RAPID COMMUNICATION

Association Between Pretransplant Interferon-α and Outcome After Unrelated Donor Marrow Transplantation for Chronic Myelogenous Leukemia in Chronic Phase


Treatment options for patients diagnosed with chronic myelogenous leukemia (CML) in chronic phase (CP) who lack a suitable related donor for marrow transplantation include hydroxyurea, interferon-α (IFN-α), or transplantation from an unrelated donor (URD). Most studies support the view that treatment with IFN-α results in prolonged survival compared with hydroxyurea therapy. Some patients are offered URD transplantation as a second-line treatment; however, the impact of pretransplant IFN-α on the outcome of URD transplantation is uncertain. To address this question, we evaluated the effect of pretransplant IFN-α therapy in 184 patients undergoing URD transplantation for CML in CP at a single center. Of the 184 patients, 114 did not receive IFN-α, whereas 22, 23, and 25 patients received IFN-α for, respectively, 1 to 5, 6 to 12, and more than 12 months before transplant. Pretransplant IFN-α therapy administered for ≥6 months was associated with an increased risk of severe (grades III-IV) acute graft-versus-host disease (GVHD; relative risk [RR], 3.0; 95% confidence interval [CI], 1.4 to 6.2; P = .004) and mortality (RR, 2.1; 95% CI, 1.3 to 3.5; P = .003) relative to less than 6 months or no IFN-α therapy. Increased mortality occurred between 100 and 365 days after transplant (P = .005), was limited to patients with severe acute GVHD, and was due to chronic GVHD refractory to immuno-suppressive therapy. Other variables associated with mortality included HLA-DRB1 or DQB1 (but not HLA-A or B) mismatched donors, age greater than 50 years, weight ≥110% of ideal body weight, and the absence of cytomegalovirus (CMV) or fungal prophylaxis. For patients treated with IFN-α for less than 6 months before transplant, who were ≥50 years of age, received a HLA-A, B, DRB1, and DQB1 matched URD transplant, and received CMV and fungal prophylaxis after transplant (n = 48), survival was 87% ± 5% at 5 years. These data provide a rationale for immediate transplantation in preference to extended treatment with IFN-α when the patient is ≥50 years of age and has an HLA-compatible unrelated volunteer donor.

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INTERFERON-α (IFN-α) has demonstrated activity against chronic myelogenous leukemia (CML) and in most randomized studies has offered benefit when instituted in early chronic phase (CP).1-3 Cytogenetic responses (≤90% Philadelphia chromosome-positive metaphases) occurred in 20% to 60% of patients, becoming apparent after a median of 12 months of treatment.4 Major cytogenetic responses (<35% Philadelphia chromosome-positive metaphases) were achieved in 10% to 40% of patients, but molecular remissions, defined by the absence of bcr-abl mRNA determined by polymerase chain reaction, have rarely been described.5 Survival at 4 years was 90% for patients achieving a major cytogenetic response after 12 months of therapy with IFN-α, 75% for patients achieving a partial cytogenetic response (35% to 90% Philadelphia chromosome-positive metaphases),4 and 10% to 50% for those failing to achieve a cytogenetic response.5 Median overall survival for patients treated with IFN-α alone varies from 5 to 6 years,1,5-4 compared with 3 to 4.5 years for hydroxyurea or busulfan therapy.1,5-11 IFN-α combined with cytarabine has significantly improved cytogenetic response and survival compared with IFN-α alone.12

Allogeneic transplantation from an HLA-identical sibling donor offers curative treatment for the majority of patients with CML in CP and a 5-year survival of 65% to 90%, depending on the interval from diagnosis to transplant.13 Survival is similar after transplantation in CP from a single locus HLA-A or B mismatched family donor,14,15 whereas survival after transplantation from a family member mismatched for a single HLA-DR antigen is worse (~50% at 5 years).16 Only 35% of patients have an HLA-identical sibling donor, whereas a further 5% benefit from an extended family search.14 The recruitment of a large number of volunteer donors has resulted in the availability of HLA-A, B, DR serologically matched unrelated donors (URD) for up to 75% of Caucasian patients in the US National Marrow Donor Program and other registries worldwide. Recent studies have demonstrated the importance of donor matching for DRB117 and DQB118 to reduce the risk of severe acute graft-versus-host disease (GVHD) and donor matching for HLA-A, B and C19 alleles to decrease the risk of graft failure. Although early studies suggested inferior survival after URD compared with sibling donor transplantation,20-24 better prevention of cytomegalovirus (CMV) and fungal disease has substantially improved outcome after URD transplantation.25

