Use of α Interferon for the Treatment of Relapse of Chronic Myelogenous Leukemia in Chronic Phase After Allogeneic Bone Marrow Transplantation

By Celestia S. Higano, Wendy H. Raskind, and Jack W. Singer

Eighteen patients with relapse of chronic myelogenous leukemia (CML) after allogeneic bone marrow transplantation (BMT) were treated with recombinant human α2a interferon (IFN). Relapse was defined as greater than 90% metaphases containing the Philadelphia chromosome (Ph) and hematologic abnormalities consistent with chronic-phase (CP) CML. There were 11 males and seven females, with a median age of 38 years (range, 3 to 55). Three patients relapsed after second BMT. Only one patient had received T-cell–depleted marrow initially. The initial IFN dose of 3 × 10^6 U/m²/d was escalated to the maximum tolerated dose or to a maximum of 6 × 10^6 U/m²/d. IFN controlled the white blood cell (WBC) counts in 14 of 16 patients who had abnormal counts, and in all six patients with an elevated platelet count. Six patients (33%) have had a complete disappearance of the Ph and two have had a partial response (<35% Ph+ metaphases). One patient has a decrease in Ph+ metaphases after 9 months of IFN. Five patients had no significant cytogenetic response after 9 to 12 months, and four developed clinical accelerated phase or blast crisis after 3 to 6 months on therapy. Of four patients with a sex marker, the Ph+ population was of donor origin in three and of host origin in one. Clonal cytogenetic abnormalities other than Ph were present in 13 patients and did not predict for lack of response to IFN. IFN is effective in suppressing the Ph clone in some patients who relapse with CML after allogeneic BMT and controls the blood counts in the majority.

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After giving signed informed consent, patients were treated on a protocol approved by the Investigational Review Board of the Fred Hutchinson Cancer Center.

Treatment

IFN. IFN α2a (Roferon) was supplied by Hoffmann-LaRoche (Nutley, NJ). Patients were instructed in reconstituting the lyophilized drug and in subcutaneous injection of IFN.

Induction. The initial dose of IFN was 3 × 10^6 U/m²/d. The dose was to be escalated to 4.5 × 10^6 U/m²/d after 1 month and to 6.0 × 10^6 U/m²/d after 2 months as tolerated. The maximally tolerated dose was to be continued for at least 1 year.

Dose modifications. The dose of IFN was reduced by 50% if the patient’s performance status declined to less than 80% on the Karnofsky scale, if the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased greater than five times the control value or if the bilirubin was greater than 2.5 mg/dL, or if the serum creatinine was greater than 2.2 mg/dL, if the platelet count was less than 50 × 10^9/L, the absolute neutrophil count was less than 0.8 × 10^9/L, or if there was loss of greater than 5% ideal body weight. If significant neurological toxicity such as reduced memory span, depression, or Parkinson-like symptoms developed, the IFN was stopped for 2 weeks and restarted at 50% of the previous dose.

Off-study criteria. Any patient who developed accelerated disease or blast crisis, or whose counts could not be controlled with IFN alone, was taken off study. Patients were to be taken off study for persistent grade 3 or 4 toxicity of any nature. If the cytogenetic evaluation showed greater than 90% Ph+ metaphases after 1 year of IFN, despite hematologic control, patients were taken off study and offered an alternative form of therapy.

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Maintenance. When complete disappearance of Ph+ cells was achieved and maintained for at least 6 months, patients were to be treated with a maintenance dose of 1.5 × 10^9 U/m^2 three times per week for at least 1 year. The dose and schedule were modified, when necessary, according to cytogenetic information.

Follow-up studies. Patients had a weekly complete blood cell count (CBC) during the dose escalation phase of the induction regimen. After the maximum tolerated dose was established and the CBC remained stable, the CBC was checked every 2 to 4 weeks at the discretion of the primary physician. Liver function tests were to be performed every 1 to 3 months and clinical toxicities were to be monitored weekly during dose escalation and monthly thereafter. Bone marrow aspirations were requested every 3 to 4 months. Fresh heparinized bone marrow and peripheral blood were sent to Seattle by overnight mail. In some patients, the presence of the bcr/abl rearrangement was determined by Southern blot analysis (Lifecodes, Valhalla, NY).

