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Multicenter prospective study of interferon-α versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: a preliminary analysis

Abstract Interferon-α (IFN-α) therapy was compared with bone marrow transplantation (BMT) in patients with chronic myelogenous leukemia (CML) in a multicenter, prospective study. Of 254 evaluable patients, 175 received IFN-α and 79 received allogeneic BMT, 50 of whom received transplants from human leukocyte antigen (HLA)-identical related donors and 29 from HLA-matched unrelated donors. Complete hematologic response was achieved by 148 patients (89%) in the IFN-α group and 53 (78%) in the BMT group. In the IFN-α group, a complete cytogenetic response was induced in 25 patients (15%), a partial cytogenetic response in 37 (23%), and a minor cytogenetic response in 41 (25%). At a median follow-up of 38 months, in the IFN-α group the predicted 5-year survival rate was 79%, and the predicted 5-year rate of remaining in chronic phase was 66%. In the BMT group the predicted 5-year survival rate was 72% for related-donor BMT and 67% for unrelated-donor BMT. Among low Sokal-risk patients, 5-year survival did not differ between IFN-α therapy and BMT, irrespective of age. In higher Sokal-risk patients, survival for related-donor BMT and unrelated-donor BMT tended to be better than that with IFN-α therapy in younger patients. On the other hand, in older patients, survival in the BMT group, especially for those receiving unrelated-donor BMT, appeared to be inferior to that in the IFN-α group. Unrelated-donor BMT can be recommended for high-risk younger patients. However, for older patients, it should be performed after careful consideration of prognostic factors such as age, Sokal score, and response to IFN-α.

Keywords Interferon-alpha · Chronic myelogenous leukemia · Bone marrow transplantation · Prospective multicenter study

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Introduction

We have been conducting three series of studies in patients with chronic myelogenous leukemia (CML) in chronic phase since 1988. The first study was a prospective, randomized trial comparing interferon-α (IFN-α) with busulfan [10, 11]. Therapy with IFN-α resulted in a significantly superior cytogenetic response and survival rates compared with busulfan treatment. The second study was conducted to evaluate whether the combination of conventional chemotherapy with IFN-α was superior to IFN-α alone and prospectively to compare conventional chemotherapy plus IFN-α with bone marrow transplantation (BMT) [9]. The combination of IFN-α with conventional chemotherapy had a benefit since a better hematologic response was achieved early and the effect of IFN-α could be assessed earlier than therapy with IFN-α alone, although this did not influence cytogenetic response and survival. The survival rate in the related-donor BMT (R-BMT) group was excellent, but that in the unrelated-donor BMT (U-BMT) group was not satisfactory in the second study.

This third, prospective, nonrandomized study was conducted to compare IFN-α therapy with BMT, especially with U-BMT. The objective was to determine the optimal indications for and timing of U-BMT, which remain controversial [13].

Patients and methods

Patients

Patients with newly diagnosed CML in chronic phase were enrolled if they fulfilled the following criteria: (1) Philadelphia (Ph) chromosome positivity; (2) no serious heart, lung, kidney, or liver disorders; (3) no severe infectious or psychiatric disorders; (4) no other neoplasm; (5) ECOG performance status 0–2; (6) age 15 years or older; and (7) no hypersensitivity reaction against IFN-α. Patients in accelerated phase or in blast crisis [8] were not eligible. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional review boards of all participating institutions.

Study design

This was a prospective study comparing IFN-α therapy with BMT in patients with newly diagnosed CML in chronic phase. The endpoints were hematologic and cytogenetic response, duration of chronic phase, and survival time. In the induction phase, hydroxyurea 1500 to 2000 mg was administered daily. IFN-α alone could be used if white blood cell (WBC) counts were $< 2\times10^{10}$/l at diagnosis. When WBC counts were $< 6\times10^{9}$/l, 6 MIU recombinant human IFN alfa-2b (Intron A, Schering-Plough Pharmaceuticals, Madison, N.J.) or 3 MIU human IFN-α (Sumiferon, Sumitomo Pharmaceutical Inc., Tokyo, Japan) was administered subcutaneously daily, and hydroxyurea administration was stopped.

