

## ORIGINAL ARTICLE

# Long-term follow-up of allogeneic bone marrow transplantation for patients with chronic phase chronic myeloid leukemia prepared with a regimen consisting of cyclophosphamide, cytarabine and single-dose total body irradiation conditioning

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We evaluated long-term toxicities and outcomes in 96 patients with chronic phase chronic myeloid leukemia treated with a single bone marrow allograft regimen. Conditioning was cytosine arabinoside, cyclophosphamide (120 mg/kg) and single fraction total body irradiation (500 cGy). Median follow-up was 12.8 years (0.4–19.9 years). Graft failure occurred in one patient, nonfatal veno-occlusive disease in 13 patients (14%). Overall incidences of acute (a) and chronic (c) graft-vs-host disease (GVHD) were 77 and 63%. The 100-day and 1-year transplant-related mortality (TRM) were 1 and 9.2%, respectively, with no change through 5 years. Five- and 10-year event-free survival rates were 56 and 49%, overall survival (OS) rates 72 and 70%, respectively. Forty patients have relapsed: 8 cytogenetic (20%), 10 hematologic (25%) and 22 molecular (55%). Most have been salvaged with donor-leukocyte infusion, second transplants and/or imatinib therapy. Survival was worse for patients transplanted >2 years from diagnosis (10-year OS 56 vs 78%,  $P = 0.01$ ), for patients over 50 years old (10-year OS 44 vs 75%,  $P = 0.05$ ) and for patients without cGVHD (10-year OS 53 vs 86%,  $P < 0.001$ ). This regimen resulted in successful engraftment, low risk of TRM and long-term survival. In an era when imatinib is first line therapy, this regimen offers a potentially low-toxicity, highly successful alternative in the event of poor imatinib response.

*Bone Marrow Transplantation* (2007) 40, 423–430; doi:10.1038/sj.bmt.1705755; published online 2 July 2007

**Keywords:** CML; allogeneic bone marrow transplant; low-dose total-body irradiation

## Introduction

Chronic myeloid leukemia is a clonal stem cell disorder characterized by the Philadelphia chromosome and the resultant constitutively active BCR-ABL tyrosine kinase. Management of chronic myeloid leukemia (CML) has become more complex due to the availability of improved diagnostic procedures and life-prolonging therapies. Therapies include interferon-based regimens, allogeneic stem cell transplantation and the BCR-ABL tyrosine kinase inhibitor imatinib mesylate. Allogeneic stem cell transplantation is still considered the only potential curative therapy for CML, but it is often restricted to those individuals who are fortunate enough to have matched sibling donors and to younger patients because of significant transplant-related morbidity and mortality with increasing age. To ensure adequate cytoreduction and immunosuppression to allow for engraftment, conventional total body irradiation (TBI) based conditioning regimens usually include TBI at a dose of 1000 cGy or greater delivered in multiple fractions. These preparative regimens are associated with significant treatment-related morbidity and mortality, particularly radiation-induced pneumonitis.<sup>1,2</sup> To minimize these effects, alternative regimens have been explored varying the dose, dose rates and fractionation schedules.<sup>3–8</sup> It has been shown in canine models that, at an equivalent dose and rate, fractionated TBI is significantly less immunosuppressive compared to single-dose TBI,<sup>9</sup> although both regimens were observed to have comparable myeloablative effects.<sup>10</sup> Single-dose TBI delivered at a high-dose rate was subsequently shown to be significantly more immunosuppressive than single-dose TBI delivered at a lower rate, but without significant toxicities.<sup>11</sup> We adopted a conditioning regimen using reduced-dose TBI delivered with a high-dose rate to preserve the myeloablative effect while reducing the incidence of interstitial pneumonitis.<sup>12</sup> This dose and rate were chosen based on local experience, where higher doses were associated with a high incidence of radiation-induced interstitial pneumonitis.<sup>13,14</sup>

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Received 6 July 2006; revised 10 May 2007; accepted 14 May 2007; published online 2 July 2007

The main objectives of this retrospective study were to evaluate the outcome of patients with chronic phase CML undergoing matched related donor transplants treated with a single-dose TBI-based conditioning regimen and to identify factors predicting survival.