Cytogenetic Analyses

Aliquots of heparinized marrow were cultured at a density of 0.5 to 1.0 × 10^6 cells/mL in RPMI with 20% fetal calf serum or Chang medium and serum. At 24 and 48 hours, cultures were harvested after exposure to colcemid (0.02 to 0.05 mg/mL) for 20 minutes, cells were fixed three times in 3:1 methanol:glacial acetic acid and stored at 0°C at least overnight before slides were made. Slides were aged at 40°C and G-banded with trypsin and Giemsa. All analyzable metaphase cells were scored until a maximum of 50 cells was reached. The mitotic index was often markedly reduced in patients receiving IFN.

RESULTS

Patient Characteristics

From May 1987 to January 1991, 19 patients were enrolled. One patient was not eligible because he required azathioprine to control chronic GVHD. Patient and transplant characteristics are outlined in Table 1. There are 11 males and seven females. The median age was 38 years, with a range of 3 to 55 years. All 18 patients had allografts, Y-Body Analysis

In selected patients, the Y-body was assayed by in situ hybridization according to previously reported methods.6

Reverse Transcription/Polymerase Chain Reaction Amplification

Reverse transcription (RT)/polymerase chain reaction (PCR) for bcr/abl was performed in a limited number of patients according to a modification7 of the protocol described by Kawasaki et al.8

Response Criteria

Complete hematologic remission was defined as WBC count less than 9 × 10^9/L with no immature forms (blasts, promyelocytes, myelocytes, metamyelocytes) and platelet count less than 450 × 10^9/L. Cytogenetic response criteria have been defined by Talpaz et al.; complete cytogenetic response is defined as complete disappearance of the Philadelphia chromosome on at least one test; partial response is defined as reduction of the Ph+ population to 1% to 34% of metaphases.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>CML Stage</th>
<th>BMT Donor/Sex</th>
<th>Conditioning</th>
<th>GVHD a/c</th>
<th>Relapse Date</th>
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Cytogenetic nonresponders

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Too early

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<th>Patient No.</th>
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Abbreviations: A, related allogeneic; a, acute; Bu, busulfan; C, chronic; CSP, cyclophosphamide; Cy, cyclophosphamide; dx, diagnosis; F, female; GVHD, graft-versus-host disease; M, male; m, million; MTX, methotrexate; PRED, prednisone; si, subclinical, limited to skin and/or liver; TBI, total body irradiation; U, unrelated allogeneic; VP-16, etoposide.
16 from a matched sibling, one (no. 13) from a matched unrelated donor, and one (no. 8) from a one-antigen mismatched son. Three patients (no. 5, 12, and 15) went on-study after relapse following a second transplant. At the time of first BMT, 12 patients were in CP, 3 (no. 3, 8, and 15) were in accelerated phase (AP), and three (no. 11, 12, and 13) were in blast crisis (BC). At the time of second transplant, two patients (no. 5 and 12) were in CP, one (no. 15) in AP. All patients were in a clinically defined CP at the time of study entry.

The median time from diagnosis to first BMT was 11 months (range, 1 to 82), and the median time to relapse after BMT was 11 months (range, 1 to 48). A median of 3 months (range, <1 to 41) elapsed from the time of initial cytogenetic relapse to study entry.

Of the 15 patients who underwent a single BMT, 13 received cyclophosphamide (Cy) and total body irradiation (TBI) for conditioning, one (no. 18) received busulfan (Bu) and Cy, and one (no. 11) received etoposide and TBI. Prophylaxis for GVHD consisted of cyclosporine (CSP) and methotrexate (MTX) in 12 patients, CSP and prednisone in one (no. 11), CSP in one (no. 18), and T-cell depletion in one (no. 6).

Three patients (no. 6, 8, and 13) received IFN before BMT. In patient 6, IFN successfully controlled the WBC and platelet counts for approximately 4 months before BMT. No assessment of cytogenetic response was made. Patient 8, who was in AP, was treated briefly with IFN in an effort to control counts for 6 weeks before BMT. Patient 13 started IFN 4 months after diagnosis of CML and achieved a hematologic but not a cytogenetic response. Over a 2-year period, IFN was discontinued intermittently for toxicity and was ultimately stopped because of loss of hematologic response. At the time of study entry, the patient had not received IFN for 66 months.

