a primary or secondary cause of death in 15% of cases. Graft failure must be considered a serious potential complication of unrelated donor marrow transplant therapy for CML. Investigators undertaking this therapeutic modality may wish to develop contingency plans for the potential of graft failure, including storage of "backup" autologous peripheral blood or marrow stem cells.

The incidence of grades III and IV acute GVHD was 54% in this series. This is strikingly higher than expected in the case of related donor transplantation therapy for CML and again suggests that nonidentity between donor and recipient for either HLA or non-HLA transplantation antigens may have an important effect. The use of T-depleted marrow reduces the incidence of grades III and IV acute GVHD sig-

Table 2. Factors Associated With DFS After Unrelated Donor Marrow Transplant Proportional Hazards Analysis

Characteristic	RR	95% CI	*P* Value	Favorable
Level of donor-recipient disparity	0.60	0.41–0.89	.01	Serologic HLA A, B, DR match
Recipient age (per decade)	0.82	0.70–0.97	.02	Younger age
Disease status at transplant	0.69	0.48–0.99	.04	First chronic phase
GVHD prophylaxis	0.68	0.43–1.08	.01	T-lymphocyte depletion

Abbreviation: CI, confidence interval.

Table 3. Primary or Secondary Causes of Death

Problem	No. of Cases	% Deaths
Infections*	40*	4U*
Acute or chronic GVHD	35	35
Interstitial pneumonitis	26	26
Graft failure	15	15
Recurrent leukemia	5	5
Second malignancies	3	3

* For example, infections were listed as a primary or secondary cause of death in 40 cases among 101 deaths (40% of cases).

nificantly compared with the use of non-T-depleted bone marrow; a finding also observed in related donor transplant therapy for CML. No other patient characteristic tested, including donor/recipient matching status, recipient age, disease stage, or recipient CMV status, was independently associated with the development of acute GVHD. Similarly, the 52% incidence of extensive chronic GVHD is extremely high in this series and is probably attributable to nonidentity at either HLA or non-HLA transplantation antigens. Use of T-lymphocyte-depleted bone marrow was the only transplant variable that could be independently associated with a reduced incidence of extensive chronic GVHD. Acute and chronic GVHD were implicated in 35% of the deaths in the series. These data suggest that the development of GVHD following unrelated donor therapy for CML is a problem of grave clinical importance. Currently available HLA A, B, and DR serologic testing may not be sensitive enough to detect clinically relevant donor/recipient nonidentity. This raises the possibility that application of newer methods to determine HLA class I and class II identity may be useful to predict donor/recipient pairs in which graft failure and GVHD will not occur. These methods include analysis of restriction fragment length polymorphisms,[27,28] allospecific oligonucleotide typing techniques,[29,30] isoelectric focusing,[31] and actual nucleotide sequencing[32] as well as analysis of T-cell precursors (CTLp) to assess the T-cell repertoire of the recipient.[33] These data also suggest that studies testing innovative approaches to GVHD prophylaxis including use of marrow depleted of T lymphocytes ex vivo by a variety of techniques are indicated in this setting.

Hematologic relapse has occurred in 15 patients to date. Of interest, transplant at a prolonged interval from diagnosis was independently associated with increased risk of relapse in proportional hazards analysis. At present, relapse cannot be independently associated with advanced disease stage at time of transplantation or with the use of T lymphocyte-depleted marrow, although these transplant characteristics have previously been associated with relapse in related donor transplant therapy for CML.[26,34-38] Both the low relapse rate and the failure to associate relapse with advanced disease stage or T depletion may simply reflect a relatively short median follow-up in this series.

At last contact, 64 patients survive without hematologic evidence of relapse following unrelated donor transplant therapy for CML. Better disease-free survival is independently associated with transplant in chronic phase rather than with advanced disease. The actuarial incidence of disease-free survival at 2 years for patients transplanted early in chronic phase is significantly higher than that of patients transplanted later in chronic phase. These observations are similar to those observed in the related donor transplant setting.[34,35] The use of donor/recipient pairs matched at the HLA A, B, and DR loci is also independently associated with better disease-free survival. These findings confirm a previously reported insignificant trend suggesting better outcome in CML recipients of matched unrelated donor marrow.[16]

Better DFS was also associated with younger recipient age. This conforms with results seen in the related donor transplant setting. Of interest, however, 15 of 55 patients transplanted between the ages of 40 and 55 years are surviving disease free. The compounded effect of older age and the use of mismatched marrow is evidenced by the relatively poor DFS at 2 years seen in patients over 30 years of age receiving marrow from mismatched donors compared with younger recipients and with older recipients of matched marrow (Fig 5). Poor results under these circumstances suggest that efforts should be redoubled in the case of these older mismatched patients to find a matched donor. On the other hand, this group may lend itself to clinical studies in which innovative approaches to transplantation such as T-lymphocyte depletion are tested.