## Materials and methods

### Patient population

Between October 1986 and February 1996, 103 related donor allogeneic bone marrow transplants for CML in chronic phase were performed at the University of Toronto Allogeneic Blood and Marrow Transplant Program. Only human leukocyte antigen (HLA) identical or 1-antigen mismatch sibling donor bone marrow transplants (96) were considered for this study. Patient, donor, disease characteristics and outcome data were extracted from a transplant database and a retrospective chart review of patient medical records, according to a protocol approved by the University Health Network Research and Ethics Board. We chose 1986 as the start date for our evaluation because, at that time, two major changes were introduced into the supportive care of transplant recipients: (i) the initiation of graft-vs-host disease (GVHD) prophylaxis with cyclosporine; and (ii) preemptive treatment of cytomegalovirus (CMV) reactivation with ganciclovir.

### HLA typing

Typing was serological for HLA A, B, and DR loci until 1993. Subsequently, molecular typing was used for the DRB1 locus. Donors and recipients needed to be matched at the HLA A, B and DR or DRB1 loci to be considered HLA identical. HLA C, DQ or DP typing was not routinely performed.

### Preparative regimen

**Chemotherapy.** Patients were uniformly treated with a continuous intravenous infusion of cytosine arabinoside at 100 mg/m<sup>2</sup> on days -8 to -4, followed by cyclophosphamide at 60 mg/kg/day intravenously on days -3 and -2 and TBI described below.

**TBI.** All patients were treated on a non-isocentric telecobalt (<sup>60</sup>Co) unit with an extended source to skin distance of 130–150 cm. On day 0, the prescribed dose of 500 cGy was delivered through anterior (supine) and posterior (prone) fields to the patient's midline, with a dose rate between 25 to 56 cGy/min at prescription point. The variation in the dose rate was chiefly due to the decay of the <sup>60</sup>Co source with time. Tissue equivalent bolus material was placed on the patient to compensate for dose heterogeneity due to variations in patient thickness with the aim of achieving midplane dose variation of  $\pm 5\%$  of prescribed dose. Shielding was not used.

### Supportive Care

**ABO incompatibility.** Recipients of grafts with major ABO incompatibility (32%) underwent recipient plasmapheresis or red cell depletion of the donor bone marrow.

**GVHD prophylaxis and treatment.** All patients were given standard cyclosporine and methotrexate as acute GVHD (aGVHD) prophylaxis. Cyclosporine was given as an oral dose of 10 mg/kg/day in divided doses starting day -1 and discontinued by 8 weeks (tapering beginning at 6 weeks) after transplant, unless GVHD developed. Methotrexate 15 mg/m<sup>2</sup> i.v. was given on day +1 and 10 mg/m<sup>2</sup> i.v. was given on days +3, +6, +11 after transplant, mucositis, creatinine clearance and direct bilirubin permitting. T-cell depletion was not performed.

aGVHD was graded according to the criteria by Glucksberg<sup>15</sup> and chronic GVHD (cGVHD) according to the criteria by Sullivan.<sup>16</sup> Patients who developed GVHD were treated by a variety of approaches including steroids (prednisone, methylprednisolone), azathioprine and anti-thymocyte globulin.

**Transfusion support.** Blood product support included prophylactic transfusion of single donor platelets for a platelet count of  $< 10 \times 10^9/l$  and 2 U of packed red blood cells for hemoglobin  $< 80 g/l$  or symptomatic anemia. All blood and platelet products were irradiated, but not routinely filtered.

**Isolation and prophylactic antimicrobials.** Patients were managed in reverse isolation, single non-filtered rooms from day 0 until the absolute neutrophil count was greater than  $500 \times 10^6/l$  for two consecutive days. All patients received bacterial prophylaxis with trimethoprim-sulfamethoxazole starting on the first day of conditioning until neutrophil counts recovered. Ciprofloxacin was used in cases of allergy. Once the neutrophil count was greater than  $1.0 \times 10^9/l$ , trimethoprim-sulfamethoxazole twice a week was given as *Pneumocystis carinii* prophylaxis until day +365 or until immunosuppressive medications were no longer required, whichever was longer. In the case of allergy, inhaled pentamidine Q2–4 weeks was used. Acyclovir was given as herpes simplex prophylaxis between day +1 until day +28 post transplant. No routine fungal prophylaxis was given during this time period. Patients transplanted from a CMV-seropositive donor or who were CMV seropositive before transplant received preemptive ganciclovir therapy based upon positive day +35 surveillance bronchoscopy or positive CMV antigenemia results.

