Clinical Investigation of Human Alpha Interferon in Chronic Myelogenous Leukemia

By Moshe Talpaz, Hagop M. Kantarjian, Kenneth B. McCredie, Michael J. Keating, Jose Trujillo, and Jordan Gutterman

Fifty-one patients with previously untreated or minimally treated chronic myelogenous leukemia in chronic phase received human alpha interferon 3 to 9 x 10^6 units intramuscularly (IM) daily until complete hematologic remission, then at doses ranging from 3 x 10^6 units every other day to 9 x 10^6 units daily. Forty-one (80%) patients achieved a hematologic response, 36 (71%) of them attaining a complete hematologic remission with normal peripheral WBC and differential counts. Responding patients showed continuous but slow normalization of several other blood and marrow parameters including platelet counts, serum lactic dehydrogenase and B12 levels, and marrow cellularity and maturation index. Suppression of the Philadelphia chromosome on serial cytogenetic studies of marrow metaphases was documented in 20 of the 36 patients who achieved complete hematologic remission (56%; 39% of total group), eight of whom (22%) had a decrease of the Philadelphia chromosome-positive metaphases to less than 35%. These changes were persistent for 6 months or longer in 18 patients, seven of whom had continuous suppression of the Philadelphia chromosome to less than 90% for a median of 30+ months (range 21+ to 39+ months). After a median follow-up period of 37 months, 25 patients remain in continued disease control with interferon therapy. The projected 3-year survival rate is 76%, with a yearly death rate of 6%, 9%, and 9% in the first 3 years. Response, Philadelphia chromosome suppression, and survival were significantly better among patients in the low-risk category compared to intermediate- and high-risk categories, as defined by a multivariate analysis-derived prognostic model. The projected 3-year survival rate was 94% for patients who achieved a complete hematologic remission on interferon therapy and 45% for those who did not. Thirteen patients have developed blastic crisis, six with lymphoid and three with undifferentiated morphology. We conclude that human leukocyte alpha interferon effectively controls chronic myeloid leukemia and allows reappearance of diploid hemopoietic cells in some patients.

CHRONIC myelogenous leukemia (CML) disease has a biphasic clinical course. The initial chronic phase is easily controlled with therapy and lasts for a median of 2 to 4 years. This then evolves into a phase of resistant, rapidly fatal blastic crisis. Various therapies have resulted in significant but limited progress. The median survival after diagnosis has improved from 19 months for untreated patients to a range of 30 to 45 months for those receiving single agents such as myleran or hydroxyurea and 45 to 55 months for patients treated with intensive combination chemotherapy. However, the progressive and ultimately fatal nature of CML has not been altered significantly; most patients still die from blastic crisis, with no consistent cure fractions recorded. Allogeneic bone marrow transplantation is a promising approach in CML because of its curative potential, but its application and optimal timing are limited by donor availability, patient age, and the high incidence of morbidity and mortality in a disease that has a long chronic phase. These factors emphasize the need for new modalities to treat patients with CML.

Interferons have opened new possibilities for managing patients with cancer. Human alpha interferon (IFN-α), produced by virus-stimulated leukocytes, has undergone extensive trials and has shown promising results in several tumor categories including hairy cell leukemia and renal cell cancer.

We have previously reported on our preliminary studies with IFN-α in CML showing its cytoreductive activity. The activity of interferon in CML has also been documented recently using the pure recombinant alpha interferon material. In this report we summarize our long-term results with the partially pure IFN-α in patients with Philadelphia chromosome-positive chronic-phase CML, evaluating efficacy and toxicity, describing the cytogenetic changes associated with therapy, and analyzing patterns of blast crisis, mortality rates, and overall prognosis.

PATIENTS AND METHODS

Population study. Between August 1981 and December 1984, 51 patients with Philadelphia chromosome-positive chronic-phase CML entered the study after giving informed consent. All patients were advised of procedures and attendant risks, in accordance with institutional guidelines, and gave informed consent. Eligibility criteria required the presence of less than 30% blasts in peripheral blood and bone marrow, absence of extramedullary disease, and minimal previous therapy. The patients’ characteristics are detailed in Table 1. The median age was 42 years (range 20 to 70 years). The majority of patients had received no therapy, and 20 had been treated with single-agent chemotherapy for periods of less than a month. Forty-six patients (90%) started therapy within six months after the diagnosis. The patients’ classification into low-, intermediate-, and high-risk categories, based on a multivariate analysis of pretreatment characteristics, was similar to that of the general CML population. Forty-eight patients had the common 9;22 balanced translocation. Among these, two had evidence of disease acceleration with cytogenetic clonal evolution: one had additional chromosomal...
material on the short arm of chromosome 16 (16p+) in 25% of the marrow metaphases; the other showed a balanced translocation between the long arms of chromosomes 8 and 17.