The dose and frequency of administration of IFN-α were adjusted to between 3 and 10 MU/day to maintain WBC counts between 3 and 5×10^{9}/l. If WBC counts increased to $> 6\times10^{9}$/l during IFN-α therapy, hydroxyurea was added. When WBC counts again decreased to $< 6\times10^{9}$/l, chemotherapy was stopped. IFN-α with or without the chemotherapeutic agents was administered until the leukemia entered a confirmed accelerated phase.

If patients < 50 years of age had human leukocyte antigen (HLA)-identical related donors, they were scheduled to undergo BMT which was to be performed as early as possible after diagnosis, and not at more than 1 year. Until BMT, the disease was controlled by chemotherapy with or without IFN-α. If patients had no HLA-identical related donor, IFN-α was administered and they were registered with the Japan Marrow Donor Program to search for HLA-matched unrelated donors. The analysis of HLA matching was based on typing for HLA-A, B, and DR antigens by serologic and genomic methods. If HLA genomically matched unrelated donors were available, U-BMT was performed as early as possible.

Response criteria

Complete hematologic response was defined as peripheral WBC count $< 10\times10^{9}$/l with less than 1% immature myeloid cells, and the disappearance of all clinical signs and symptoms of disease, including palpable splenomegaly. Partial hematologic response was defined as a decrease in WBC count of between 10×10^{9} and 20×10^{9}/l, or as WBC count of $< 10\times10^{9}$/l with palpable splenomegaly, or more than 1% of immature peripheral myeloid cells, or clinical signs and symptoms. Failure was defined as neither complete nor partial hematologic response [14]. Cytogenetic response was defined according to the criteria of Talpaz et al. [14] by examining 20 metaphases. A complete cytogenetic response indicated total elimination of the Ph chromosome, a partial cytogenetic response indicated suppression of the Ph chromosome to 5–34% of cells in metaphase, and a minor cytogenetic response indicated suppression of the Ph chromosome to 35–95% of cells in metaphase. No cytogenetic response denoted persistence of Ph chromosomes in all analyzable cells in metaphase. A major cytogenetic response represented either a complete or a partial response.

Statistical analysis

Overall survival was calculated from the time of registration until death, and the duration of chronic phase was calculated from the time of registration to accelerated phase or blast crisis. Kaplan-Meier estimates were used to calculate survival and the duration of the chronic phase. Comparisons of treatment in these measurements were made using the log-rank test and the generalized Wilcoxon test. Further comparisons between treatments were performed using the two-tailed *t*-test or the χ-squared test. All analyses were performed using StatView software (SAS Institute, Cary, N.C.). Comparisons were based on the intention-to-treat principle. The effect of cytogenetic response on survival and the duration of the chronic phase was tested using "landmark analysis", in which survival is measured from a specified "landmark" time (18 months) after the start of treatment [1].

Results

From February 1995 to November 1999, 279 patients with newly diagnosed CML were prospectively enrolled in this study from 68 institutions throughout Japan, and 254 were evaluable at the time of this report. IFN-α and chemotherapy were administered to 175 patients, and 79 underwent BMT, 50 of whom received BMT from HLA-identical related donors (47 from siblings and 3 from parents) and 29 from HLA-matched unrelated donors. Patient characteristics were similar in both groups except for age, WBC count, hemoglobin level, spleen size, and Sokal risk (Table 1).

Hematologic and cytogenetic responses

A complete hematologic response was achieved in 148 of 175 patients (89%) in the IFN-α group and in 53 of 79 (78%) in the BMT group before transplantation. A partial hematologic response was noted in 14 (8%) in the IFN-α group and 10 (15%) in the BMT group. In the IFN-α group, a major cytogenetic response was noted in 62 (38%) of 175 patients (Table 2).

Survival and duration of chronic phase in the IFN-α group

Survival and the duration of chronic phase were analyzed on an intention-to-treat basis. At a median follow-up of 38 months (range 9–66 months), the predicted 5-year overall survival rate was 79% in the IFN-α group (Fig. 1), and the predicted 5-year rate of remaining in chronic phase was 66%. When survival was assessed according to cytogenetic response, the predicted 5-year survival rate was 100% in patients with a complete cytogenetic response, 93% in patients with any cytogenetic response, 85% in patients with a minor cytogenetic response, and 54% in patients with no cytogenetic response. The predicted 5-year survival rate was 92% in patients with any cytogenetic response, and 54% in patients with no cytogenetic response ($P < 0.0001$ by log-rank test, Fig. 2). The predicted 5-year rate for remaining in chronic phase was 76% in patients with any cytogenetic response and 48% in those with no cytogenetic response ($P < 0.0001$ by log-rank test).

