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Prior treatment with α-interferon does not adversely affect the outcome of allogeneic BMT in chronic phase chronic myeloid leukemia

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Abstract

Background and Objective. **Controlled clinical trials have shown that Interferon-alpha (IFN-α) is able to control myeloid proliferation and to suppress the Ph+ clonal hemopoiesis in early chronic phase chronic myeloid leukemia (CML): a growing number of patients are treated with this agent from diagnosis. However, if a CML patient has an HLA-identical sibling, bone marrow transplant (BMT) represents the best choice of treatment. Since IFN-α is known to modify the immunologic response and to increase marrow fibrosis, information is needed on the outcome of patients transplanted after IFN-α treatment.**

Design and Methods. **We analyzed retrospectively 32 Ph+ CML patients submitted to BMT in the last 6 years in Institute "Serágnoli". All the patients were in 1st chronic phase, their median age was 37 years, the donors were HLA-identical (27/32) or 1 Ag-mismatched (5/32) siblings. *Big* BuCy was the conditioning regimen employed for all and GVHD prophylaxis was based on CsA in 4 patients and Csa+MTX in 28 patients; all patients received homogeneous pre and post-transplant supportive care, antimicrobial and antiviral prophylaxis. These patients were divided into 2 groups according to the treatment before BMT: 16 received IFN from diagnosis to BMT (mean dose 6.9 MU/daily) for at least 6 mos (mean 23 mos, range 8-75) and 16 received chemotherapy alone (hydroxyurea [HU]).**

Results. **Hematological recovery was comparable in the two groups: time to 0.5×10^9/L PMN was 20.5 days (range 11-32) in the IFN group and 20 days (range 10-32) in the HU group; time to 50×10^9/L platelets was 28 days (range 20-117) in the IFN group and 27 days (range 20-112) in the HU group. The incidence of acute GVHD was not different in the two groups for any grade of the disease; in patients who survived more than 100 days, chronic GVHD occurred in the two groups with the same frequency. Seven patients died of transplant related mortality (TRM), 4 in the IFN group and 3 in the HU group. Hematological relapse was observed in only one case in the HU group; no cytogenetic relapse occurred. Disease free survivals at 7 years are 61% and 72%, respectively; the difference is not significant.**

Interpretations and Conclusions. **Notwithstanding the low number of patients included in this study, the data reported here confirm that prior treatment with α-IFN does not adversely affect transplant outcome.**

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Today, the only curative approach for chronic myeloid leukemia (CML) is high-dose chemotherapy followed by allogeneic bone marrow transplantation (BMT). However, its application is limited to a minority of patients with HLA-matched donors, who are less then 55 years old. During the first year after diagnosis, while the search for possible HLA-matched unrelated donors is being performed, an increasing number of patients with CML are currently treated with interferon-alpha (IFN-α). It has been demonstrated that this agent is able to suppress the neoplastic Ph+ clone in a consistent proportion of patients and enables the expansion of normal hematopoietic cells still remaining in bone marrow. The effectiveness of IFN-α was tested by several randomized trials. They shown that this therapy may induce hematological response in about 80% of patients and karyotypic conversion in about 30%, with improved survival.[1-5]

The mechanisms by which IFN elicits response are still largely unknown, but *in vitro* studies have shown that it might function by inhibition of p210 bcr/abl transcription, enhancing immune regulation and modifying on stromal microenvironment.[6-12] Furthermore, IFN-α is able of enhancing the expression of major histocompatibility antigens and of activating lymphocytes mediating antigen-specific and non-specific cytotoxicity.[13,14] Considering these biological properties, it's conceivable that IFN could adversely effect the positive outcome of a transplant, both in terms of impairing engraftment and enhancing graft-versus-host disease (GVHD). A previous study has shown that IFN does not negatively effect transplant outcome,[15] while another study has shown that worse results after BMT may be attrib-

uted or associated with prolonged IFN administration.[16]

Since we have been using IFN in the treatment of CML for several years, starting in 1984-1985, as part of the *Italian Cooperative Study Group on CML*, we wish to report our experience on the association of IFN treatment and allogeneic bone marrow transplant.