In the absence of an available sibling donor, physicians are often faced with the choice of either treating patients in early CP with IFN-α or an URD transplant. Some investigators recommend an initial 12-month trial of IFN-α, followed by an URD transplant if there is no cytogenetic response to IFN-α therapy.4 Previous reports have evaluated the impact of IFN-α on...
outcome of related donor transplants with contradictory conclusions, reflecting differences in sample size and duration of IFN-α therapy considered. Others point out the many unanswered questions in this choice. The aim of this study was to assess the impact of pretransplant therapy with IFN-α on patient outcome after URD transplantation.

PATIENTS AND METHODS

Study patients. Between January 1988 and December 1994, 184 consecutive patients with Philadelphia chromosome-positive CML in CP underwent URD transplantation at the Fred Hutchinson Cancer Research Center. Treatment protocols were approved by the Institutional Review Board, and written informed consent was obtained from all patients or their legal guardians. The diagnosis and disease stage were confirmed by hematological and cytogenetic evaluations performed within 14 days before admission for transplantation. The protocol exclusion criteria were age greater than 55 years; availability of a HLA identical sibling or a one HLA-A, B or DR antigen incompatible family member; life expectancy severely limited by a disease other than malignancy; cardiac disease requiring therapy; severe hepatic disease including acute hepatitis; severe pulmonary disease including fibrosis; creatinine greater than 2 times normal; leukoencephalopathy; brain irradiation with greater than 3,000 cGy; chest irradiation with greater than 1,500 cGy; and positive human immunodeficiency virus (HIV) serology.

Pretransplant treatment of CML. Details of pretransplant treatment were obtained from patient history and referring physician notes and flow sheets. Patients were classified as IFN-α recipients if they received therapy at doses of ≥9 x 10^9 U/m²/wk for at least 4 weeks. Treatment intervals in which the patient received ≥9 x 10^9 U/m²/wk of IFN-α were added, with the total duration of pretransplant IFN-α calculated to the nearest month. The time period between the last dose of IFN-α and the day of transplant was calculated to the nearest month. Evaluation was made by chart review, with the observer (A.J.M.) blinded to patient transplantation outcomes.

HLA typing and donor matching. The analysis of HLA matching was based on typing for HLA-A and B antigens by serological methods and typing of HLA-DRB1 and HLA-DQB1 alleles by DNA hybridization with sequence-specific oligonucleotide probes (SSOP). The population of 184 URD transplants included 129 HLA matched pairs, 15 pairs mismatched for HLA-A (n = 7) or HLA-B (n = 8), 28 pairs mismatched for HLA-DRB1 (n = 12) or HLA-DQB1 (n = 16), and 12 pairs multiply mismatched, including 7 pairs mismatched for HLA-A or B and HLA-DRB1 or DQB1 and 5 pairs mismatched for HLA-DRB1 and HLA-DQB1.

Transplant procedure and supportive care. Conditioning for the 184 patients included cyclophosphamide (60 mg/kg on each of 2 consecutive days) and fractionated total body irradiation (TBI), with 80% of patients receiving 12 Gy and the others receiving exposures varying from 13.2 to 15.75 Gy. All patients received unmodified bone marrow and short course methotrexate in conjunction with cyclosporine for GVHD prophylaxis, as previously published. CMV-seronegative patients received blood products from CMV-seronegative donors or leukocyte-depleted blood products from CMV-seropositive donors. From November 16, 1990 until August 5, 1991, CMV-seropositive patients were randomized to receive ganciclovir or placebo at the time of engraftment to prevent CMV disease. Subsequently, CMV-seronegative patients received ganciclovir at the time of engraftment. Since December 17, 1993, CMV-seronegative recipients have been treated with ganciclovir at the first sign of CMV antigenemia as detected by fluorescence assay. Patients receiving ganciclovir prophylaxis at engraftment or at the first signs of CMV antigenemia and donor/recipient pairs in which both were CMV seronegative were coded as receiving CMV prophylaxis. From July 1990 to March 1992, patients were randomized to receive fluconazole or placebo from the pretransplant period until day +75 posttransplant for fungal prophylaxis. Acyclovir was administered to herpes simplex virus (HSV)-seropositive patients from the pretransplant period until day +30 or discharge from the in-patient unit. Fifty-nine patients received granulocyte-macrophage colony-stimulating factor (GM-CSF; 250 µg/m²/d) starting on day 0 as part of a phase II or phase III trial, whereas 32 patients received granulocyte colony-stimulating factor (G-CSF; 5 µg/kg/d) due to the absence of neutrophil recovery at day +21.

