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Absence of influence of prior treatment with interferon on the outcome of allogeneic bone marrow transplantation for chronic myeloid leukemia

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Summary:

Timing of transplantation in the chronic phase of chronic myeloid leukemia (CML) and previous treatment with interferon remains controversial. We have tried to discover what influence pretreatment with interferon alpha (IFN-A) has on the results of allogeneic bone marrow transplantation for CML patients treated in a single institution. Fifty-one consecutive patients with chronic phase Ph-positive CML who received an allogeneic bone marrow transplantation from a HLA-identical familial donor were evaluated. Thirty had been treated with IFN-A (IFN+ group) prior to BMT and twenty-one had not (IFN– group). Both groups were homogeneous for clinical characteristics such as age, sex, previous chemotherapy, disease status, and time from diagnosis to transplant. No difference was found in neutrophil and platelet count recovery between the IFN+ and IFN– group. The incidence of acute and chronic GVHD, VOD and severe mucositis was not significantly different. Relapse and both overall survival and DFS were similar for both groups. No adverse effects of prior IFN exposure on the outcome of HLA-identical sibling donor BMT for chronic phase CML patients were found in this study.

Keywords: interferon; allogeneic BMT; CML

Allogeneic bone marrow transplantation (BMT) remains the most effective treatment for patients with chronic myeloid leukemia (CML) in any stage of the disease to date and CML is currently the single most common indication for either related or unrelated BMT.[1,2] For patients under 50 years of age who were transplanted in chronic phase from HLA-identical sibling donors, the probability of long-term survival is 50–80%.[3,4] Age, disease phase, donor–recipient compatibility, interval from diagnosis to BMT and use of T cell-depleted bone marrow have been identified as the main factors affecting survival in different clinical series.[5–9] Nevertheless, either because of donor availability or patient age, only 20–30% of CML patients are eligible for an allogeneic BMT. Among the alternative options interferon alpha (IFN-A) has become the treatment of reference in patients under 70 based on the greater survival rate observed when compared with conventional chemotherapy in several large randomized trials.[10–12] Moreover, since median survival is nearly 60–70 months in patients treated with interferon and those patients with major cytogenetic responses have not reached this median, the decision to perform a life-threatening treatment such as allogeneic BMT could be delayed in some patients until after a time of interferon.

Interferon has immunomodulating effects such as inducing expression of class I HLA antigens[13] and increasing tumor cytotoxicity by macrophages, natural killer cells and T lymphocytes. It also has radiosensitizing properties,[14] and inhibits hematopoietic progenitors and fibroblasts.[15] These effects may be relevant to BMT results. Many patients undergoing BMT have previously received IFN-A because of their age or prognostic factors, and there are contradictory reports concerning the influence of this treatment on transplant outcome.[16,17] Since some of these published series are quite heterogeneous, we decided to analyze whether prior IFN treatment could influence engraftment, toxicity, graft-versus-host disease (GVHD) incidence, relapse and survival probability in 51 patients receiving allogeneic BMT in our institution.

Patients and methods

Fifty-one consecutive patients underwent allogeneic bone marrow transplantation from an HLA-identical sibling donor as therapy for first chronic phase Ph-positive CML in our institution between March 1990 and November 1996. Clinical characteristics are shown in Table 1. The median age of recipients was 33 years (range 17–56). Thirty out of these 51 patients had been previously treated with recombinant interferon alpha 2A (Roche, Madrid, Spain) as previously described.[18]

Transplant procedure

All patients were nursed in single rooms ventilated with a high efficiency particular air (HEPA) filtration system. BUCY2 (busulfan 4 mg/kg/day orally on days −7, −6, −5 and −4 and cyclophosphamide 60 mg/kg/day i.v. on days

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Table 1 Characteristics of patients according to IFN therapy before allogeneic BMT

	IFN-alpha +	*IFN-alpha –*	*P*
No. of patients	30	21	
Age	33 (17–55)	35 (17–56)	0.31
Sex (male/female)	13/17	11/10	0.70
Busulphan pretreatment (%)	4 (13)	5 (25)	0.45
Hydroxyurea pretreatment (%)	29 (99)	20 (99)	0.99
Status (%)			
0–I	21 (70)	16 (76)	0.72
II–IV	9 (30)	5 (24)	
Interval from diagnosis to BMT (days)	510 (333–5220)	493 (150–2145)	0.66
Preparative regimen (%)			0.10
CY-TBI	2 (7)	5 (25)	
BUCY2	28 (93)	16 (75)	
Graft size ($\times 10^8$/kg nucleated cells)	3.77 + 0.93	3.44 + 0.4	0.21
Post-BMT follow-up (days)	1030 (279–2118)	1848 (452–2692)	0.06