Patients and Methods

Between 1983 and 1995, 96 patients with CML received an allogeneic bone marrow transplant in our Institution. Until the end of 1988 no patient had been treated with IFN before transplant. In 1989 we began performing the first transplants in persons who had been pretreated with IFN. A total of 48 consecutive CML patients were submitted to BMT from fully HLA-identical or 1-Ag-mismatched family donors. Sixteen were in advanced phase and 32 in first chronic phase. Our analysis is restricted to the 32 patients in chronic phase who received the same conditioning regimen and almost the same GVHD prophylaxis; one half of them were pretreated with IFN and the others with hydroxyurea.

Chronic phase was defined by a finding of less than 10% non-granulated blast cells or less than 30% blast cells and promyelocytes in peripheral blood; a bone marrow aspirate containing less than 15% blast cells or less than 50% blast cells and promyelocytes; a spleen palpable less than 10 cm below the left costal margin and absence of any other extra-hematological involvement.[4] Conditionig regimen consisted of busulfan 16 mg/kg (ideal body weight) over 4 days followed by cyclophosfamide 200 mg/kg over 4 days for all the 32 patients. Details of conditioning regimen are described elsewhere.[17] GVHD prophylaxis consisted of cyclosporin (CsA) given intravenously until resumption of oral food intake and than orally for 12 months plus a short course of methotrexate (days 1,3,6,11) in all patients except 4 who received only CsA. Donor bone marrow was collected from both posterior iliac crest by standard techniques. Twenty-seven patients received the graft from fully HLA-matched family donors and 5 from 1-Ag-mismatched family donors: 4 were pretreated with IFN and 1 with HU. Engraftment was defined as achievement of a granulocyte count of more than 0.5×10^9/L and a platelet count of more than 50×10^9/L, with a minimum survival of more than 20 days.

GVHD

Acute GVHD was graded according to classical Seattle criteria in patients who survived more than 21 days after marrow infusion.[18] Patient who survived longer than 100 days were evaluated for chronic GVHD and assessed by established clinical parameters.[19]

Pretreatment

The 32 patients transplanted in chronic phase were stratified in two groups on the basis of pretransplant treatment: 16 patients had been treated with hydroxyurea and 16 with IFN for at least six months from diagnosis. The demographics of the patients, the interval between diagnosis and transplant, the degree of HLA matching, the conditioning regimen and the GVHD prophylaxis of the 32 patients are listed in Table 1.

Transplant related mortality

Transplant related mortality (TRM) was defined as any cause of death other than the underlying disease.[20]

Relapse

Cytogenetic relapse was defined as the detection of Ph+ positive metaphases six months after BMT and persisting for another six months, without therapeutic intervention. Hematological relapse was defined as the reappearance of typical blood characteristics.

Analysis

For the comparisons of the two groups of patients the Chi square test and the Wilcoxon test were employed; all time calculations were made by the Kaplan and Meier[21] product limits method and were compared by the Log-rank test.[22] Survival was calculated from transplant to death or to last follow-up; disease free survival was calculated from transplant to relapse or death or to last follow-up; transplant related mortality was calculated from transplant to

Table 1. Characteristics of patients according to the treatment before allogeneic transplant.

	IFN yes	*IFN no*
N. of patients	16	16
Male/female	12/4	8/8
Age (mean)±SD	37±9	37±8
Sokal score*		
Low	9	9
Intermediate	4	3
High	3	3
Interval Δ⇒BMT (mos) (mean±SD)	29±17	23.5±11
< 1 year	2	3
1-3 years	10	12
> 3 years	4	1
CP pts at BMT	16/16	16/16
Conditioning regimen	BU/CY	BU/CY
GVHD prophylaxis:		
CsA+MTX	13	15
CsA	3	1
Donor type:		
HLA-identical	12	15
1-Ag-mismatched	4	1
N. of mononuclear cells infused(x10^8/kg)	2.7±1	3.1±1

**For one patient in HU group data at diagnosis were not available.*

Table 2. Details of therapy for the patients treated with Interferon before allogeneic transplant.