Engraftment. Patients were evaluable for graft failure when survival exceeded 28 days. Graft failure was defined by the following: (1) the absolute neutrophil count did not surpass 500/µL at any time before second transplant, relapse or death; (2) the absolute neutrophil count decreased to less than 100/µL for at least three consecutive determinations at least 1 day apart after initial engraftment and did not recover before relapse, second transplant, or death; or (3) absence of donor T cells as documented by informative variable number tandem repeat polymorphisms or by fluorescent in situ hybridization with a Y-chromosome–specific probe in gender mismatched transplants. Platelet independence was defined as the maintenance of an unsupported platelet count exceeding 20,000/µL for 7 consecutive days.

GVHD. Acute GVHD was as assessed in patients surviving at least 14 days, excluding patients with primary graft failure. Severity of acute GVHD was graded by the Glucksberg criteria. Acute GVHD grades II-IV was treated with prednisone 2 mg/kg for 14 days and then tapered at 0.2 mg/kg every 5 days based on response. GVHD response to prednisone therapy over the first 80 days posttransplant was graded as follows: sensitive, indicating GVHD improvement in one or more organs without recurrence on the standard prednisone taper; dependent, indicating GVHD recurring on prednisone taper before day 80; and refractory, indicating GVHD progression after 7 days of prednisone therapy or failure to improve in one or more organs after 14 days of prednisone therapy. Patients were assessed for chronic GVHD between day +80 and day +100 and graded by standard criteria.

Relapse. Relapse was defined by the persistence of any Philadelphia chromosomes in metaphases after day +50 on two occasions at least 1 month apart and after an attempt had been made to withdraw any immunosuppressive therapy, or by the presence of frank hematological relapse. Censors were defined as the day of last contact.

Statistical analysis. Clinical endpoints included times to reach an absolute neutrophil count greater than 500/µL and a self sustaining platelet count greater than 20,000/µL, graft failure, cumulative incidence of severe acute and chronic GVHD, time to relapse, and survival. Continuous covariates were compared by two-sided Wilcoxon rank-sum tests, whereas differences between categorical variables were compared by two-tailed Fisher’s exact tests. Cumulative incidence estimates were used to measure the incidence of acute GVHD, clinical extensive chronic GVHD, relapse, and transplant-related mortality. Survival estimates were obtained by the method of Kaplan and Meier. The χ² test was used to test for homogeneity of event distribution across strata for events in which the duration of follow-up exceeded the time to the last occurrence of complications such as acute GVHD and clinical extensive chronic GVHD. The log-rank test was used to test homogeneity of time to event distributions across strata in which follow-up of all subjects failed to exceed the last time point that an event occurred in the study population, such as relapse, nonrelapse mortality, and survival. The independence of covariates with significance levels less than 10% in the univariable analyses was tested by logistic regression or by Cox regression. Covariates were added to the models in a stepwise fashion based on their significance in univariable analyses. All covariates that added information to the model at the .05 significance level as measured by the likelihood ratio test were included in the final model.

Variables examined in all analyses included patient and donor age, donor/patient gender match, donor parity, parous female donor/male recipi-
ENT pairings, donor/patient CMV match, CMV and fungal prophylaxis, disease duration, pretransplant weight $\leq 110\%$ of ideal body weight, HLA match, pretransplant busulfan, pretransplant IFN-α, time off IFN-α pretransplant, uncorrected marrow cell dose, and TBI dose. Duration of therapy with IFN-α before transplant was initially categorized as none, 1 to 5 months, 6 to 12 months, and greater than 12 months. After examination of the data, the duration of therapy with IFN-α before transplant was subsequently categorized as 0 to 5 and $\geq 6$ months based on the similarity of outcome for 0 and 1 to 5 months of pretransplant IFN-α, and the similarity of outcome for 6 to 12 and greater than 12 months of pretransplant IFN-α. All evaluations were based on data available as of December 31, 1996. Statistical analyses were performed using STATA statistical software 5.0 (Stata Corp, College Station, TX).