Response

Hematologic response. Sixteen patients (Table 1) had an elevated WBC count ranging from 11.5 to 98.2 x 10^9/L, with a median of 18.3 x 10^9/L, and six patients (no. 1, 6, 8, 12, 15, and 17) had an elevated platelet count ranging from 547 to 1,500 x 10^9/L. The WBC count was controlled in 14 patients, including six patients (no. 1, 3, 6, 9, 14, and 17) with no cytogenetic response. IFN controlled the platelet count in all six patients, five of whom had no cytogenetic response (no. 1, 6, 12, 15, and 17). The WBC count was never controlled by IFN in three patients (no. 4, 12, and 13) who went on to develop AC/BC during the first 3 months on therapy. Control was transient in one (no. 15) patient who developed AP during the sixth month on IFN.

The median initial WBC and platelet counts of patients who achieved a cytogenetic response were 15.0 x 10^9/L and 240 x 10^9/L, respectively, whereas those of nonresponders were 27.5 x 10^9/L and 368 x 10^9/L, respectively. Of the six patients who presented with an elevated platelet count, only patient 8 had a cytogenetic CR.

The WBC count was controlled in all patients after a median of 21 days (range, 3 to 111 days). The rate of WBC response in patients with a cytogenetic response was similar (median, 21 days; range, 3 to 89) to that of nonresponders (median, 25 days; range, 7 to 111). IFN controlled elevated platelet counts after a median of 24 days of therapy (range, 14 to 48 days). One patient (no. 8) was hospitalized for fever and chest pain after 8 days of IFN treatment. Twenty-four days after starting IFN, an abrupt marrow aplasia developed. Hematologic recovery occurred over 2 weeks, but IFN was not restarted for 7 months because of pulmonary problems.

Cytogenetic response. All 18 patients are evaluable for cytogenetic response. Six patients (no. 2, 7, 8, 10, 11, and 18) have had complete cytogenetic response on at least one sample, two patients (no. 5 and 16) have had a partial response, and one patient (no. 14) has a decrease in the percent of Ph+ metaphases after 9 months. Figure 1 demonstrates the time course of cytogenetic responses for all eight responding patients. Five patients (no. 1, 3, 6, 9, and 17) did not have a decrease in the percentage of Ph+ metaphases after 9 to 12 months of IFN. The remaining four patients (no. 4, 12, 13, and 15) developed clinical AP/BC within 3 to 6 months on therapy and were taken off study.

The median time to achieve a cytogenetic complete response was 3 months (range, 1 to 18). The median duration of response was 13+ months (range, 6+ to 20+). The bcr/abl rearrangement was not detected by Southern blot analysis in peripheral blood or marrow of four patients (no. 2, 7, 8, and 10) who were complete cytogenetic responders. Patients 11 and 18 were not tested. In a fifth patient (no. 18) with a cytogenetic complete response after 3 months of IFN, low-level persistence of the bcr/abl rearrangement was documented by RT/PCR analysis of peripheral blood.

Of the two patients (no. 5 and 16) who have achieved a cytogenetic partial response, one (no. 5) who had undergone second BMT maintained a partial response for 24 months. When cytogenetic analysis demonstrated a loss of response, the patient was treated with IFN plus donor buffy coat. Although the Ph clone is no longer detectable, the patient had severe three-system GVHD from which she is now recovering. The other patient has had a decline from 100% to 27% Ph+ metaphase cells after 6 months on IFN.

In four patients who had a cytogenetic response and had opposite-sex donors (no. 2, 5, 8, and 18), the Ph− population after IFN therapy was of donor origin in three patients. The fourth patient (no. 2), a male, had cytogenetically normal host and Ph+ host cells without detectable donor (female) cells at the time IFN was started. After treatment with IFN, the Ph clone disappeared and only male, Ph− host cells were detected. In situ hybridization with a Y-specific probe confirmed that at least 96% of peripheral blood mononuclear cells and at least 94% of peripheral blood granulocytes were host (male)-derived. Although chimerism between Ph− donor and host populations has been observed, complete remission in host cells in this setting has not been previously described.

Four additional patients (no. 1, 9, 14, and 16) had Ph− metaphases at some time during IFN therapy, but did not qualify as cytogenetic responders. Only one of these pa-
Patients (no. 1) had an opposite-sex donor and the Ph− metaphases were of donor origin.