Although the use of marrow depleted of T lymphocytes was independently associated with a decreased incidence of acute and chronic GVHD, no significant independent association between the use of such marrow and better DFS could be seen in this series. This observation may simply reflect the small number of patients receiving T-depleted marrow in the series because an insignificant trend toward better DFS in recipients of T-depleted marrow was identified in the proportional hazards model. The impact of T depletion must be interpreted with caution. This GVHD prophylaxis method was used in only 3 of 21 transplant centers. Other center-specific factors could contribute to the effects attributed to T depletion. Furthermore, a direct association between T depletion and relapse has been demonstrated in related donor transplant therapy for CML.[36-38] Although no independent effect of T depletion on the incidence of relapse is seen here, prolonged follow-up may be necessary to detect such an association. Two other potential complications of T-lymphocyte depletion in the mismatched donor setting include graft failure and development of B-cell lymphoma. Although no such associations could be made in this study, they remain as ominous potential complications that must be considered as new acute GVHD prophylaxis approaches involving varying degrees of ex vivo or in vivo T-lymphocyte depletion are tested in the unrelated donor setting.

The majority of patients (50%) assessed at 1 year had normal levels of activity; however, 41% of patients had at least

Table 4. Karnofsky Activity Assessment at 1 Year

Score	No. of Cases	%
100	38	50
90–80	31	41
70–30	7	9

mild or moderate impairment of activity and an additional 9% of patients had profound impairment of activity. No association between impaired activity levels at 1 year and the use of mismatched marrow or transplant at older age could be identified. These observations do suggest that prolonged convalescence after unrelated donor transplantation is a real possibility that should be raised when patients undergo counseling before transplantation.

This study suggests that therapy for CML with marrow transplantation using unrelated donors can provide stable engraftment in a majority of recipients and prolonged DFS in some cases. The beneficial effects of marrow transplantation are particularly apparent when transplant is performed in younger patients in chronic phase and when HLA-matched donor marrow is used. Although T-lymphocyte depletion markedly diminishes the incidence of acute and chronic GVHD, the overall effect of T depletion on the outcome of unrelated donor bone marrow transplantation therapy for CML is not known and can be determined only after prolonged follow-up. Problems associated with failure to achieve engraftment and with a high incidence of GVHD as well as delayed convalescence in some cases can be anticipated in patients with CML undergoing unrelated donor transplantation. The efficient identification of matched unrelated donors through the NMDP and a rapidly expanding network of donor registries with international links will make unrelated donor BMT available to more patients with CML. Further clinical studies are needed to determine the efficacy of newly developed methods for identification of matched donor/recipient pairs, the risks and benefits associated with aggressive acute GVHD prophylaxis, and the importance of other variables that may effect the outcome of unrelated donor marrow transplantation for CML and other lethal diseases.

ACKNOWLEDGMENT

The authors acknowledge Drs Karl Blume, Paul Martin, and Paul McCurdy for their critical review of the manuscript. They also acknowledge the excellent support of Pat Coppo and her administrative staff of the NMDP search coordinating unit as well as the cooperation of the NMDP donor, collection, and transplant centers.

REFERENCES

1. McGlave PB: The biology and therapy of chronic myelogenous leukemia, in Champlin R (ed): Bone Marrow Transplantation. Boston, MA, Martin Nijhoff, 1990, p 235

2. Beatty PG, Clift RA, Mickelson EM, Nisperos B, Flournoy N, Martin PJ, Sanders JE, Stewart P, Buckner CD, Storb R, Thomas ED, Hansen JA: Marrow transplantation from related donors other than HLA identical siblings. N Engl J Med 313:765, 1985

3. Anasetti C, Beatty PG, Storb R, Martin PJ, Mori M, Sanders JE, Thomas ED, Hansen JA: Effect of HLA incompatibility on graft-versus-host disease, relapse, and survival after marrow transplantation for patients with leukemia or lymphoma. Hum Immunol 29:79, 1990

4. Horowitz SD, Bach FH, Groshong T, Hong R: Treatment of severe combined immunodeficiency with bone marrow from an unrelated, mixed-leucocyte-culture-nonreactive donor. Lancet 2:431, 1975

5. O'Reilly RJ, Dupont B, Pahwa S, Grimes E, Smithwick EM, Pahwa R, Schwartz S, Hansen JA, Siega FP, Sorell M, Svejgaard A, Jersild C, Thomsen M, Platz P, L'Esperance P, Good RA: Reconstitution in severe combined immunodeficiency by transplantation of marrow from an unrelated donor. N Engl J Med 297, 1977