RESULTS

**Patient characteristics.** Demographic and treatment characteristics are shown in Table 1. One hundred fourteen patients (62%) did not receive IFN-α, whereas 70 (38%) were treated with IFN-α before transplantation for a median of 10 months (range, 1 to 64 months): 22 for 1 to 5 months, 23 for 6 to 12 months, and 25 for greater than 12 months. IFN-α was discontinued a median of 2 months (range, 0 to 47 months) before URD transplantation for the following reasons: lack of compliance with IFN (n = 21), patient or physician preference for transplantation (n = 19), lack of cytogenetic remission by 1 year of treatment (n = 16), or uncontrolled blood cell counts (n = 14). Five of 70 (7%) patients had developed chronic toxicity attributed to IFN: psoriasis (n = 2), hypothyroidism (n = 2), or immune hemolytic anemia (n = 1). Based on the analysis of the association between posttransplant survival and duration of treatment with IFN-α in 4 patient groups, classified as no IFN-α and IFN-α for 1 to 5, 6 to 12, or greater than 12 months, subsequent analyses of GVHD, relapse, and mortality considered the two categories of pretransplant therapy with IFN-α for 0 to 5 months or $\geq 6$ months. Patients receiving IFN-α for $\geq 6$ months were less likely to weigh $\geq 110\%$ of their ideal body weight, had lower serum albumin, had lower performance status score, had longer disease duration at the time of transplant, and were transplanted in the later years of the study period.

**Engraftment.** Twelve patients (6.7%) failed to engraft or developed late graft failure. There was no detectable association between pretransplant therapy with IFN-α and graft failure.

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
<th>IFN 0-5 mo (n = 136)</th>
<th>IFN $\geq$ 6 mo (n = 48)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>Category or Value</strong></td>
<td><strong>No. of Patients (%)</strong></td>
<td></td>
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<td>HLA compatibility</td>
<td>Match</td>
<td>95 (69%)</td>
<td>34 (70%)</td>
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<td></td>
<td>A or B mismatch</td>
<td>9 (7%)</td>
<td>6 (13%)</td>
</tr>
<tr>
<td></td>
<td>DRB1 or DQB1 mismatch</td>
<td>24 (18%)</td>
<td>4 (9%)</td>
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<td></td>
<td>Multiple mismatch*</td>
<td>8 (6%)</td>
<td>4 (8%)</td>
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<td>Patient age (yr)</td>
<td>$\leq$ 20</td>
<td>10 (7%)</td>
<td>4 (9%)</td>
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<tr>
<td></td>
<td>20-35</td>
<td>60 (44%)</td>
<td>19 (41%)</td>
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<td></td>
<td>36-50</td>
<td>62 (46%)</td>
<td>22 (46%)</td>
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<td></td>
<td>$&gt; 50$</td>
<td>4 (3%)</td>
<td>3 (6%)</td>
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<td>Gender match (donor to patient)</td>
<td>M to M</td>
<td>37 (27%)</td>
<td>12 (25%)</td>
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<td>M to F</td>
<td>42 (31%)</td>
<td>11 (23%)</td>
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<td></td>
<td>F to M</td>
<td>30 (22%)</td>
<td>11 (23%)</td>
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<tr>
<td></td>
<td>F to F</td>
<td>27 (22%)</td>
<td>14 (29%)</td>
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<td>Donor parity</td>
<td>F to M</td>
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<td>7 (15%)</td>
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<td>Patient weight $\geq 10%$ above ideal</td>
<td>75 (55%)</td>
<td>17 (35%)</td>
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<td>Busulfan</td>
<td>25 (19%)</td>
<td>7 (15%)</td>
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<td>CMV prophylaxis†</td>
<td>98 (72%)</td>
<td>37 (77%)</td>
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<td>Fungal prophylaxis†</td>
<td>69 (51%)</td>
<td>31 (65%)</td>
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<td>CML duration (yr)</td>
<td>(diagnosis to transplant)</td>
<td>60 (44%)</td>
<td>6 (13%)</td>
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<td></td>
<td>$\leq$ 1</td>
<td>60 (44%)</td>
<td>6 (13%)</td>
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<td>1-3</td>
<td>54 (40%)</td>
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<td></td>
<td>$&gt; 3$</td>
<td>22 (16%)</td>
<td>19 (40%)</td>
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<td>Transplant year</td>
<td>1988-90</td>
<td>54 (40%)</td>
<td>10 (21%)</td>
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<td></td>
<td>1991-92</td>
<td>41 (30%)</td>
<td>22 (46%)</td>
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<tr>
<td></td>
<td>1993-94</td>
<td>41 (30%)</td>
<td>16 (33%)</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Median (range)</td>
<td>3.8 (2.4, 4.6)</td>
<td>3.3 (2.6, 4.5)</td>
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<tr>
<td>Kernofsky status</td>
<td>Median (range)</td>
<td>100 (70, 100)</td>
<td>90 (70, 100)</td>
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<tr>
<td>Donor age</td>
<td>Median (range)</td>
<td>38 (20, 57)</td>
<td>38 (23, 53)</td>
</tr>
<tr>
<td>Marrow cell dose</td>
<td>Median (range)</td>
<td>3.3 (0.65, 14.3)</td>
<td>3.4 (1.7, 11.4)</td>
</tr>
</tbody>
</table>