### Definition of endpoints

The end points of this study were engraftment, transplant-related mortality, GVHD, relapse and survival.

Engraftment was defined as the time to reach a transfusion-independent sustained platelet count of  $50 \times 10^9/l$ , the time to reach a neutrophil count of  $0.5 \times 10^9/l$  and the time to red cell transfusion independence. Transplant-related mortality was defined as death without relapse that was attributable to the transplant procedure. Relapse was defined as the time from transplant to disease recurrence. Hematologic relapse was defined as morphologic evidence of disease on peripheral blood or marrow testing at any post-transplant evaluation. Cytogenetic relapse was defined as the detection of the Philadelphia chromosome by routine G-banding. Molecular

relapse was defined as detection of the BCR-ABL gene by Southern blot analysis and, more recently, detection of the BCR-ABL transcript by reverse transcriptase-polymerase chain reaction (RT-PCR). Event-free survival (EFS) was calculated from the date of transplant to date of relapse or death or last follow-up. Overall survival (OS) was calculated from the date of transplant to death or last follow-up.

### Statistical analysis

Survival estimates were calculated using the Kaplan–Meier product limit method. Potential prognostic variables were examined using log-rank tests. The analysis of whether cGVHD was related to survival was restricted to patients who had follow-up of at least 100 days (only one patient was excluded). Survival was also examined for the subset of patients who had relapsed, to test whether the type of relapse was related to survival. Transplant-related mortality rates were calculated using the cumulative incidence function with the event defined as death without relapse that was attributable to the transplant procedure and the competing risk, death due to any other cause. *P*-values  $\leq 0.05$  were considered statistically significant.

## Results

### Patient characteristics

Ninety-six matched or 1-antigen mismatched sibling allogeneic transplants for chronic phase CML were performed at our institution between October 1986 and February 1996. Patient characteristics are summarized in Table 1. The median age was 38 years (range 18–62), and 62

(65%) patients were male. Thirty-five patients (36%) were older than 40 years. Sixty-nine (72%) received transplants within 2 years of diagnosis of CML. Pre-transplant interferon was administered to 31 (34%) patients and was discontinued within 3 months before transplant in 23 (74%) of these patients. Nineteen (20%) of the male transplant recipients received a graft from a female donor. Eighty-nine (93%) were HLA identical and 7 (7%) were 1-antigen mismatched. Median follow-up was 12.8 years (0.4–19.9 years).

### Engraftment

The median time to reach a platelet count of  $50 \times 10^9/l$  was 22 days (9–205). The median time to reach a neutrophil count of  $0.5 \times 10^9/l$  was 25 days (16–205). The median time to red cell transfusion independence was 21.5 days (0–570). Graft failure occurred in one patient, which was felt to be as a consequence of unrecognized renal failure on day 1 with the infusion of full-dose prophylactic methotrexate. He ultimately died on day +204 post transplant of sepsis and pneumonia.

### Transplant-related complications

**GVHD/veno-occlusive disease.** Of the 95 patients evaluable, the overall incidence of aGVHD was 77%. Grade I and II aGVHD developed in 22 and 20%, respectively. Grade III and IV aGVHD occurred in 35%. cGVHD was seen in 63% of patients. Limited cGVHD occurred in 49% and extensive cGVHD occurred in 14%. Two patients died of cGVHD on days +191 and +199 post transplant. Veno-occlusive disease (VOD) was seen in 13 patients (14%) with no fatalities.

**Regimen-related toxicity.** Idiopathic interstitial pneumonitis defined as reticulonodular densities on chest X-ray associated with dyspnea and cough occurred in 4 of 94 evaluable patients (4.3%). Bronchiolitis obliterans defined as dyspnea and cough with small airway changes on pulmonary function tests did not occur. Cataracts occurred in 11 of 94 evaluable patients (11.7%).

**Transplant-related mortalities.** Nine patients died from treatment-related conditions; causes of death are listed in Table 2. The main causes of TRM were sepsis (4) and cGVHD. (2) Other causes included graft failure (1), steatohepatitis (1) and viral induced liver necrosis (1). The estimated 100-day and 1-year TRM were 1 and 9.2%, respectively, with no change through to 5 years.

