HLA-Matched Unrelated Donor Hematopoietic Cell Transplantation after Nonmyeloablative Conditioning for Patients with Chronic Myeloid Leukemia

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ABSTRACT
We evaluated 10/10 HLA antigen–matched unrelated hematopoietic cell transplantation (HCT) after nonmyeloablative conditioning with fludarabine 3 × 30 mg/m2 and 2 Gy of total body irradiation as treatment for patients with chronic myeloid leukemia who were ineligible for conventional HCT. Data from 21 consecutive patients in first chronic phase (CP1; n = 12), accelerated phase (AP; n = 5), second CP (CP2; n = 3), and blast crisis (n = 1) were analyzed. Stem cell sources were bone marrow (n = 4) or granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells (G-PBMCs; n = 17). The patient who underwent transplantation in blast crisis died on day 21 (too early to be evaluated for engraftment) from progressive disease. Sustained engraftment was achieved in 5 of 12 patients who underwent transplantation in CP1, 4 of 5 patients who underwent transplantation in AP, and 2 of 3 patients who underwent transplantation in CP2, whereas 9 patients rejected their grafts between 28 and 400 days after HCT. Specifically, 1 of 4 marrow recipients and 10 of 17 G-PBMC recipients achieved sustained engraftment. Graft rejections were nonfatal in all cases and were followed by autologous reconstitution with persistence or recurrence of chronic myeloid leukemia. Seven of 11 patients with sustained engraftment—including all 5 patients in CP1, 4 of 5 patients who underwent transplantation in AP, and 2 of 3 patients who underwent transplantation in CP2, whereas 9 patients rejected their grafts between 28 and 400 days after HCT. Specifically, 1 of 4 marrow recipients and 10 of 17 G-PBMC recipients achieved sustained engraftment. Graft rejections were nonfatal in all cases and were followed by autologous reconstitution with persistence or recurrence of chronic myeloid leukemia. Seven of 11 patients with sustained engraftment—including all 5 patients in CP1, 4 of 5 patients who underwent transplantation in AP, and neither of the 2 patients in CP2—were alive in complete cytogenetic remissions 118 to 1205 days (median, 867 days) after HCT. Two of the remaining 4 patients died of nonrelapse causes in complete (n = 1) or major (n = 1) cytogenetic remissions, and 2 died of progressive disease. Further efforts are directed at reducing the risk of graft rejection by exclusive use of G-PBMC and increasing the degree of pretransplantation immunosuppression.

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KEY WORDS
Chronic myeloid leukemia ● Hematopoietic cell transplantation ● Unrelated donor ● Nonmyeloablative ● Chimerism ● Graft rejection

INTRODUCTION
Despite promising results with imatinib mesylate [1], allogeneic hematopoietic cell transplantation (HCT) has remained the only proven curative therapy for chronic myeloid leukemia (CML) [2,3]. Cures have been attrib-
geted busulfan and cyclophosphamide conditioning, survival rates of 86% at 3 years have been achieved in relatively young (median age, 43 years) and otherwise healthy patients with CML in first chronic phase (CP1) given HLA-matched related HCT [8].

Additionally, considerable experience has been obtained with unrelated HCT. Five-year overall survival has been 74% for CP1 patients younger than 50 years who received HCT within 1 year of diagnosis [9]. However, 2-year survival has been <40% in patients 50 to 55 years of age [9], and transplantations have generally not been performed in patients older than 55 years [10,11]. This is unfortunate, because the median patient age at diagnosis for CML is 67 years.

Graft-versus-tumor effects have been well documented for CML, as evidenced by the ability of donor lymphocyte infusions (DLIs) to induce durable complete remissions in patients who relapse after allogeneic HCT [12,13]. To extend the use of allogeneic HCT to include older patients with CML and those with comorbid conditions, several groups of investigators have introduced reduced-intensity [14-17] or truly nonmyeloablative [18-22] conditioning regimens. Those regimens have fewer toxicities than ablative ones but are sufficiently immunosuppressive for allogeneic engraftment and rely on graft-versus-tumor effects for tumor eradication [23]. On the basis of initial experimental canine studies [24] and subsequent studies in HLA-identical sibling recipients [18], we have developed a nonmyeloablative regimen that uses 2 Gy of total body irradiation (TBI) and fludarabine 30 mg/m² as conditioning for unrelated HLA-matched HCT [25,26]. Postgrafting immunosuppression with mycophenolate mofetil (MMF) and cyclosporine (CSP) is aimed at both enhancing engraftment and controlling graft-versus-host disease (GVHD). Three phase I/II studies have explored variations in the duration and dosing of postgrafting immunosuppression for unrelated HLA-matched HCT in patients with various hematologic malignancies [25,26]. Here, we retrospectively analyzed outcomes among 21 consecutive patients with CML who were included in those studies.