Cytogenetic Pattern
- Translocation 9;22 only: 46 (90)
- Other translocations: 3 (6)
- Clonal evolution: 2 (4)

Prognostic category
- Low risk: 22 (43)
- Intermediate risk: 16 (31)
- High risk: 11 (22)
- Not evaluable: 2 (4)

Previous therapy
- None: 31 (61)
- Myleran or hydroxyurea: 18 (35)
- Others: 2 (4)

Criteria for response, toxicity, and removal from study. Response criteria were defined as follows:
- Complete hematologic remission: This required normalization of peripheral WBC counts to levels lower than 10,000/µL and normal differentials with no immature forms (blasts, promyelocytes, myelocytes, or metamyelocytes); normalization of platelet counts to less than 450 × 10^3/µL; and disappearance of all clinical symptoms and signs of disease, including palpable splenomegaly. Maximal suppression of the Philadelphia chromosome was defined as four subgroups of (1) no cytogenetic response if the Philadelphia chromosome persisted in all analyzable metaphases, (2) minimal cytogenetic response if its expression was suppressed to percentages of 35% to 95%, (3) partial cytogenetic response if suppression was to levels of 5% to 34%, and (4) complete cytogenetic response if total elimination of the Philadelphia chromosome was noted in marrow metaphases.
- Partial hematologic remission: This category was defined as a decrease in the WBC counts to at least 50% of pretreatment level and to at least below 20,000/µL; it included patients whose peripheral WBC counts had become normal but who had persistent splenomegaly or immature peripheral cells.
- Failure: This group included all patients who had less than partial hematologic remissions.

Criteria for removal from the study. These included (1) development of blast crisis with 30% or more blasts in the bone marrow or peripheral blood or the development of extramedullary disease; (2) failure to respond to therapy as evidenced by a continuous increase in WBC count or less than 25% decrease in WBC counts from pretreatment levels over a period of 14 weeks; (3) an initial response followed by subsequent increase in WBC count to more than 40,000/µL, uncontrolled by continued interferon therapy (patients with a cyclic peripheral leucocyte count pattern were continued on therapy unless the WBC counts were consistently higher than pretreatment values); and (4) unacceptable toxic reactions as defined above.

Statistical analysis. Survival and disease control duration curves were plotted by the method of Kaplan and Meier. Disease control duration time was calculated from the date of start of therapy until development of resistance, toxicity, or blast crisis. Tests of differences in survival distributions were based on a generalized Wilcoxon test. Comparisons of differences among subgroups were made using chi-square tests for remission rates and degree of cytogenetic response.

RESULTS

Remission induction. All 51 patients in the study were evaluable with a median follow-up duration of 37 months. Induction therapy with IFN-α resulted in complete hematologic remission in 36 patients (71%). Five patients (10%) achieved a partial hematologic remission, three of these being classified as such because of persistent splenomegaly; and ten patients failed to improve (Table 3).

All 36 patients who obtained complete hematologic remission had, by definition, normalized peripheral WBC counts and differentials. The median time to achieve a complete hematologic remission was 14 weeks, with a range of 2 to 55
Pretreatment characteristics were not available in two patients to determine their risk category: one had resistant disease, and one achieved complete hematologic remission but no suppression of the Philadelphia chromosome.

### Table 2. Toxicity Criteria

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, chills, influenza-like symptoms; bone and muscle aches</td>
<td>Self-limiting, no therapy needed</td>
<td>Require antipyretics or anti-inflammatory agents</td>
<td>Require narcotics and/or hospitalization</td>
<td>Life threatening</td>
</tr>
<tr>
<td>Fatigue, performance status (Zubrod scale)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss (Percentage of body weight)</td>
<td>0-5</td>
<td>6-10</td>
<td>11-15</td>
<td>&gt; 15</td>
</tr>
<tr>
<td>Renal function (creatinine in mg/100 mL)</td>
<td>up to 2.5</td>
<td>&gt; 2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function</td>
<td>up to 2.5</td>
<td>&gt; 2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/100 mL)</td>
<td>300-600</td>
<td>&gt; 600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Does not interfere with daily activities or require medical intervention</td>
<td>Moderate impairment of activities, requires medical therapy</td>
<td>Severe impairment of activities, requires discontinuation of interferon and medical therapy</td>
<td>Coma, seizures, confusion, parkinsonism, severe depression</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocyte count (per μL)</td>
<td>1,000-2,000</td>
<td>&lt;1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count (x 10^3/μL)</td>
<td>50-100</td>
<td>25-50</td>
<td>&lt;25</td>
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</tr>
</tbody>
</table>

weeks. Two different patterns of response were observed. Twenty-six of the 36 patients (72%) had a steady gradual decline of peripheral counts and achieved remission after a median period of 9 weeks (range 2 to 28 weeks). The other ten patients (28%) manifested a cyclic pattern of response with WBC and platelet count in cycles of 4 to 8 weeks. Therapy induced lower peaks for WBC and platelet counts with each subsequent cycle; the median time to achieve remission in these patients was 26 weeks (range 8 to 55 weeks). Twenty-four of the 36 patients had had palpable splenomegaly that disappeared on follow-up studies. The responses of patients in each prognostic category were compared and are shown in Table 3.