*Multiple mismatch denotes donor and recipient incompatibility for one antigen at HLA-A or B plus one at DRB1 or DQB1 or one at DRB1 plus one at DQB1.
†CMV and fungal prophylaxis are defined in the Patients and Methods.
IMPACT OF IFN-α ON OUTCOME OF UNRELATED BMT

(P = .8). Median time to achieve an absolute neutrophil count greater than 500/µL was 22 days (range, 14 to 38 days) and platelet transfusion independence was 22 days (range, 5 to 167 days). Neutrophil and platelet recovery were not affected by pretransplant IFN-α. Platelet recovery was delayed by the presence of any HLA disparity between patient and donor (P = .04) and was accelerated for patients less than 20 years old (P = .02).

GVHD. One hundred thirty-eight of 175 evaluable patients (79%) developed grades II-IV acute GVHD and 69 of 175 evaluable patients (39%) developed grades III-IV acute GVHD. Pretransplant treatment with IFN-α for ≥6 months was not associated with the development of grades II-IV acute GVHD (79% v 79%, P = 1). Conversely, the incidence of grades III-IV acute GVHD was 55% in patients treated with IFN-α for ≥6 months pretransplant, compared with 34% for those treated for less than 6 months (P = .009; Fig 1). Pretransplant patient performance status score and serum albumin levels were not associated with increased GVHD. By multivariate analysis, pretreatment with IFN-α for ≥6 months (relative risk [RR], 3.0; 95% confidence interval [CI], 1.4 to 6.2; P = .004) and multiple HLA mismatches (RR, 6.1; 95% CI, 1.5 to 25; P = .01) were associated with an increased risk of grades III-IV acute GVHD, whereas CMV prophylaxis was protective (RR, 0.3; 95% CI, 0.2 to 0.7; P = .002). Restricting the multivariate analysis to HLA-matched URD transplants, ≥6 months of IFN-α remained predictive for the development of grades III-IV acute GVHD (55% v 28%; RR, 3.4; 95% CI, 1.5 to 8.1; P = .005).

Acute GVHD was prednisone-dependent or refractory in 50 of 175 (29%) evaluable patients. Patients who had received pretransplant treatment with IFN-α for ≥6 months were at increased risk of prednisone-dependent or refractory acute GVHD (43% v 23%; P = .01). Multivariate analysis identified three factors predictive for the development of prednisone-dependent or refractory acute GVHD: multiple HLA mismatches (RR, 12; 95% CI, 2.9 to 52; P = .001), CMV prophylaxis (RR, 0.3; 95% CI, 0.1 to 0.6; P = .001), and ≥6 months of IFN-α (RR, 2.9; 95% CI, 1.3 to 6.5; P = .008). When the analysis was restricted to HLA-matched URD transplants, ≥6 months of pretransplant IFN-α remained predictive for the development of prednisone-dependent or refractory acute GVHD (37% v 18%; RR, 3.1; 95% CI, 1.2 to 8.1; P = .02).

One hundred two of 142 (72%) patients who were engrafted and in cytogenetic remission at day +100 developed clinical extensive chronic GVHD. The incidence of clinical extensive chronic GVHD was similar for patients treated pretransplant with IFN-α for 0 to 5 months (76/104 [73%]) or ≥6 months (26/38 [68%]).