**PATIENTS AND METHODS**

**Patients**

Data from 21 consecutive patients with CML in CP1 (n = 12), CP2 after blast crisis (BC) (n = 3), accelerated phase (AP; n = 5), or BC2 (n = 1) and who underwent transplantation between January 2000 and March 2004 under Fred Hutchinson Cancer Research Center (FHCRC) multi-institutional protocols 1463 (n = 14), 1641 (n = 5), and 1668 (n = 2) were analyzed as of June 31, 2004 (Table 1). The median patient age was 54 years (range, 33-66 years). The median time from diagnosis to HCT was 26 months (range, 5-121 months). Two patients had experienced treatment failure with myeloablative allogeneic HCT as the result of either disease progression or graft rejection. Six patients had experienced treatment failure with imatinib therapy because of intolerance (n = 3) or lack of cytogenetic responses to the drug given at 800 mg/d (n = 3). Four patients (all included in protocol 1463) received marrow and 17 received granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells (G-PBMCs) as stem cell sources. Two patients each had single HLA class I allele mismatches with their donors, whereas the remaining 19 patients were matched for 10/10 HLA antigens/alleles. Participating institutions included the FHCRC, the University of Washington Medical Center, the Veterans Affairs Medical Center (all in Seattle, WA; n = 12), Stanford University (Palo Alto, CA; n = 4), the University of Colorado (Denver, CO; n = 2), the University of Utah (Salt Lake City, UT; n = 2), and Baylor University (Dallas, TX; n = 1). Patients were considered ineligible for conventional allogeneic HCT because of age (older than 50 years; n = 17), medical comorbidities (n = 2), or failed preceding myeloablative allogeneic HCT (n = 2). The study protocols were approved by the institutional review boards at FHCRC and each of the collaborating sites. All patients signed consent forms approved by the local institutional review boards.

**Conditioning Regimen, Postgrafting Immunosuppression, and Follow-up**

Patients were conditioned with fludarabine 30 mg/m²/d on days −4, −3, and −2 and with 2 Gy of TBI on the day of HCT [26]. Postgrafting immunosuppression included MMF and CSP in all 3 protocols. Protocol 1463 administered MMF 15 mg/kg orally twice a day from the evening of day 0 until day +40, with taper through day +96. CSP was administered at 6.25 mg/kg orally twice a day, from day −3 to day +100, with taper through day 180 [26]. Protocol 1641 included MMF 15 mg/kg orally thrice a day from the evening of day 0 until day +40, with taper through day +96, and CSP was given identically to protocol 1463. In protocol 1668, MMF was given at 15 mg/kg orally thrice a day from the evening of day 0 until day +30 and at 15 mg/kg orally twice a day from day +31 until day 150, with a subsequent taper through day 180, whereas CSP was given at 6.25 mg/kg orally twice a day from day −3 to day +80.

Diagnosis, clinical grading, and treatment of GVHD were performed as previously reported [26,27]. Standard prophylaxis against *Pneumocystis carinii*, fungal infections, toxoplasmosis, and cytomegalovirus infections was used [26].

Pathology, cytogenetics, and reverse transcriptase–polymerase chain reaction (RT-PCR) monitoring were performed on days 28, 56, 84, and 180 and yearly thereafter. In patients who underwent transplantation in Seattle, quantitative RT-PCR was performed by
<table>
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<th>Time between Diagnosis and HCT (mo)</th>
<th>Patient Age (y)/Sex</th>
<th>Comorbidities at HCT</th>
<th>Stem Cell Source</th>
<th>CD34 Cell Doses (×10^6/kg)</th>
<th>CD33 Cell Doses (×10^8/kg)</th>
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<th>Rejection (Day)</th>
<th>Acute GVHD (Grade)</th>
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BC2 indicates second blast crisis; CP2, second chronic phase; AP, accelerated phase; CP1, first chronic phase; M, male; F, female; HCT, hematopoietic cell transplantation; URD, unrelated donor; VOD, veno-occlusive disease of the liver; CRF, chronic renal failure; MRD, HLA-matched related donor; AVM, arteriovenous malformation; G-PBMC, granulocyte colony-stimulating factor–mobilized peripheral blood mononuclear cells; ND, not done; NE, not evaluable; PD, progressive disease; CCR, complete cytogenetic response; MCR, major cytogenetic response; CML, chronic myeloid leukemia.