Bone marrow transplantation

A total of 79 patients underwent allogeneic BMT after giving written informed consent for all aspects of the procedure. In this study, 24 unrelated donors were matched serologically for HLA-A, B, and DR antigens to recipients and 3 were mismatched, and 20 patients were matched for genomic typing of HLA and 5 were mismatched. The status of the disease at the time of transplantation was chronic phase in all patients in the R-BMT group, and in the U-BMT group it was chronic phase in 26 patients, accelerated phase in 2 patients, and

Table 1 Patient characteristics in the IFN-α, R-BMT, and U-BMT groups

	IFN-α ($n=175$)	R-BMT ($n=50$)	U-BMT ($n=29$)	*P*-value		
				IFN-α vs R-BMT	IFN-α vs U-BMT	R-BMT vs U-BMT
Male (%)	63	66	55	0.77	0.73	0.37
Age (years)						
Median	54	36	31	< 0.0001	< 0.0001	0.40
Range	19–79	19–53	17–48	–	–	–
WBC ($\times 10^9$/l)	78 ± 89	118 ± 91	141 ± 108	0.001	0.0003	0.41
Platelets ($\times 10^9$/l)	58 ± 42	52 ± 31	72 ± 79	0.73	0.86	0.65
Spleen size (%)						
< 10 cm	90	81	75	0.11	0.03	0.55
≥10 cm	10	19	25	–	–	–
PS (%)						
0–1	98	94	85	0.06	0.003	0.29
2–4	3	6	14	–	–	–
Sokal score	1.01 ± 0.84	0.76 ± 0.27	0.80 ± 0.40	0.003	0.04	0.80

Table 2 Hematologic and cytogenetic response rates (%)

Response	IFN-α ($n=175$)	BMT[a]		
		All ($n=79$)	R-BMT ($n=50$)	U-BMT ($n=29$)
Hematologic				
Complete	148 (89)	53 (78)	33 (83)	20 (71)
Partial	14 (8)	10 (15)	3 (8)	7 (25)
None	5 (3)	3 (4)	3 (8)	0 (0)
Not assessed	0 (0)	1 (3)	1 (3)	2 (4)
Cytogenetic				
Complete	25 (15)	3 (4)	2 (5)	1 (4)
Partial	37 (23)	5 (7)	5 (12)	0 (0)
Minor	41 (25)	19 (28)	8 (20)	11 (41)
None	42 (26)	28 (41)	17 (41)	11 (41)
Not assessed	19 (12)	13 (19)	9 (22)	4 (15)

$P = 0.11$ in hematologic response and $P = 0.03$ in cytogenetic response between the IFN-α group and BMT group (χ-squared test)
[a]Best response before BMT

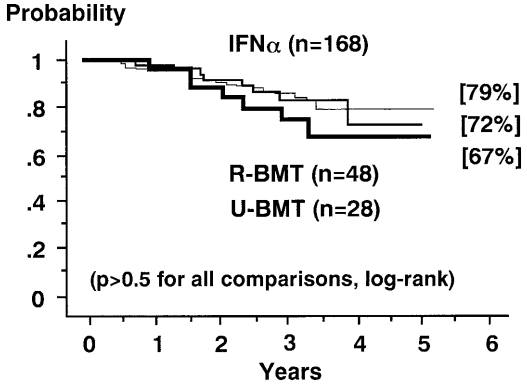

Fig. 1 Probability of survival after registration in patients treated with IFN-α or undergoing R-BMT or U-BMT. Percentages in square brackets indicate the predicted 5-year survival rate (*fine line* IFN-α, *medium line* R-BMT, *thick line* U-BMT). $P > 0.5$ (log-rank test) for all comparisons