Relapse. Eight of 172 (5%) durably engrafted patients developed cytogenetic relapse of CML at a median of 311 days posttransplant (range, 56 to 1,090 days). Pretransplant therapy with IFN-α was not associated with the development of relapse posttransplant.

Survival. One hundred six patients remain alive with an actuarial 5-year survival of 55% ± 4% and a median follow-up of 1,474 days (range, 609 to 3,028 days). Survival was significantly worse for those patients who had received pretransplant IFN-α for ≥6 months (43% ± 8%) than for those treated with IFN-α for 0 to 5 months (60% ± 5%; Fig 2; P = .05). There was no difference in survival for patients treated with IFN-α for 1 to 5 months pretransplant (67% ± 10%) and those not treated with IFN-α (59% ± 5%; P = .7). By multivariate analysis, IFN-α therapy for ≥6 months pretransplant was independently associated with an increased risk of posttransplant death (RR, 2.1; 95% CI, 1.3 to 3.5; P = .003). Pretransplant patient performance status score and serum albumin levels were not associated with decreased survival. In the multivariable model, time from diagnosis to transplantation did not achieve significance, did not significantly alter the log likelihood ratio (Table 2), and did not change the regression coefficient or confidence interval associated with therapy with IFN-α for ≥6 months (not shown). There was no apparent effect of time from diagnosis to transplant for the 114 patients who had not received treatment with IFN-α pretransplant. In relation to time interval from diagnosis to transplant ≤1 year, the relative risk was 0.9 for the interval greater than 1 to ≤3 years (P = .9), and the relative risk was 1.0 (P = .9) for the interval greater than 3 years. Treatment with IFN-α for ≥6 months before transplant remained associated with increased mortality (RR, 2.0; 95% CI, 1.1 to 3.7; P = .03) when the analysis was restricted to HLA-matched URD transplants. The association...
between pretransplant IFN-α for ≥6 months and survival was independent of the time interval between the last treatment with IFN-α and transplantation (P = .4).

The cumulative incidence of transplant-related mortality was significantly higher for those patients receiving IFN-α for ≥6 months than those receiving IFN-α for 0 to 5 months before transplant (56% vs 38% at 5 years; P = .05). Mortality from causes other than relapse during the first 100 days was 15% in patients who had received IFN-α for ≥6 months before transplant and 13% in patients who had received IFN-α for 0 to 5 months (P = .7). Increased nonrelapse mortality occurred between day 100 and day 365 posttransplant in patients who had received IFN-α ≥6 months before transplant (37% vs 15%, P = .003; Fig 3) and was limited to those patients who developed prednisone-dependent or refractory acute GVHD (Table 3). The difference between the two patient groups was due to deaths from refractory clinical extensive chronic GVHD with or without infection. There was no difference in the rates of subsequent nonrelapse mortality for patients alive at 1 year posttransplant. Nonrelapse mortality between 1 and 5 years was 16% in patients who had received pretransplant IFN-α for 0 to 5 months and 18% in patients who had received IFN-α for ≥6 months (P = .8).

For those patients treated with IFN-α for 0 to 5 months pretransplant, who were ≤50 years of age, received a HLA-A, B, DRB1, DQB1 matched URD transplant for CML in CP, and received CMV and fungal prophylaxis after transplantation (n = 48), the cumulative incidence of grades III-IV acute GVHD was 21%, the estimated 5-year survival was 87% ± 5%, and the 5-year survival free of cytogenetic relapse was 74% ± 6% (Fig 4).

**DISCUSSION**

The aim of this study was to evaluate the impact of pretransplant therapy with IFN-α on the outcome of marrow transplantation from URDs for CML in CP. After adjusting for other pretransplant risk factors previously shown to be associated with survival,23 we found that IFN-α administered for ≥6 months was associated with lower survival. This was due to an increase in the incidence of severe acute GVHD that was difficult to control with prednisone therapy. Increased mortality occurred between day 100 and day 365 and was due to complications of chronic GVHD that was refractory to treatment.