6. Foroozonfar N, Hobbs JR, Hugh-Jones K, Humble JG, James DCO, Selwyn S, Watson JG, Yamamura M: Bone marrow transplantation for aplastic anemia from an HLA-A and MLC-identical unrelated donor. Lancet 1:210, 1977

7. Speck B, Zwaan FE, van Rood JJ, Eernisse JG: Allogeneic bone marrow transplantation in a patient with aplastic anemia using a phenotypically HLA-A-identical unrelated donor. Transplantation 16:24, 1973

8. Lohrmann HP, Dietrich M, Goldmann SF, Kristensen T, Fliedner TM, Abt C, Pflieger H, Flad H-D, Kubanek B, Heimpel H: Bone marrow transplantation for aplastic anemia from a HLA-A and MLC-identical unrelated donor. Blut 31:347, 1975

9. Hansen JA, Clift RA, Thomas ED, Buckner CD, Storb R, Giblett ER: Bone marrow transplantation of marrow from an unrelated donor to a patient with acute leukemia. N Engl J Med 303:565, 1980

10. Gordon-Smith EC, Fairhead SM, Chipping PM, Hows J, James DCO, Dodi A, Batchelor JR: Bone marrow transplantation for severe aplastic anemia using histocompatible unrelated volunteer donors. Br Med J 285:835, 1982

11. Duquesnoy RJ, Zeevi A, Marrari M, Hackbarth S, Camitta B: Bone marrow transplantation for severe aplastic anemia using a phenotypically HLA-identical, SB-compatible unrelated donor. Transplantation 35:566, 1983

12. McGlave D, Scott E, Ramsay N, Arthur D, Blazar B, McCullough J, Kersey J: Unrelated donor bone marrow transplantation therapy for chronic myelogenous leukemia. Blood 70:877, 1987

13. Hows JM, Lin JL, Marsh J, Swirsky D, Jones L, Apperley JF, James DCO, Smithers S, Batchelor JR, Goldman JM, Gordon-Smith EC: Histocompatible unrelated volunteer donors compared with HLA nonidentical family donors in marrow transplantation for aplastic anemia and leukemia. Blood 1986; 68:1322

14. Beatty PG, Ash R, Hows JM, McGlave PB: The use of unrelated bone marrow donors in the treatment of chronic myelogenous leukemia: Experience of four centers. Bone Marrow Transplant 4: 287, 1989

15. Ash R, Casper JT, Chitambar CR, Hansen R, Bunin N, Truitt RL, Lawton C, Murray K, Hunter J, Baxter-Lowe LA, Gottschall JL, Oldham K, Anderson T, Camitta B, Menitove J: Successful allogeneic transplantation of T cell depleted bone marrow from closely HLA matched unrelated donors. N Engl J Med 332:485, 1990

16. McGlave PB, Beatty P, Ash R, Hows JM: Therapy of chronic myelogenous leukemia with unrelated donor bone marrow transplantation: Results in 102 cases. Blood 75:1728, 1990

17. Beatty PG, Hansen JA, Longton GM, Thomas ED, Sanders JE, Martin PJ, Bearman SI, Anasetti C, Petersdorf EW, Mickelson EM, Pepe MS, Appelbaum FR, Buckner CD, Clift RA, Petersen FB, Stewart PS, Storb RF, Sullivan KM, Tesler MC, Witherspoon RP: Marrow transplantation from HLA-matched unrelated donors for treatment of hematologic malignancies. Transplantation 51:443, 1991

18. McCullough J, Hansen JA, Perkins H, Stroncek D, Bartsch G: Establishment of the National Bone Marrow Donor Registry, in Gale RP, Champlin RE (eds.): Bone Marrow Transplantation: Current Controversies, vol 91. New York, NY, Liss, 1989, p 641

19. McCullough J, Hansen J, Perkins H, Stroncek D, Bartsch G: The National Marrow Donor Program: How it works, accomplishments to date. Oncology 3:67, 1989

20. Kernan NA (for The Research and Publication Committee of the NMDP): Outcome of 459 marrow transplants derived from unrelated donors for treatment of acquired and congenital lymphohematopoietic disorders or metabolic disorders: Initial report from the National Marrow Donor Program (NMDP). Blood 78:77a, 1991 (abstr, suppl 1)

21. Kaplan E, Meier P: Non-parametic estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

22. Mantel N: Evaluation of survival data and two new rank order statistics arising in its considerations. Cancer Chemother Rep 50: 163, 1970

23. Cox DR: Regression models and life tables (with discussion). J R Stat Soc 34:187, 1972

24. Anasetti C, Amos D, Beatty PG, Appelbaum FR, Bensinger W, Buckner CD, Clift R, Doney K, Martin PJ, Mickelson E, Nisperos B, O'Quigley J, Ramberg R, Sanders JE, Stewart P, Storb R, Sullivan KM, Witherspoon RP, Thomas ED, Hansen JA: Effect of HLA compatibility on engraftment of bone marrow transplants in patients with leukemia or lymphoma. N Engl J Med 320:197, 1989