*Dead.
†Alive.
‡Had PD after HCT but achieved CCR after 1 course of farnesyl transferase inhibitor and extensive chronic GVHD.
§The patient had 28% donor T-cell chimerism on day 28, this predicted a high risk of subsequent graft rejection. He received pentostatin (4 mg/m^2) on day 43 followed by donor lymphocyte infusion 2 days later. This resulted in a significant increase in donor chimerism among all subpopulations, and the patient is currently surviving with sustained graft >118 days after HCT.
RESULTS

Peripheral Blood Cell Changes, Donor Engraftment, and Graft Rejection

Patients experienced declines in both neutrophil and platelet counts after conditioning. Neutrophil and platelet nadirs were $0.1 \times 10^9/L$ (range, 0.0-0.9 \times 10^9/L) and $43 \times 10^9/L$ (range, 6-373 \times 10^9/L), respectively. Median numbers of red blood cell and platelet transfusions were 8 (range, 0-32) and 0 (range, 0-10), respectively. Median durations of neutropenia (defined as absolute neutrophil count <0.5 \times 10^9/L) and thrombocytopenia (defined as platelet count <20 \times 10^9/L) were 7 days (range, 0-20 days) and 0 days (range, 0-17 days), respectively. One patient died on day 21 (too early to be evaluated for engraftment) from BC (Table 1). Initial donor engraftment (defined as >5% donor T-cell chimerism) was observed in 18 (90%) of the 20 remaining patients and was sustained in 1 of 4 marrow and 10 of 17 G-PBMC recipients, whereas 9 patients did not engraft or rejected initial grafts 28 to 400 days after HCT. All graft rejections were nonfatal and were followed by autologous hematopoietic reconstitution and persistence or recurrence of CML.

Day 28 T-Cell Chimerism Levels ≤40% Predicted Subsequent Graft Rejection

Day 28 T-cell chimerism was assessed in 19 patients (Table 1). Eight of 9 patients with donor T-cell chimerism levels ≤40% on day 28, compared with 1 of 10 with levels >40%, subsequently rejected their grafts ($P = .001$). Patient 14, who had a day 28 donor T-cell chimerism level of 28%, received pentostatin (4 mg/m²) on day 43, followed by DLI on day 45, in a successful attempt to prevent graft rejection. Donor chimerism levels among T cells, granulocytes, and marrow mononuclear cells increased after pentostatin administration and DLI (Figure 1A), and the patient experienced sustained engraftment.

Outcomes in Patients with Graft Failure or Graft Rejection (n = 9)

Among the 9 patients with graft rejection, 4 in CP1 achieved unsustained complete cytogenetic remissions 56 to 107 days after HCT, whereas 3 in CP1, 1 in AP, and 1 in CP2 had persistence of CML. The 4 patients with cytogenetic remissions eventually experienced disease progression that began in 1 case 198 days before graft rejection was diagnosed and that began in the other 3 cases 112, 113, and 230 days after graft rejection. At the time of the analyses, 3 patients had died of progressive disease, and 6 were alive with CML.

Outcomes in Patients with Sustained Engraftment (n = 11)

Sustained engraftment was demonstrated in 5 of 12 patients with CP1, 4 of 5 patients with AP, and 2 of 3 patients with CP2. Grade II and III acute GVHD occurred in 6 (55%) and 3 (27%) patients with sustained engraftment, respectively; no grade IV acute GVHD was observed. Extensive chronic GVHD was seen in 8 patients.

Seven of 11 patients with sustained engraftment, including 4 of 5 in CP1, 3 of 4 in AP, and none of 2 in CP2, achieved sustained complete cytogenetic remissions, whereas 1 patient who underwent transplantation in CP2 achieved a major cytogenetic remission (Table 1). The fifth patient with CP1 developed BC 189 days after HCT but then achieved a complete cytogenetic remission and became BCR/ABL negative by quantitative RT-PCR after a short course of therapy with a farnesyl transferase inhibitor (3 days of lonafarib [SCH66336, Sarasar] given at 200 mg twice daily) and experienced development of chronic exten-
One patient with CP2 and 1 with AP died of progressive disease, and 1 patient each in CP2 and AP died of nonrelapse causes; 1 of the 2 had a major cytogenetic response, and the other was in complete cytogenetic remission. Figure 1B shows the evolution of BCR/ABL messenger RNA in 4 patients with CML in CP1 and 1 patient with CML in AP who had sustained engraftment. Molecular remissions were achieved 84 to 524 days (median, 230 days) after HCT. Values of 0.1 indicate negative quantitative RT-PCR.

**Figure 1.** A, Peripheral blood donor T cell, granulocyte, and marrow mononuclear cell chimerism levels in patient 14, with CML in CP1. The patient had 28% donor T-cell chimerism on day 28, and this predicted a high risk of subsequent graft rejection. He received pentostatin (4 mg/m²) on day 43, followed by donor lymphocyte infusion 2 days later. This resulted in a significant increase in donor chimerism among all subpopulations, and the patient is currently surviving with a sustained graft >118 days after HCT. B, Evolution of BCR/ABL messenger RNA in 4 patients with CML in CP1 and 1 patient with CML in AP who had sustained engraftment.