**Survival and prognostic factors.** At last follow-up, 27 patients had died (15 relapse, 9 TRM, 3 other). Five and ten year estimates of EFS are 56 and 49%, respectively (Figure 1). Estimates of 5- and 10-year OS survival rates are 72% and 70% respectively (Figure 2). Results of univariate analysis of prognostic factors for OS are shown in Table 3. Improved outcome was predicted by: transplant less than 2 years from diagnosis, patient age 50 years or below and development of cGVHD (Figure 3). Survival was not influenced by recipient or donor gender, donor type, CMV status, ABO mismatch or development of aGVHD.

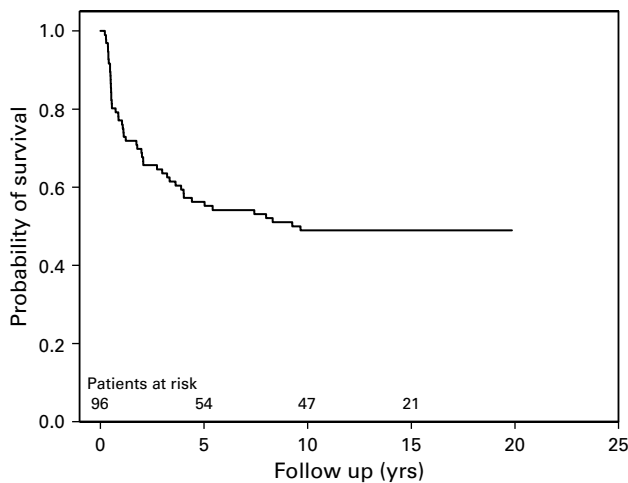
**Table 1** Patient characteristics

Median age, years (range)	38 (18–62)
<i>Patient age (years)</i>	
$\leq 40$	61 (64%)
40–50	26 (27%)
$> 50$	9 (9%)
<i>Patient gender</i>	
Male	62 (65%)
Female	34 (35%)
<i>Donor type</i>	
Full match	89 (93%)
One-antigen mismatch	7 (7%)
<i>Time from diagnosis to transplantation (months)</i>	
$\leq 24$	69 (72%)
$> 24$	27 (28%)
Interferon trial before transplant	31 (34%)
<i>Interferon held before transplant (months)</i>	
$< 3$	23 (74%)
$> 3$	8 (26%)
<i>Matching of donor and recipient</i>	
Sex matched	56 (59%)
Female/male	19 (20%)
Male/female	20 (21%)

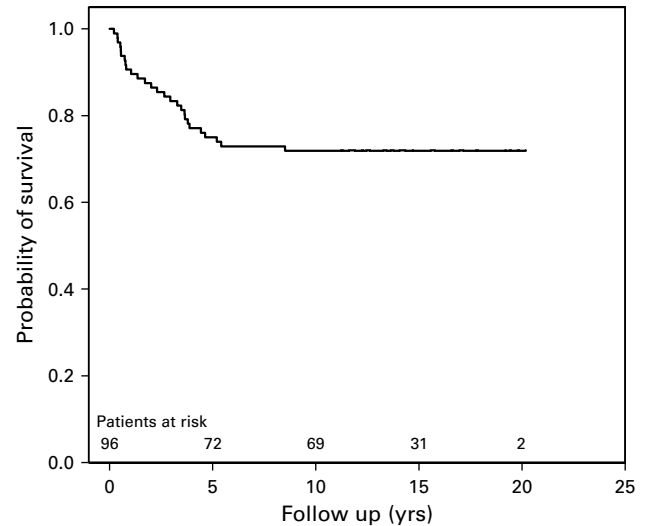
**Table 2** Causes of treatment-related mortality

Patient number	Time from transplant to death (days)	Cause of death
21	191	CGVHD
23	145	Viral induced liver necrosis
42	204	Graft failure
48	77	Sepsis ( <i>Aspergillus</i> )
53	139	Sepsis
76	1384	Sepsis
79	199	CGVHD
84	267	Steatohepatitis
88	496	Sepsis

Abbreviation: cGVHD = chronic graft-vs-host disease.

**Figure 1** Probability of event-free survival after HLA-identical on 1-antigen mismatch sibling donor BMT for CML in first chronic phase.