Prior to BMT, three patients (no. 5, 11, and 12) had clonal chromosomal abnormalities in addition to Ph. Two of these patients (no. 5 and 12) had undergone a prior BMT, and the third patient (no. 11) was in BC at the time of BMT. At study entry, nine patients (no. 1, 2, 3, 5, 7, 8, 11, 12, and 16) had clonal structural chromosomal aberrations detected in addition to the t(9;22). The original pre-BMT clones were not detected in the three patients who had abnormalities. Clonal structural abnormalities were seen in cells of four additional patients (no. 6, 9, 14, and 17) at some time during IFN treatment. It is likely that the structural changes were present before IFN therapy was started, but were not previously detected. Such changes are likely due to the conditioning regimen. Trisomy 8 was detected in two patients (no. 4 and 11). Despite the presence of at least one clonal chromosomal abnormality in addition to Ph, four of these patients (no. 2, 7, 8, and 11), including one with trisomy 8, achieved a complete cytogenetic remission and one patient (no. 5) had a partial response.

Of the four patients who achieved a complete cytogenetic response and had at least one additional clonal chromosomal abnormality before starting IFN, no karyotypic abnormalities were noted in serial samples from patients 7, 8, and 11. Patient 2, the only subject known to have host Ph− hematopoiesis as determined by sex markers, had multiple clonal abnormalities before IFN therapy. Some of these clones persisted, others disappeared, and new clones have been detected intermittently during the course of therapy.

**Outcome of nonresponders.** Nine patients did not respond to IFN. As noted above, four of these patients (no. 4, 12, 13, and 15) developed AC/BC within the first 3 to 6 months of IFN. The remaining patients were treated for 9 to 13 months without a significant decline in the percentage of Ph+ metaphases and were taken off study.

Three patients who developed AC/BC (no. 12, 13, and 15) remain alive 12+, 10+, and 1+ months after going off study. Two of these patients (no. 12 and 13) are being
considered for a third BMT. The fourth patient (no. 4) died in BC 9 months after stopping IFN. Of the remaining five patients, one patient (no. 1) went on to second BMT at the time of acceleration and died of transplant-related complications on day 10; one patient (no. 3) was maintained on hydroxyurea for 29 months and died in BC; one patient (no. 6) is maintained on hydroxyurea and anagrelide; one patient (no. 9) continues on IFN three times weekly and hydroxyurea; and one patient (no. 17) was recently taken off study.

Dose Escalation and Maintenance
Most patients did not tolerate the planned dose escalation. The median tolerated induction dose was 3.1 × 10^6 U/m^2 (range, 1.0 to 6.0 × 10^6). There was no difference in median induction doses between the cytogenetic responders and the nonresponders.

Five (no. 2, 7, 8, 10, and 11) of the six patients who achieved a cytogenetic complete response have been on treatment for more than 1 year. One patient (no. 7) was tapered from a daily to a 5 days per week IFN schedule. The second patient (no. 2) was tapered to a dose of 2 × 10^6 U every other day, but when cytogenetic analysis showed loss of complete response with 25% Ph+ metaphases, a 5 day per week schedule was begun and the Ph was again totally suppressed. In the remaining two cases (no. 10 and 11), IFN had been administered at a reduced dose on a every other day schedule; one patient (no. 11) discontinued IFN because of exacerbation of chronic GVHD, and he remains in CR. The other patient (no. 8) stopped IFN because of malignant hypertension, multiple bouts of pulmonary problems due to bronchiolitis obliterans, and poor tolerance. This patient has had both hematologic and cytogenetic relapse, and has restarted daily low-dose IFN.

Side Effects
Most patients experienced a flu-like syndrome that resolved approximately 2 weeks after starting IFN. Chronic low-grade fatigue was a common complaint with long-term therapy; however, working patients were able to maintain full-time employment.

Significant toxicity occurred in six patients (no. 1, 3, 4, 7, 9, and 17) and consisted of fatigue, weight loss, nausea and vomiting, diarrhea, confusion, or depression. Five of the six patients with grade 3 or 4 toxicity did not respond to IFN. The sixth patient (no. 7), a responder, had cellulitis at the IFN injection sites and lost 14 kg, which he regained when the infection was under control.