**DISCUSSION**

The patients with CML reported here took part in 3 phase II protocols that explored engraftment, toxicities, and efficacy of a nonmyeloablative conditioning regimen for unrelated HCT in patients with various hematologic malignancies. Although the conditioning regimen of fludarabine and 2 Gy of TBI remained the same, the protocols differed slightly from each other with regard to stem cell sources (marrow versus G-PBMC) and the duration and dosing of postgrafting MMF and CSP.

A main finding among patients with CML has been failure of sustained engraftment, which was observed in
9 of 20 evaluable cases. This observation contrasted with observations in CML patients given related grafts after conditioning with 2 Gy of TBI and fludarabine, all 10 of whom achieved sustained engraftment [30], and also with findings in 64 other patients given unrelated grafts for acute myeloid leukemia, 61 of whom (95%) achieved sustained engraftment [31]. In each case, graft failure was followed by autologous marrow recovery with a return to the status quo. This is different from conventional HCT, for which graft failures have been seen in 5% to 15% of CML patients, and subsequent marrow aplasia was the rule [9,10]. A high rate of graft rejection among CML patients receiving grafts from unrelated donors after reduced-intensity conditioning has also been reported by other investigators. A graft failure rate of 44% (3 of 8 patients) was described after a reduced-intensity conditioning regimen that combined fludarabine, busulfan, and antithymocyte globulin [32], and, recently, Hallemeyer [33] observed graft failure in 5 of 22 evaluable patients given unrelated G-PBMC as treatment of CML after conditioning with 5.5 Gy of TBI and cyclophosphamide. A previous analysis of data from the first 89 patients with various hematologic malignancies given unrelated grafts after conditioning with fludarabine and 2 Gy of TBI showed that marrow grafts were associated with a higher incidence of graft failure than G-PBMC grafts [26]. Recent analyses of data in 130 consecutive patients given unrelated grafts after nonmyeloablative conditioning showed that a higher number of grafted CD8+ (P = .005) and CD34+ (P = .01) cells resulted in a lower probability of graft rejection [34]. Two of the 4 current marrow recipients experienced graft failure, 1 of the 4 died too early for evaluation, and the only patient with engraftment had experienced treatment failure with 2 previous high-dose conventional allogeneic HCTs. Nevertheless, 7 of the 17 G-PBMC recipients also rejected their grafts. Increasing the dosing of postgrafting MMF from 15 mg/kg every 12 hours to 15 mg/kg every 8 hours reduced the rejection rate in G-PBMC recipients from 5 in 10 to 2 in 7, but not convincingly so. Clearly, more effective pretransplantation immunosuppression will be required to ensure uniform engraftment. A dose relationship with respect to TBI and allogeneic marrow engraftment has been demonstrated [35,36] in a preclinical canine model. This led us to conduct a dose-escalation study to determine the minimal dose of TBI required to promote engraftment in ≥90% of CML patients given grafts from unrelated donors.

Eight of 9 current patients with day 28 donor T-cell chimerism levels ≤40% rejected their grafts, thus confirming previous observations in patients with other hematologic malignancies [37]. These findings led to the design of a protocol aimed at preventing graft rejection through administration of pentostatin (to reduce host-versus-graft reactions) followed by DLI, as was used in 1 of the current patients, who had a day 28 donor T-cell chimerism level of 28%. Although the strategy was apparently successful in this patient, more experience will be needed to confirm its efficacy [38].

Sustained complete cytogenetic remissions have been achieved in all but 1 of the patients with CML in CP1 or AP who had stable engraftment. The relatively long time periods required for remissions to be complete were consistent with the concept that remissions were due to graft-versus-tumor effects. Nonrelapse mortality in patients with sustained engraftment was 0% at 100 days and was 11% at 1 year after HCT. This was encouraging given the age of the patients, the median time interval (2 years; range, 0.5-10 years) between diagnosis and HCT, and the advanced disease stage in 9 of the patients. The 1-year probabilities of overall survival in patients with CP1, AP, and CP2 who had sustained engraftment were 100%, 66%, and 0%, respectively. These observations attested to the relative safety of the current regimen and suggested that HCT should be considered early in the disease course, preferentially when patients were still in CP1. Ideal candidates for this approach would be patients who either are intolerant of imatinib mesylate or do not achieve 3-log BCR/ABL reductions after 1 year of treatment with the drug [1].

In summary, unrelated donor HCT after nonmyeloablative conditioning with fludarabine and low-dose TBI was feasible with relatively low nonrelapse mortality. Sustained complete cytogenetic remissions were achieved in most patients who had stable engraftment, but graft rejection occurred in 45% of patients. Further efforts are directed at reducing the risk of rejection by exclusive use of G-PBMC and by increasing the degree of pretransplantation immunosuppression.

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REFERENCES