**Relapse.** Forty patients have relapsed (42%); 8 cytogenetic (20%), 10 hematologic (25%) and 22 (55%) molecular. Eighteen have died, as a result of relapse in blast phase, relapse while on interferon therapy or TRM from a second transplant. The 10-year OS was 88% for those with a cytogenetic relapse, 40% for those with a hematologic relapse and 50% for those with a molecular relapse ( $P=0.11$ ) (Figure 4). Relapsed patients received a variety of treatments, singly or in combination, including  $\alpha$ -interferon (27 patients), donor-leukocyte infusion (DLI) (23 patients), second allogeneic transplant (5 patients) and/or imatinib mesylate (9 patients). Twenty-five patients have become Philadelphia chromosome negative.

**Figure 2** Probability of overall survival after HLA-identical of 1-antigen mismatch sibling donor BMT for CML in first chronic phase.

## Discussion

The purpose of the conditioning regimen in hematopoietic stem cell transplantation is to eliminate the underlying disease and to provide adequate cytoreduction and immunosuppression to allow for successful engraftment. Conventionally, this has been achieved by the administration of maximally tolerated doses of multiple chemotherapeutic agents with nonoverlapping toxicities, with or without radiation. TBI-containing regimens have been the foundation of conditioning regimens since the origin of HCT, based upon early studies in the dog and other animal models.<sup>17</sup> All conditioning regimens are associated with potentially life threatening toxicities, particularly with increasing age, despite improvements in supportive care. Several approaches have been evaluated in an attempt to minimize toxicity such as fractionation of the radiation dose and delivering it over several days.<sup>18</sup> Recently, a number of centers have tested nonmyeloablative stem cell transplants as another method of reducing regimen-related toxicities. Many of the studies in this area have included patients with various hematological conditions, which included a small number of CML patients. In the studies we identified,<sup>19–24</sup> disease-free survival ranged from 38–85% and OS ranged from 32–85% with median follow-up ranging between 8–42 months. These results are promising, but given the relatively short follow-up, long-term efficacy of nonmyeloablative stem cell transplants in patients with CML remains to be determined.

Over two decades ago, we adopted a conditioning regimen combining a single dose of TBI at 500 cGy with cyclophosphamide and cytarabine in the effort to reduce the incidence of radiation pneumonitis while preserving the myeloablative effect. This conditioning regimen was very well tolerated with a 100-day and 1-year TRM of 1 and 9.2%, respectively, with no additional TRM out to 5 years. Few patients developed interstitial pneumonitis (4.3%) or clinically significant VOD (14%). Thus, this regimen offers

**Table 3** Univariate analysis of prognostic factors of overall survival

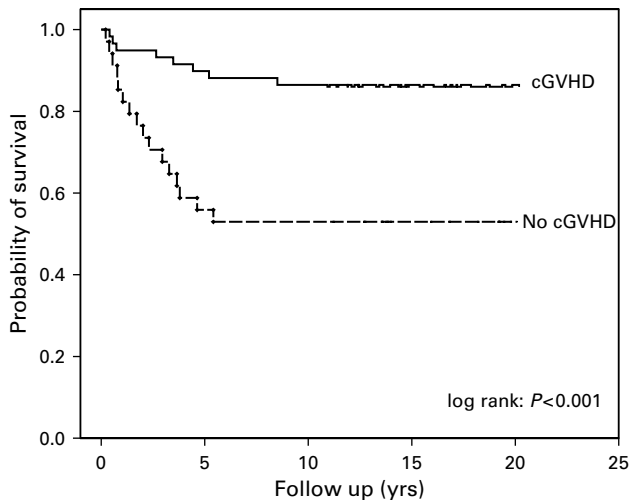
Prognostic factor	% 5 years OS (95% CI)	% 10 years OS (95% CI)	Log rank test for difference between groups
<i>Age</i>			
≤ 50 (n = 87)	77 (67–85)	75 (64–83)	P = 0.05
> 50 (n = 9)	56 (20–80)	44 (14–72)	
<i>Recipient gender</i>			
Male (n = 62)	73 (60–82)	71 (58–81)	NS
Female (n = 34)	79 (66–93)	74 (55–85)	
<i>Time: diagnosis to transplant</i>			
≤ 2 years	80 (68–87)	78 (67–86)	P = 0.01
> 2 years	63 (42–78)	56 (35–72)	
<i>Donor type</i>			
Full match	75 (65–83)	72 (61–80)	NS
One-antigen mismatch	71 (26–92)	71 (26–92)	
<i>Donor gender</i>			
Male (n = 61)	79 (66–87)	74 (61–83)	NS
Female (n = 34)	71 (52–83)	71 (52–83)	
<i>ABO groups</i>			
'Bad' mismatch <sup>a</sup> (n = 16)	69 (40–86)	56 (30–76)	NS
Other (n = 65)	77 (65–85)	75 (63–84)	
<i>CMV status – patient</i>			
Positive (n = 45)	76 (60–86)	73 (58–84)	NS
Negative (n = 46)	78 (63–88)	74 (59–84)	
<i>CMV status – donor</i>			
Positive (n = 32)	81 (63–91)	75 (56–87)	NS
Negative (n = 39)	74 (58–85)	74 (58–85)	
<i>Acute GVHD</i>			
No (n = 22)	73 (49–87)	68 (45–83)	NS
Yes (n = 73)	77 (65–85)	74 (62–83)	
<i>Chronic GVHD</i>			
No (n = 33)	56 (38–71)	53 (35–68)	P < 0.001
Yes (n = 59)	90 (79–95)	86 (75–93)	
<i>VOD</i>			
No (n = 80)	78 (67–85)	74 (63–82)	NS
Yes (n = 13)	77 (44–92)	77 (44–92)	
<i>Prior treatment</i>			
Interferon (n = 31)	77 (58–89)	71 (52–84)	NS
No interferon (n = 61)	77 (64–86)	75 (63–84)	
<i>Interferon held before transplant</i>			
< 3 months (n = 23)	83 (60–93)	78 (55–90)	NS
> 3 months (n = 8)	63 (23–86)	50 (15–77)	