The effect of treatment with IFN-α for ≥6 months on the development of severe acute GVHD and survival was indepen-
dent of the time interval from the last treatment with IFN-α to the transplant. Thus, pretransplant IFN-α therapy has a long-lasting effect that predisposes to the development of severe acute GVHD after transplantation. Interferons are known to enhance HLA class I gene expression and therefore the presentation of major and minor histocompatibility antigens, which in turn could lead to more severe GVHD reactions. However, the effect of IFN-α on HLA gene expression is expected to be transient and is unlikely to explain the long-lasting effect of IFN after its discontinuation. Reasons for the long-lasting effect of IFN-α after its discontinuation are not clear. Prolonged treatment with IFN-α results in chronic toxicity, including depression, fatigue, anorexia, and weight loss. We found that patients treated with IFN-α for 6 or more months had lower body weight, lower serum albumin levels, and lower performance status scores than patients treated with IFN-α for less than 6 months. It is conceivable that the weakened physical condition from chronic IFN-α toxicity contributed an increased risk of transplant-related complications, including death.

In a previous analysis of URD transplantation for CML at our institution, we found that prolonged time from diagnosis to transplantation was an adverse prognostic factor for survival. The current study has also considered the impact of pretransplant treatment with IFN-α. Because time from diagnosis and length of treatment with IFN-α are correlated, it can be difficult to determine whether these variables act independently on survival or interact in some way. When time from diagnosis was added to the multivariable model already considering the variable IFN-α for ≥6 months, the likelihood ratio test indicated that the model was only marginally improved (P = 0.06). On the other hand, the addition of the variable IFN-α for ≥6 months significantly improved the model that was already considering the effect of time from diagnosis (P = 0.007). Furthermore, there was no association between time from diagnosis and survival for the 114 patients who were not treated with IFN-α pretransplant. Therefore, the association between pretransplant administration of IFN-α and posttransplant outcome is independent of the effect of time from diagnosis to transplant. In addition, our study suggests that the association between prolonged interval from diagnosis to transplant and poor survival may be due to pretransplant therapy with IFN-α.

Two previous reports have evaluated the impact of pretransplant IFN-α on the posttransplant course. A study from the M.D. Anderson Cancer Center reviewed 77 patients undergoing HLA-identical sibling transplantation, including 41 patients in CP, 23 who were treated with IFN-α for 9 to 343 weeks before transplant. The study found no statistically detectable differences in the rate of grades II-IV acute GVHD or 3-year survival. The investigators noted a suggestion towards improved survival for patients who had not been treated with IFN-α before transplant (66% ± 13% vs 56% ± 10%), with an initial separation of the survival curves during the first 12 months after transplant. Beelen et al included 133 patients with CML in CP who received transplants from HLA-identical siblings (n = 103) or alternative donors (n = 30). Pretransplant IFN-α was categorized as ≤12 months or greater than 12 months based on the median time to observe a cytogenetic response. No difference was seen in the incidence of grades II-IV acute GVHD, but survival was reduced in patients treated with IFN-α for greater than 12 months. The investigators noted an increased risk of death from infectious causes after day 120 for patients treated with IFN-α for greater than 12 months, similar to our results. They also noted a high rate of graft failure after alternate donor transplantation if the recipients were treated with IFN-α before transplantation. We were unable to confirm an association between patient treatment with IFN-α before transplant and marrow graft dysfunction.

In keeping with previous reports, we found that a single mismatch for HLA-A or B did not increase the risk of grades III-IV acute GVHD or decrease survival as compared with fully HLA-matched URD transplants. These patients were all less than 36 years of age and 14 of 15 were mismatched within cross-reactive antigen groups. In contrast, a single HLA-DRB1 or HLA-DQB1 mismatch was associated with worse outcome. Poorest survival followed multiple mismatched transplants. These results confirm previous observations regarding the importance of allele matching for HLA-DRB1 and DQB1 in URD transplantation.

The survival of patients treated with IFN-α for 0 to 5 months before transplant, who were 50 years of age or less, received a HLA-matched URD transplant, and received CMV prophylaxis was 87% ± 5% at 5 years, similar to survival after HLA-identical sibling transplantation and comparable to the survival described for patients achieving a major cytogenetic response to treatment with IFN-α. With no relapses observed after 3 years, it is likely that most of the patients alive 5 years after an URD transplant are cured of CML. The data presented here provide a rationale for immediate transplantation in preference to prolonged treatment with IFN-α when the patient is 50 years of age or less and has available a HLA-matched or HLA-A or B mismatched URD.

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