One patient (no. 11) developed chronic GVHD after starting IFN on day 72 post-BMT and IFN was ultimately discontinued after 1 year in complete remission.

One patient (no. 6) had what resembled a transient ischemic attack (TIA) with loss of vision in one eye. A complete neurological work-up including head magnetic resonance imaging and spinal fluid examinations was normal. A similar episode recurred at a later time while on IFN. This patient has been off IFN for 23+ months (no cytogenetic response) and has not had another episode.

DISCUSSION
This is the first prospective study examining the use of IFN to treat relapse of CP CML after BMT. It differs from other reports in that "relapse" was rigidly defined, requiring both cytogenetic and hematologic evidence for study entry; all but one patient relapsed after receiving non-T-depleted marrow for first BMT, and all patients received maximum tolerated daily doses of IFN for induction. Previous case reports11-14 have also documented that IFN can control blood counts and can occasionally produce complete cytogenetic responses. Most of the patients in these reports relapsed after receiving T-cell–depleted marrow and were treated with IFN administered on a thrice weekly schedule.

Administration of IFN to patients who relapse with CP CML after BMT is feasible and effective. Just as in those with newly diagnosed CML treated with IFN, control of hematologic parameters occurred in 75% of patients. The proportion of post-BMT patients who achieve complete cytogenetic response (33%) appears to be at least equivalent to that (19%) reported for newly diagnosed patients and occurs more rapidly and with lower doses of IFN.

Relapse of CML in the posttransplant setting may be amenable to immunomodulatory therapy because of the presence of foreign donor lymphocytes and the possibility of exploiting the graft-versus-leukemia effect.15,16 Whereas IFN appears to be effective in de novo treatment of CML because of its antiproliferative effects on CML progenitor cells, there may be additional mechanisms operating in the posttransplant patient. IFN increases the expression of the major histocompatibility antigens, which may facilitate recognition and suppression of leukemic host cells by donor lymphocytes. IFN may also increase the number of natural killer cells, some of which may have lymphokine-activated killer activity with antileukemic effect after allografting.17 As previously reported by Kolb et al18 and exemplified by patient 5, it may be possible to take further advantage of these effects in IFN refractory patients by adding donor buffy coat.

Acquisition of a new clonal cytogenetic abnormality is considered predictive of the development of AP in CML patients who have not undergone BMT. However, in the posttransplant setting, new clonal rearrangements were present in the majority of patients studied. Four of the six patients who had a cytogenetic complete response, and one of two patients with a cytogenetic partial response, had at least one clonal chromosomal abnormality (including trisomy 8) in addition to the Ph. Although most of these clones are likely due to chromosome damage resulting from the conditioning regimen, clonal evolution of CML indicative of acceleration, particularly in the case of trisomy 8, cannot be ruled out. In either case, the finding of additional clones in a patient who appears otherwise to be in CP does not appear to predict for nonresponse to IFN or to the development of AP when patients are treated with IFN.

Although effective treatment doses in newly diagnosed CML patients range from 3 to 9 ×10^6 U/m^2/d, most posttransplant patients did not tolerate dose escalation beyond 3 ×10^6 U/m^2/d, generally because of myelosuppres-
sion. Just as in de novo treatment, dose schedule appears to be important in the posttransplant setting. Although maintenance doses were intended to be administered three times weekly, in most cases daily or five times per week administration was necessary to maintain a complete response. Differences in dose schedule may account for lower cytogenetic response rates in other studies that have retrospectively examined the use of IFN to treat post-BMT relapse.\textsuperscript{12,14}

Despite the theoretical possibility that GVHD might be exacerbated by IFN administration, only one patient experienced significant worsening of underlying GVHD. This patient started IFN before day 100 posttransplant and it is unclear whether IFN played a role in the development of GVHD. This patient achieved a complete cytogenetic response, while five other patients with complete cytogenetic response have no chronic GVHD.

Although IFN is effective in treating posttransplant relapse of CP CML, its impact on survival remains unknown and long-term follow-up will be required. This study suggests that there may be a role for the use of IFN in the immediate posttransplant setting in high-risk patients or for patients with early cytogenetic relapse only. Ongoing trials are evaluating the efficacy of these approaches.

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Use of alpha interferon for the treatment of relapse of chronic myelogenous leukemia in chronic phase after allogeneic bone marrow transplantation

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