Abbreviations: GVHD = graft-vs-host disease; VOD = veno-occlusive disease.

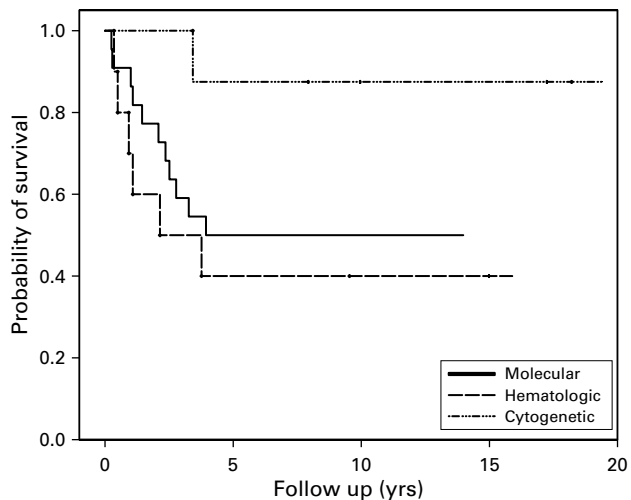
<sup>a</sup>Anything into group O, A into B, B into A, AB into A or B.

the advantages of a myeloablative regimen with reduced intensity as defined by organ toxicity. With this regimen, the relapse rate was slightly higher than in previously published reports,<sup>25</sup> which may attest to the reduced intensity of this regimen, but over half of these patients were salvaged with a variety of therapies with very little toxicity. With a median of 12.8 years of follow-up, OS at 10 years is 71%, which compares favorably with outcomes using a standard conditioning regimen reported in a similar patient population of low-risk patients reported by the European Group for Blood and Marrow Transplanta-

tion.<sup>26</sup> This retrospective analysis reported the outcome of 373 consecutive transplants performed at 38 European institutions between 1980 and 1988. All transplants were for first chronic phase of CML, using unmanipulated marrow cells from HLA-identical sibling donors. The probability of survival and leukemia-free survival at 8 years were 54 (95% CI, 49–59) and 47% (95% CI, 41–52), respectively. The probabilities of developing aGVHD (II–IV) at 100 days and cGVHD at 4 years after transplant were 47 (95% CI, 41–53) and 52% (95% CI, 46–58), respectively. The probabilities of transplant-related mor-



**Figure 3** Probability of survival according to the presence or absence of cGVHD.



**Figure 4** Probability of survival from relapse according to type of relapse.

tality and leukemic relapse 8 years after BMT were 41 (95% CI, 36–48) and 19% (95% CI, 14–25), respectively.