UPN	Disease phase	IFN treatment duration (mos)	IFN mean dose ($Ux10^6$/die)	Interval IFN withdrawal⇒ BMT
89	CP	24	8.5	1 month
92	CP	18*	6	17 days
96	CP	14*	8.1	1 month
103	CP	24	8.3	23 days
112	CP	12*	3	6 months
114	CP	24	8.3	7 days
132	CP	35	9.7	21 days
177	CP	45	4.5	1 month
182	CP	39	5.9	1 month
191	CP	12	2.4	22 days
194	CP	19	4.2	1 month
196	CP	8	8	5 months
205	CP	75*	9	2 months
223	CP	41	8.3	3 months
224	CP	9	8.7	1 month
232	CP	22	7.6	4 months
mean±SD		26±17	7±2	1.8±5.8

**Indicates the four patients who had treatment failure.*

Table 3. Hematological recovery after transplant according to treatment before BMT.

	IFN yes	IFN no
N. of patients	16	16
Median day to 0.5×10^9/L PMN	21.1±6.2	21.3±6.0
Median day to 50×10^9/L PLTs	33.9±22.7	34.3±23.4*

**Never reached in 2 patients.*

Table 4. GVHD prophylaxys and acute GVHD incidence according to the treatment before BMT.

	IFN yes (16 pts)		IFN no (16 pts)	
Acute GVHD grade	CsA	CsA+MTX	CsA	CsA+MTX
0	1	6*	0	9*
I	1	3**	1	4
II	1	2	0	1
III	0	0	0	0
IV	0	2*	0	1
Total	3	13	1	15

**Each asterisk denotes one patient who was 1-Ag-mismatched with the donor.*

death for any cause other than leukemia. All patients were updated as of Septmeber 1997; median observation time after transplant was 50 months (range 2-88) in the IFN group and 57 months (range 4-89) in the HU group.

Results

No significant difference was observed between the 16 IFN and the 16 hydroxyurea pretreated patients with respect to age, Sokal score at diagnosis, conditioning regimen, GVHD prophylaxis and number of mononucleated cell infused. Male sex was more frequent in the IFN group (12/16 vs 8/16, p=0.27); median time from diagnosis to transplant was 29 months in the IFN group and 23.5 months in the HU group, respectively (p=0.22). Table 2 details the 16 patients pretreated with IFN, the duration of the IFN therapy (mean 23 mos, range 8-75), the IFN mean dose/daily (6.9 MU, range 2.1-9.7) and the time from IFN withdrawal to transplant (mean 1.8 mos, ranging from 7days to 6 mos). Two patients were in major karyotypic conversion at the time of the transplant (more than 66% Ph-negative metaphases). In HU group, the mean treatment duration from diagnosis to BMT was 18±10 months (median 13.5).

Hematological recovery

All patients had sustained engraftment. The median time to granulocyte recovery (0.5×10^9/L) was 20.5 days (range 11-32) in the IFN group and 20 days (range 10-32) in the HU pts. Median time to platelet recovery (50×10^9/L) was 28 days (range 20-117) in the IFN group and 27 days (range 20-112) in the HU pts; two patients in HU group didn't reach the platelet recovery mark. These data are shown in Table 3; there were no differences between the two groups.

GVHD

The incidence of acute GVHD was not different in the two groups for any grade of the disease. Severe acute GVHD occurred only in 2 patients in the IFN group and in 1 patient in the HU group. Table 4, detailing these data, also indicates the four patients who received CsA only and those who were 1-Ag-mismatched. Twenty-six patients, who survived more than 100 days, were analyzable for chronic GVHD (13 in the IFN group and 13 in the HU group). The incidence was the same: no cGVHD occurred in 8 and 9 case, respectively, limited cGVHD was observed in 4 cases in both groups and extensive occurred in 1 case in the IFN group (Table 5).

Transplant related mortality

Seven patients died of TRM, 4 in the IFN group (GVHD/infection 2 pts, veno-occlusive disease 1, chronic GVHD/infection 1) and 3 in the HU group (GVHD/infection 1 pt, infection associated with mild GVHD 1, interstitial pneumonia 1). The actuarial incidence of TRM is shown in Figure 1.

Relapse

No cytogenetic relapse occurred. Hematological relapse was observed in only one case in HU group. Although this patient (UPN 124) was considered in chronic phase at the time of transplant, she had moderate thrombocytosis and this probably reflected an accelerated phase.