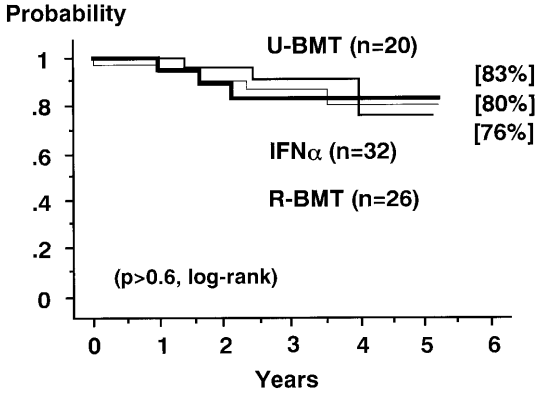

Fig. 3 Probability of survival after registration in patients aged ≤ 36 years treated with IFN-α or undergoing R-BMT or U-BMT (*fine line* IFN-α, *medium line* R-BMT, *thick line* U-BMT). Percentages in square brackets indicate the predicted 5-year survival rate ($P > 0.6$ log-rank test)

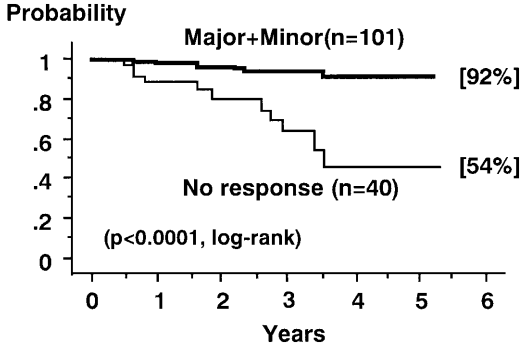

Fig. 2 Kaplan-Meier survival curves for patients treated with IFN-α by cytogenetic response (major and minor vs no response). Percentages in square brackets indicate the predicted 5-year survival rate ($P < 0.0001$ log-rank test)

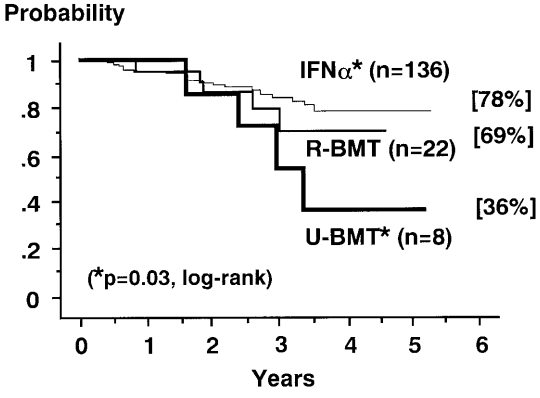

Fig. 4 Probability of survival after registration in patients aged > 36 years treated with IFN-α or undergoing R-BMT or U-BMT (*fine line* IFN-α, *medium line* R-BMT, *thick line* U-BMT). Percentages in square brackets indicate the predicted 5-year survival rate ($P = 0.03$ log-rank test)

blast crisis in 1 patient. The time from registration to transplantation ranged from 3 to 43 months (median 7 months) in the R-BMT group and from 7 to 45 months (median 19 months) in the U-BMT group. The predicted 5-year overall survival for the R-BMT group was 72% and that for the U-BMT group 67% (Fig. 1). When survival was assessed posttransplantation, the predicted 4-year overall survival rate was 76% for the R-BMT group, and the predicted 3.5-year overall survival rate was 68% for the U-BMT group.

Comparison of BMT with IFN-α therapy

Figure 1 shows overall survival from the time of registration for patients who underwent R-BMT or U-BMT and for patients who were assigned to IFN-α therapy. At a median follow-up of 38 months, overall survival did not differ significantly among the R-BMT, U-BMT, and IFN-α group. In the IFN-α group, overall survival in the low-risk group was better than that in the intermediate- and high-risk (higher-risk) group according to the Sokal relative risk classification ($P = 0.09$ by log-rank test). However, in the R-BMT and U-BMT groups there was no significant correlation between survival and Sokal risk.

Figures 3 and 4 show survival from the time of registration by patient age. The cut-off value of 36 years was selected because it was the median age of the BMT group. Survival in the BMT group was approximately the same as in the IFN-α group in patients aged ≤ 36 years. However, survival in the U-BMT group was worse than that in the IFN-α group in patients aged > 36 years.