–3 and –2) was employed as a preparative regimen in most of the patients (44 cases) while seven patients received cyclophosphamide 60 mg/kg/day i.v. on days –5, –4 and fractionated total body irradiation (1200 cGy). DPH was used as anticonvulsant prophylaxis in the BUCY group. Bone marrow was infused on day 0. Neither intravenous inmmunoglobulins nor hematopoietic growth factors were administered.

All patients received non-T cell-depleted bone marrow from an HLA-identical sibling donor. A median of 3.61×10^8 (2.23–6.61) nucleated bone marrow cells per kilogram of recipient body weight was infused.

Prophylaxis and treatment for cytomegalovirus (CMV) disease were as follows: seropositive patients and those who were seronegative with a seropositive donor received intravenous high-dose prophylactic acyclovir (500 mg/m^2/8 h) from day –5 to day +30. Pre-emptive therapy with intravenous gancyclovir was administered if CMV was demonstrated in blood or on bronchoalveolar lavage performed on days +35 and +80.

All blood products transfused were irradiated to 2500 cGy.

Cyclosporin A (CsA) and a short course of methotrexate, according to the Seattle protocol for GVHD prophylaxis, were employed in all patients as previously described.[19]

Acute GVHD was classified according to Deeg's criteria.[20] Only patients with overall clinical grade >II were treated. First-line therapy was methylprednisolone at 2 mg/kg/day. Patients with therapy-resistant GVHD received anti-thymocyte globulin (ATG) and/or monoclonal antibodies to the CD25 receptor (BB10).[21] Chronic GVHD was graded as limited or extensive according to the classical criteria. Only extensive forms were treated using different protocols that included prednisone alone, prednisone and azathioprine, prednisone and CsA on alternate days, and two patients received thalidomide.

Veno-occlusive disease (VOD) was diagnosed according to clinical findings when the three major criteria were present.[22]

Hematologic relapse of leukemia was defined on clinical grounds supported by cytogenetic findings. Cytogenetic relapse was defined as the reappearance of the Philadelphia chromosome, whereas hematologic relapse was defined by the combination of cytogenetic relapse and the hematological criteria of CML. In all long-term survivors at least three early marrow analyses of conventionally banded chromosomes were performed (on days +30, +100 and +360) and at least one analysis per year was carried out after that in all patients.

Graft failure was diagnosed if greater than 0.5×10^9/l absolute neutrophil counts and self-sustaining platelet counts greater than 20×10^9/l were not reached by day 30 after marrow infusion together with severe marrow hypocellularity.

Statistical analysis

Values are expressed as medians and ranges or percentages. For qualitative variables a χ^2 test and Fisher exact test were used, while a Student's *t*-test was employed for quantitative values. Survival probability was measured from transplant to death and patients were censored by the end of follow-up; time to relapse was measured from transplant to relapse censored by death or end of follow-up. Survival curves were estimated by the method of Kaplan and Meier and the levels of statistical significance for differences between curves were calculated by the log-rank test.

All the statistical analysis was performed using the SPSS 6.1 software (SPSS, Chicago, IL, USA) packages on a Macintosh computer.

Results

No significant differences were observed between the IFN+ and IFN– groups regarding major prognostic factors such as age, previous chemotherapy, disease status, interval from diagnosis to transplant or conditioning regimen. Graft size and sex distribution were also similar for both groups. Only a slightly increased follow-up period for those patients without previous treatment with interferon was observed (Table 1).