Disease free survival

Eight patients died, 7 due to TRM as described above and 1 because of relapse; 24 patients are alive, 12 in the IFN group and 12 in the HU group. Disease free survival at 7 years is 61% and 72%, respectively; the difference is not significant (Figure 2).

Discussion

Prospective, controlled clinical trials have shown that IFN-α is able to restrain myeloid proliferation, suppress Ph+ clonal hematopoiesis and prolong survival in CML patients.[1-5] For these reasons, a growing number of persons with CML, of whom a proportion were transplant candidates, have been exposed to IFN therapy from diagnosis in the last years. IFN elicits its action on hematopoiesis at several levels. It owns some intrinsic cytotoxicity against hematopoietic progenitors, still not selective against CML clonal ancestors.[6] In addition, it rearranges adhesive properties of either CML hematopoiesis and stromal microenvironment, likely by modulating expression of adhesion receptors and function[7-10] and affects growth factor production by stromal microenvironmental cells, possibly influencing the progression of the disease.[11,12] In addition, α-IFN is a powerful immunomodulanting agent, capable of enhancing the expression of major histocompatibility antigens and of activating lymphocytes mediating antigen-specific and nonspecific cytotoxicity.[13,14] These biological properties may interfere with different steps of the marrow transplant procedure and it is reasonable to suspect a negative effect of IFN on the outcome of allogeneic transplant.

Our preliminary analysis[23,24] and recently published papers[15,16] have tried to answer this question. However, there are several points which need to be detailed, i.e. the duration of IFN therapy, the administered dose, the possible association of IFN with other drugs, the diversity of conditioning regimens and of GVHD prophylaxis and also the degree of antigenic disparity between donor and recipient. Since these points were not or could not be addressed properly in the previously published studies, it is inappropriate to draw firm conclusions from them.

We report on a limited series of patients, which is otherwise homogeneous with respect to the phase of the disease at transplant, conditioning regimen, prophylaxis of GVHD, pre-BMT treatment and interval between diagnosis. With regards to the last point, the policy of the ICSG on CML was that a patient with an HLA identical sibling should have been submitted to allo-BMT as soon as possible. However, many CML pts were considered not at risk for an early blastic transformation. Therefore, they were submitted to BMT at a median interval from diagnosis of 24.5 months in the IFN group, not very different from the HU group (21 months). The only difference between the two groups in our series is that more 1-Ag-mismatches occurred in the IFN group (4/16) compared to the HU group (1/16). Although the difference is not statistically significant, it could represent a bias against previous IFN treatment. On the other hand, existing data lend support to the notion that 1-Ag-family mismatches are not different in BMT outcome from fully identical family donors.[25]

Our patients received IFN treatment for at least 6 months. We choose this period because it represents the usual time to assess the hematologic and cytogenetic effects of IFN treatment. The minimum cut-off time on IFN of 4 weeks chosen by other authors[15,16] is probably not enough to see IFN's biological effects. As a consequence, these studies might have overestimated the number of patients really treated with IFN. Also these studies don't indicate the total amount of IFN received, which could be more relevant to transplant outcome than the duration of treatment itself and easier to compare among different series.

Table 5. Chronic GVHD occurrence in the two groups of treatment before BMT.

	IFN yes	*IFN no*
Patients at risk (surv. >100 days)	13	13
Grade:		
no	8	9
limited	4	2
extensive	1	2

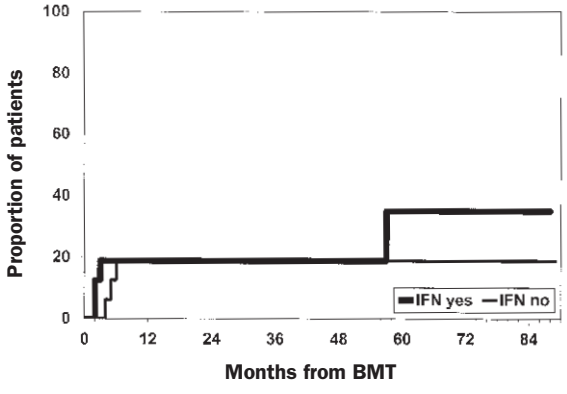

Figure 1. Transplant related mortality of patients according to treatment before allogeneic transplant.