25. Fleischhauer K, Kernan NA, O'Reilly RJ, Dupont B, Yang SY: Bone marrow allograft rejection by host-derived allocytotoxic T lymphocytes recognizes a single amino acid at position 156 of the HLA-B44 class I antigen. N Engl J Med 323:1818, 1990

26. Apperley JF, Mauro FR, Goldman JM, Gregory W, Arthur CK, Hows J, Arcese W, Papa G, Mandelli F, Wardle D, Gravett P, Franklin IM, Bandini G, Ricci P, Tura S, Iacone A, Torlontano G, Heit W, Champlin R, Gale RP: Bone marrow transplantation of chronic myeloid leukaemia in first chronic phase: Importance of graft-versus-leukaemia effect. Br J Haematol 69:239, 1988

27. Cohen D, Simons MJ, Lalouel JM, Dupont D: Nomenclature for HLA-RFLP, in Dupont B (ed): Immunobiology of HLA, vol 1. Histocompatibility Testing. New York, NY, Springer-Verlag, 1989, p 67

28. Bignon JD, Semana G, Tiercy JM, Simons M, Lalouel JM, Cohen D: DNA-RFLP analysis: HLA-DR beta workshop report, in Dupont B (ed): Immunobiology of HLA, vol 1. Histocompatibility Testing. New York, NY, Springer-Verlag, 1989, p 851

29. Tiercy JM, Zwahlen F, Betuel H, Jeannet M, Mach B: Improved HLA class II matching in bone marrow transplantation with unrelated donors by DNA oligonucleotide probing. Exp Hematol 17: 705, 1989

30. Baxter-Lowe LA, Eckels DD, Ash RC, Casper J, Hunter JB, Gorski J: Future directions in selection of donors for bone marrow transplantation: Role of oligonucleotide genotyping. Transplant Proc 23:1699, 1991

31. Yang SY: Population analysis of class I HLA antigens by one-dimensional isoelectric focusing gel electrophoresis: Workshop summary report, in Dupont B (ed): Immunobiology of HLA, vol 1. Histocompatibility Testing. New York, NY, Springer-Verlag, 1989, p 309

32. Santamaria P, Boyce-Jacino M, Lindstrom A, Barbosa J, Faras A, Rich S: Class II HLA typing: Direct sequencing of DRB, DQB and DQA genes. Hum Immunol 33:69, 1991

33. Kaminski E, Shamrock C, Hows J, Ritter M, Arthur C, McKinnon S, Batchelor JR: Frequency analysis of cytotoxic T lymphocyte precursors. Bone Marrow Transplant 3:149, 1988

34. Thomas ED, Clift RA, Fefer A, Appelbaum FR, Beatty P, Bensinger WI, Buckner CD, Cheever MA, Deeg HJ, Doney K, Flournoy N, Greenberg P, Hansen JA, Martin P, McGuffin R, Ramberg R, Sanders JE, Singer J, Stewart P, Storb R, Sullivan K, Weiden PL, Witherspoon R: Marrow transplantation for the treatment of chronic myelogenous leukemia. Ann Intern Med 104:155, 1986

35. Martin PJ, Clift RA, Fisher LD, Buckner CD, Hansen JA, Appelbaum FR, Doney KC, Sullivan KM, Witherspoon RP, Storb R, Thomas ED: HLA-identical marrow transplantation during accelerated-phase chronic myelogenous leukemia: Analysis of survival and remission duration. Blood 72:1978, 1988

36. Goldman JM, Gale RP, Horowitz MM, Biggs JC, Champlin RE, Gluckman E, Hoffmann RG, Jacobsen SJ, Marmont AM, McGlave PB, Messner HA, Rimm AA, Rozman C, Speck B, Tura S, Weisner RS, Bortin MM: Bone marrow transplantation for chronic myelogenous leukemia in chronic phase: Increased risk of relapse associated with T-cell depletion. Ann Intern Med 108:806, 1988

37. Marmont A, Frassoni F, Bacigalupo A, Podestá M, Piaggio G, Van Lint MT, Caimo A, de Fililppi S: Recurrence of Ph^1-positive leukemia after marrow transplantation for chronic granulocytic leukemia. N Engl J Med 310:903, 1984

38. Offit K, Burns JP, Cunningham I, Jhanwar SC, Black P, Kernan NA, O'Reilly RJ, Chaganti RSK: Cytogenetic analysis of chimerism and leukemia relapse in chronic myelogenous leukemia patients after T cell-depleted bone marrow transplantation. Blood 75: 1346, 1990