Twenty-three percent of the patients treated with IFN-A achieved a major genetic response. The duration of IFN-A treatment, interval from discontinuation of IFN to BMT and hematologic and cytogenetic responses are shown in Table 2. Median time of duration of IFN-A treatment was

Table 2 Characteristics of IFN-alpha-treated patients

Duration of IFN pretreatment (days)	465 (45–1215)
Interval from IFN discontinuation to BMT (days)	60 (9–270)
Last hematologic response (%)	
complete	19/30 (63)
partial	5/30 (17)
null	4/30 (14)
unknown	2/30 (6)
Last cytogenetic response	
complete	1/30 (3)
partial	6/30 (20)
minimal	5/30 (17)
null	17/30 (57)
unknown	1/30 (3)

Table 3 Outcome of BMT

	+IFN	*–IFN*	*P*
Engraftment: (days)			
Neutrophils $>0.5 \times 10^9$/l	22 (12–33)	20 (16–29)	0.08
Platelets $<25 \times 10^9$/l	21 (10–91)	21 (14–53)	0.78
Acute GVHD II–IV (%)	8/30 (27)	8/21 (38)	0.55
Chronic GVHD (%)	10/25 (40)	6/17 (35)	0.83
Veno-occlusive disease	3/19	3/18	0.37
Severe mucositis	7/19	3/18	0.71
Relapse	1	2	
Non-leukemic death	6/30	5/20	
Alive/death	23/7	14/6	
Overall survival at 5 years	75 ± 8	69 ± 10	0.72*
Event-free survival	75 ± 8	60 ± 11	0.55*

*Log-rank test.

465 days, with only four patients receiving IFN-A for less than 1 year. In three of these IFN-A was stopped because of poor tolerance.

Table 3 shows comparison in clinical outcome after BMT for both groups. None of the parameters analyzed showed statistically significant differences between either group of patients. Projected overall survival and event-free survival at 5 years for both groups were 69 ± 10 and 60 ± 11 for those patients who did not receive interferon and 75 ± 8 and 75 ± 8 for patients treated with interferon (see *P* value of log-rank test on Table 3) (Figure 1). Causes of death were also analyzed in both groups (Table 4) and again no difference was demonstrated. Of interest was one patient treated with interferon who experienced late graft-failure 6 months after BMT with no evidence of GVHD or leukemia relapse. This patient received a second infusion of donor PBSC mobilized by G-CSF alone and was prepared with cyclophosphamide (200 mg/kg); however, she died from grade IV acute GVHD. We found no higher incidence of late infections in the IFN+ group (data not shown) among the group of patients who survived.

Discussion

From a clinical point of view, allogeneic stem cell transplantation is still the only procedure that can cure CML. Current results of allogeneic transplants from HLA-identical sibling donors have shown a significant improvement in recent years[3,23] and 5 year event-free survival rates of

Table 4 Primary cause of death according to pretransplant IFN-alpha administration

	+IFN	*–IFN*
Interstitial pneumonitis	—	1
VOD	1	—
Acute GVHD	3	4[a]
Chronic GVHD	1	—
Relapse	1	1
Late graft failure	1	—

[a]One patient also presented with interstitial pneumonitis.

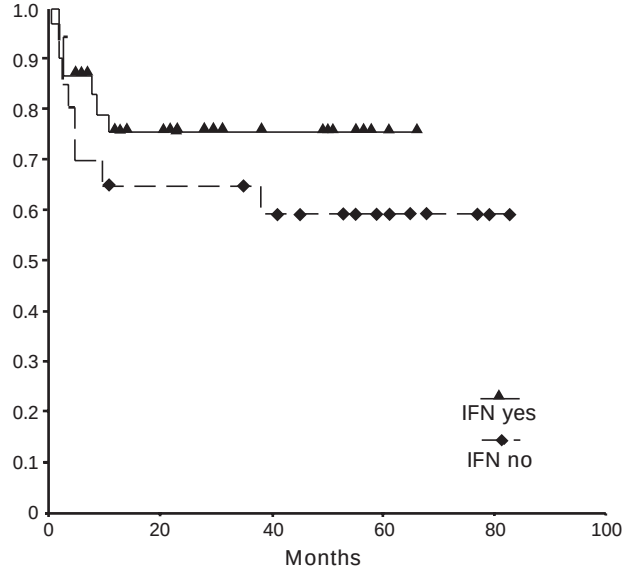

Figure 1 Event-free survival after allogeneic BMT and previous treatment with interferon.

50–80% have been reported.[3] These results were confirmed in the present series with a projected DFS at 5 years of nearly 70%. However, a number of issues remain unresolved regarding the use of allogeneic transplantation for CML: patient age, timing of the transplant procedure within the chronic phase, previous use of alternative treatments, and some of the technical aspects. Some of these factors are interdependent, and thus older patients, normally older than 40 years, are treated by chemotherapy or interferon before a final decision regarding allogeneic transplant is taken. This is based on the nature of allogeneic transplantation treatment which can either cure or kill, and the currently expected median survival observed with interferon.