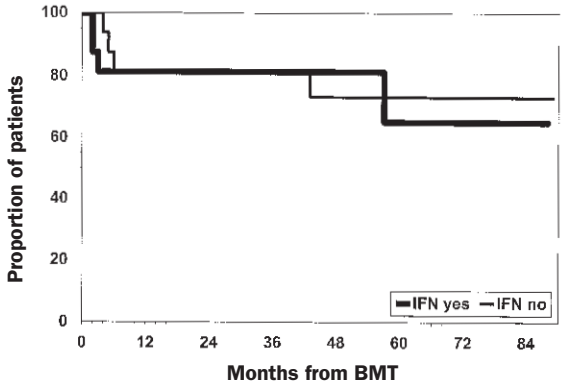

Figure 2. Disease free survival after allogeneic transplant in the two groups of pre-BMT treatment.

Our data show that IFN treatment doesn't affect the transplant outcome; all patients had engraftment and similar kinetics of hematological recovery. This was also observed by Giralt *et al.*,[15] who reported a similar granulocyte recovery in the two groups, although they considered the attainment of 1000 PMN/mm^3. Similar findings, in a way, were also observed by Beelen *et al.*:[16] although they observed many graft failures, these occurred only in 7/7 patients who received an unrelated donor transplant and had been pretreated with IFN. The remaining patients, whether pretreated with IFN or not, had similar platelet and granulocyte engraftment kinetics.

Incidence of acute and chronic GVHD was superimposable in the two groups and these observations were also reported in the other studies.[15,16]

As far as TRM is concerned, 7 patients died for causes related to the transplant procedure, 4 in the IFN group and 3 in the HU group. Our findings are similar to those reported by Giralt *et al.*,[15] but very different to those reported by Beelen *et al.*,[16] where the patients who received IFN for more than 12 months, had a higher mortality rate due to fatal infections, also after 100 days from transplant. However, it's difficult to determine in that study which is the relative importance of the considered factors, such as longer interval between diagnosis and BMT, higher proportion of fractionated TBI and lower proportion of HLA identical family donors in the IFN patients.

Relapse occurred in only 1 case, in the HU group; with a median follow-up of 54 months, no other relapses, either hematological or cytogenetic occurred in either group. This fact may be attributed to the efficacy of the conditioning regimen and no speculation can be made on the role of the IFN given before transplant. Similar relapse rates were observed in other Bus based regimens, although the dose of Cy was only 120 mg/kg in some studies[26,27] and like ours in another.[28]

As a result of the rather low TRM and very low relapse rates, overall disease free survival was good, being 65% vs 72% in the two groups (IFN and HU, respectively) at seven years. This is also more striking in view of the long interval between diagnosis and transplant, which was nearly two years in the HU group and nearly two and half years in the IFN pretreated patients. However, none of our patients, all treated in the late eighties, had received oral busulfan before BMT for the treatment of the chronic phase, which is probably the main cause of increased transplant related mortality when the graft is performed later from diagnosis.[26,29]

We tried to analyze, within the IFN group, if the duration of treatment, the total dose and the interval between IFN withdrawal and transplant were associated with a different transplant outcome; however, since only four patients had treatment failure, no correlation could be found.

Our data confirm that previous IFN treatment doesn't affect outcome of patients with CML in chronic phase, after big BuCy conditioning, with Csa+MTX prophylaxis, despite a long interval from diagnosis to BMT. However, because of the relative small series, controlled trials involving a larger number of patients will be necessary to address the specific issues of IFN therapy (i.e. duration, dose, withdrawal time). This study was conducted in patients who were HLA identical or 1-Ag-mismatched with their family donors; because of the immunomodulatory properties of IFN, it is possible that similar results could not be assumed to be reproduced after MUD transplants.

Contributions and Acknowledgments

EZ formulated the design of the study. EZ and GB were responsible for the transplant procedure and the follow-up of the patients. MS, GM and NT carried out, respectively, cellular, molecular biology and cytogenetic studies, before and after BMT. AZ and ST were involved in the design of the study and in critically revising for the intellectual contents. The order in which the names appear reflects the amount of work employed for this study.

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Disclosures

Conflict of interest: none.

Redundant publications: previous preliminary reports appeared in abstract form[23] and in a non-peer rewieved symposium supplement.[24]

Manuscript processing

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