Two additional recent reports in the literature have examined the efficacy of a low-dose TBI conditioning regimen in allogeneic transplantation, which was motivated by previous experience published from our center.<sup>12</sup> In a phase II trial, Khoury *et al.*<sup>36</sup> evaluated the role of a low- (550 cGy) high-dose-rate (35 cGy/min) single-exposure TBI, following administration of CP for HLA sibling matched allogeneic peripheral blood stem cell transplantation in 30 patients with CML. The preparative regimen was well tolerated without grade 4 toxicities or oral mucositis and graft failure did not occur. A severe aGVHD was observed in 5 patients (17%). With a median follow-up of 23 months, cytogenetic or hematologic relapse was detected in three patients (10%), two of whom subsequently entered remis-

sion following a taper of immunosuppression. Nonrelapse mortality occurred in five patients (17%) and the Kaplan–Meier estimate of survival at 2 years was 83%.

In a phase II study from the same center, Blum *et al.*<sup>27</sup> evaluated the same regimen of 550 cGy TBI administered as a single dose at 30 cGy/min following administration of CP in twenty-seven good-risk (acute leukemia in first remission and CP-CML) and 53 poor-risk (other) patients. Graft failure did not occur. TRM through at least 2 years was 7% in the good-risk and 19% in the poor-risk diagnostic groups. Grade 4 (fatal) organ toxicity occurred in only two patients (2.5%). Median follow-up for the surviving patients was 1234 days. Relapse occurred in 15% of the good-risk group and 45% of the poor-risk group. The Kaplan–Meier estimates of 3-year disease-free and OS of the good-risk group were 77 and 85%, respectively, and of the poor-risk group were 34 and 36%, respectively.

The follow-up in both of these studies is still short, but the results are encouraging.

The present study reported features that influenced OS. With this regimen, survival was significantly worse for those transplanted greater than 2 years from diagnosis (10-year OS 56 vs 78%,  $P=0.01$ ), for patients over the age of 50 years (10-year OS 44 vs 75%,  $P=0.05$ ) and for patients that did not develop cGVHD (10-year OS 53 vs 86%,  $P<0.001$ ).

There remains controversy regarding the influence of prior pre-treatment with interferon on the outcome of allogeneic stem cell transplant. In a retrospective study from Seattle,<sup>28</sup> more severe GVHD and poorer survival was seen in the group of patients who received interferon for more than 6 months before unrelated transplant for CML in chronic phase. Beelen *et al.*<sup>29</sup> also demonstrated that pre-treatment with interferon for more than 12 months before transplant was associated with poorer survival. However, in the current study, prior treatment with interferon did not have a deleterious effect on transplant outcomes. Similarly, in a number of additional studies,<sup>30–34</sup> interferon pre-treatment appeared to have no impact on transplant outcomes.

In summary, with close to 10 years of follow-up, we have shown that low-dose, single-exposure TBI given at high-dose rate, in combination with CP, was associated with low toxicity and TRM. These outcomes are comparable to similar low-dose TBI containing regimens, and despite their much shorter follow-up (23–42 months), appear to support employing reduced-intensity conditioning regimens as an alternative to standard myeloablative regimens with their associated toxicities. In a previous report from this institution focusing on long-term follow-up and quality of life of patients receiving an allotransplant for CML, there appeared to be a constant rate of relapse over time.<sup>35</sup> However, similar to this study, most relapsed patients were salvaged successfully. This suggests that lifelong molecular monitoring is necessary. To reduce the incidence of relapse, consideration should be given to combining this regimen with post-transplant maintenance therapy, such as peginterferon, imatinib or DLI based on chimerism studies to control minimal residual disease.

As more experience is obtained treating newly diagnosed patients with chronic phase CML with imatinib, fewer up

front allografts have been performed. Results with imatinib beyond 7-8 years are not yet available, and whether there will be any late loss of response or unpredicted toxicities is unknown. The regimen described here offers an alternative to patients who do not want to consider what is likely life-long imatinib therapy for whatever reason, or potentially in patients who get less than an optimal imatinib response, as defined by failure to achieve therapeutic milestones. Although newer kinase inhibitors are in trial, there are no long-term results with any of them and definitely nothing to suggest that moving to a different noncurative therapy is preferred to a potentially curative therapy such as transplant. As can be seen with the results presented here, durable responses can be achieved with toxicities that are acceptable to many people.

### Acknowledgements

Preparation of this manuscript was funded in part by a donation from the Friends for Life Foundation.

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