The hypothetical interactions between previous treatment with interferon and allogeneic BMT may occur either secondary to a simple delay in the timing of BMT or be mediated by the biological effects of interferon on the disease or recipient. Thus, if we consider that different registries and institutions have demonstrated that transplant-related mortality is lower and leukemia-free survival higher if the transplant is performed within the first 12 months after diagnosis,[24,25] it can be argued that any delay carrying out BMT seems to have no benefit for the patient and could diminish the successful outcome of the procedure. However, it should be noted that this conclusion is based on the analysis of survival in patients treated with busulfan or hydroxyurea, and it is not certain that the same adverse effect would be observed in patients treated with interferon before transplantation.

On the other hand, interferon has shown an inhibitory effect on the growth of marrow fibroblasts and hemopoietic cells *in vitro*[15] that could interfere with engraftment. Furthermore, due to its immunomodulating properties which include enhanced expression of major histocompatibility antigens[13] and an increase in antigen-specific and non-specific cytotoxicity, it could influence the incidence of GVHD, relapse and toxicity. However, none of these hypo-

thetical effects of interferon has been observed in the present series or in other reported trials. In the present series one patient experienced loss of engraftment 6 months after the transplant (late graft failure). Although this case was the first observed in our institution among the 120 patients who have received an alloBMT for CML to date it is difficult to implicate prior interferon treatment in this event. The radiosensitizing effect of IFN[14] could also influence tumoricidal activity and toxicity of the procedure, but again, this was not the case in our study.

Most of the information available concerning the influence of prior treatment with interferon on BMT has demonstrated no adverse effects. The first analysis was performed by Giralt *et al*[16] in 77 patients, 41 of whom were in first chronic phase. He found no difference in outcome after BMT between groups. However, he did find a trend toward an improved survival in the interferon group. A major problem in this analysis is the great heterogeneity among BMT procedure employed: several GVHD prophylaxis and conditioning regimen schemes were used, a significantly longer interval from diagnosis to BMT was present in the interferon group and finally the series represents a long period from 1981 to 1991, with most of the patients in the interferon group belonging to the last years. This could explain the trend towards improved survival observed. Another more convincing analysis was performed in the UK among those patients initially enrolled in the MRC study of interferon-alpha for chronic myeloid leukemia who underwent allogeneic transplant.[26] They found no adverse effect of previous prolonged interferon-alpha administration on BMT outcome.

Only one study has shown that those patients who received interferon for more than 12 months before BMT experienced an adverse outcome after transplant.[17] This showed a 2.5-fold higher risk of transplant-related mortality, mainly because of later fatal infections. Although the design and methods employed in this study were appropriate, the results observed could represent a bias effect due to the population selected for the study. Thus, several clinical characteristics that could influence BMT outcome, such as donor age (greater in the IFN group), unrelated and partially matched transplants (greater in the IFN group), interval from diagnosis to BMT (longer in the IFN group), were not similar between the groups studied. Differences between the two groups of patients compared could thus explain the results seen in that series. Moreover, although a hypothetical effect of prior interferon on immune reconstitution after BMT could explain the observed increased rate of late infections that occurred in the interferon group, this can also be explained by the fact that the number of unrelated and mismatched transplants were greater in this group. In both type of transplants the occurrence of late fatal infections is a well-known complication.[27]

The design of a trial that could prospectively investigate the influence of prior treatment with interferon requires patients with a sibling donor to be allocated after diagnosis for randomization between transplantation during the first year of the disease or after 1 year of treatment with interferon with a subsequent transplant. Such a trial would probably be very difficult to carry out, and the possible relationship between previous inteferon exposure and BMT outcome from series such as the one presented here should be evaluated. These should be as homogenous as possible. Since this series is too small to make statistically significant analysis it may be of interest to perform a meta-analysis. Finally, another question is whether, based on this and other reports, we can assume that since interferon alpha itself does not adversely affect the outcome of a subsequent BMT, at least with sibling donors, we can perform this procedure after a prior interferon trial. As proposed by Carella *et al*,[7] it seems reasonable to use allogeneic BMT as frontline therapy in all patients younger than 40 years with a sibling donor or in those non-low-risk adults from 40 to 55 with a donor, based on current BMT results and on the fact that the onset of transformation cannot be reliably predicted in any given patient.

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