As shown in Table 3, among the low-risk patients, there was no significant difference in 5-year survival rate by age, whereas in higher-risk patients, 5-year survival after R-BMT or U-BMT tended to be better than with IFN-α therapy in patients aged ≤ 36 years. Conversely, 5-year survival after U-BMT was worse than with IFN-α therapy in patients aged > 36 years. There was no

Table 3 Survival of patients in the IFN-α and BMT groups by risk and age

Sokal relative risk[b]	Age (years)[a]	IFN-α		R-BMT		U-BMT	
		No. of patients	Survival rate (%)	No. of patients	Survival rate (%)	No. of patients	Survival rate (%)
Low (<0.8)	≤ 36	20	90 (5-year)	16	75 (4-year)	13	82 (4-year)
Low (<0.8)	>36	58	85 (5-year)	15	87 (4-year)	3	67 (5-year)
Higher (≥0.8)	≤ 36	12	65 (4-year)	10	88 (5-year)	7	86 (5-year)
Higher (≥0.8)	>36	78	74 (4-year)*	7	31 (3.5-year)	5	33 (3.5-year)*

*$P = 0.07$ (log-rank test)
[a]Cut-off value of 36 years selected because it was the median age of the BMT group
[b]Higher: Intermediate and high

significant difference in survival in patients who underwent BMT within 1 year of registration or after 1 year.

Discussion

Throughout this series of three prospective studies, the outcomes with IFN-α therapy improved. In the third study almost twice the number of patients (15%) achieved a complete cytogenetic response compared with the previous two studies [9, 10]. In the present study (1995–1999), IFN-α therapy has been established, and with experience the importance of long-term administration of IFN-α has become understood, despite the adverse effects. At the same time, the outcome of U-BMT has also improved. There was no significant difference between R-BMT and matched U-BMT, which reflects the progress reported by others [3]. In this study, genomic typing of HLA was available, and 20 patients received transplantations from genomically identical unrelated donors. In addition, U-BMT was performed earlier than in the previous study [7, 12].

To compare the results of BMT with those of IFN-α therapy, clinical and hematologic features should be matched. Since Sokal risk influenced survival in the IFN-α therapy cohort, but not in the BMT cohort, and because age influenced survival in the BMT cohort, we compared the survival of each cohort by Sokal risk and by age [3, 5]. Among the low-risk patients, 5-year survival did not differ significantly, irrespective of age, whereas in higher-risk patients, the results with R-BMT and U-BMT tended to be better for younger patients than for IFN-α therapy. On the other hand, in older patients, the results of BMT, especially of U-BMT, were worse.

Cytogenetic response is the strongest independent prognostic factor with IFN-α therapy [5], and this was included in the comparison. Based on age and Sokal relative risk, we compared the outcomes of BMT with those in patients who achieved a minor cytogenetic response with IFN-α because the 5-year survival rate for minor response in the IFN-α group was good in the previous study [10]. Survival in the U-BMT group tended to be better than in the IFN-α group in patients achieving a minor response. However, survival in the U-BMT group was worse than that in the IFN-α group among patients who were >36 years of age, although the number of patients in each group was small. The reasons for these results are because younger patients are at a lower risk of death after BMT [3], and low-risk patients are more likely to respond to IFN-α therapy [5].

The Italian Cooperative Study Group reported the results of treatment outcomes and survival in CML after R-BMT and the introduction of IFN-α. They showed that a policy of stated allogeneic BMT was found to increase survival only in those patients who were younger or at intermediate or high Sokal relative risk [6]. Gale et al. compared the survival of 58 patients from the International Bone Marrow Transplantation Registry with 196 patients who had received IFN-α or hydroxyurea in a German randomized, controlled trial [2, 4]. Their data support the view that R-BMT produces better long-term outcomes. However, when they stratified survival by Sokal score, the difference in survival rates between BMT patients and low-risk patients who received IFN-α did not achieve statistical significance. Statistically significant differences were reported in other subgroup analyses. However, no previous prospective study had compared IFN-α therapy with U-BMT [13].

Based on the results of the present study at a median follow-up 38 months, the outcome of U-BMT was not different from that of R-BMT. However, the outcome of U-BMT was worse than that of the IFN-α therapy in older patients with higher Sokal risk. The outcomes of R-BMT and U-BMT tended to be better than those of IFN-α therapy in younger patients with higher risk. Therefore U-BMT may be recommended for higher-risk, younger patients. However, other treatment options should be considered carefully for higher-risk, older patients. It is not possible to reach definitive conclusions with regard to the indications for and timing of U-BMT, because the duration of follow-up was short and the numbers in each subgroup were small, especially in the BMT group. Therefore longer follow-up is needed.

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