**Blood, marrow, and cytogenetic changes in patients who achieved complete hematologic remission**. Changes in blood and marrow parameters in the first 2 years of therapy are shown for the 36 patients who achieved complete hematologic remission (Fig 1). Decline in WBC count was the earliest manifestation of response. Thrombocytosis with platelet counts of more than 500 × 10^9/μL was present in 12 patients (33%), six of them having counts higher than 800 × 10^9/μL. Platelet counts became normal in all responding patients. Subsequent increases in platelet as well as other parameters were noted among patients who failed after initial disease control, which accounts for the extreme values shown.

Serial bone marrow studies revealed a gradual decrease in bone marrow cellularity and an increase in maturation index. Marrow changes lagged behind peripheral blood changes: marrow cellularity declined from a median of 100% to a median of 75%, and the maturation index increased from a median of 8.3 before therapy to a median of 26.0 at 12 months (Fig 1).

Return of cells with diploid karyotype were noted with continued IFN-α therapy on serial cytogenetic studies of bone marrow cells. Twenty of the responding patients (56%, or 39% of the total group) manifested evidence of suppression of the Philadelphia chromosome on follow-up cytoge-

### Table 3. Results of IFN-α Therapy

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Total</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic remission</td>
<td>36(71)</td>
<td>18(82)</td>
<td>10(62)</td>
<td>7(64)</td>
</tr>
<tr>
<td>Philadelphia status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>16(31)</td>
<td>5(23)</td>
<td>3(19)</td>
<td>7(64)</td>
</tr>
<tr>
<td>35%-95%</td>
<td>12(24)</td>
<td>9(41)</td>
<td>3(19)</td>
<td>—</td>
</tr>
<tr>
<td>5%-34%</td>
<td>3(6)</td>
<td>16(59)</td>
<td>2(13)</td>
<td>4(44)</td>
</tr>
<tr>
<td>0%</td>
<td>5(10)</td>
<td>3(14)</td>
<td>2(12)</td>
<td>—</td>
</tr>
<tr>
<td>Partial hematologic remission</td>
<td>5(10)</td>
<td>2(10)</td>
<td>3(19)</td>
<td>—</td>
</tr>
<tr>
<td>Resistant disease</td>
<td>10(20)</td>
<td>2(10)</td>
<td>3(19)</td>
<td>4(36)</td>
</tr>
<tr>
<td></td>
<td>5(100)</td>
<td>22(100)</td>
<td>16(100)</td>
<td>11(100)</td>
</tr>
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</table>

* Pretreatment characteristics were not available in two patients to determine their risk category: one had resistant disease, and one achieved complete hematologic remission but no suppression of the Philadelphia chromosome.
netic studies. Cytogenetic conversion to a partial diploid state was minimal (Philadelphia chromosome-positive in 35% to 95% of metaphases) in 12 patients (24%) and significant (Philadelphia chromosome-positive in less than 35% of metaphases) in eight patients (22% of responders, 16% of total). Suppression of the Philadelphia chromosome was slow, with changes observed after a median duration of 9 months of therapy (range 3 to 15 months). Cytogenetic conversion to a partial diploid state was short lived in two patients but persisted 6 months or longer in 18 patients, seven of whom showed evidence of continuous Philadelphia chromosome suppression for a median of 30+ months (range 21+ to 39+ months) (Table 4). The incidence of Philadelphia chromosome suppression was 59%, 44%, and 0% respectively, for low-, intermediate-, and high-risk groups ($P < 0.01$) (Table 3).

Similar changes were documented for patients' serum LDH and vitamin B12 levels, which reverted slowly to normal values with response to therapy. Sixty-four percent of patients had had LDH values above 600 U/dL before therapy, compared to 12% after 3 months, 7% after 12 months, and 0% after 18 months of therapy. Similarly, although 94% of patients had had serum B12 levels above 1,000 pg/mL before treatment, this percentage decreased to 40% at 3, 25% at 12, and 14% at 18 months.

**Disease control duration and failure patterns.** The median duration of continued disease control with IFN-α was 29 months for the whole group (Fig 2), 33+ months for patients obtaining a complete hematologic remission, and 9 months for those achieving only a partial hematologic remission.

Patient outcome is summarized in Table 5. At the time of analysis, 25 of the initial 36 patients (78%) who obtained a complete hematologic remission remain in continued hematologic remission on IFN-α therapy, whereas 11 have failed: seven developed resistant disease and are all controlled on alternate therapies with hydroxyurea or myleran, and four evolved into blastic crisis. Of the 15 patients who achieved a partial remission or no response, ten were taken off the study while in benign phase (resistance 4, toxicity 1, both 5), five of them developed subsequent blastic crisis, two died in chronic phase, and four are alive on alternate treatments.
The other five patients who had partial remission or failed on therapy developed blastic crisis. Thus 11 of the 17 patients who showed resistance to interferon therapy in benign phase remain on alternative therapies with good disease control for a median of 20 months (range 12 to 35 months). Four developed subsequent blast crisis, and two other patients died; one of accelerated disease, the other of thoracocentesis-induced pneumothorax and empyema.

Thirteen patients have already developed blastic crisis after a median therapy duration of 11 months (range 2 to 30 months) (Fig 3). Blastic crisis has developed in 9 of the 15 patients who did not achieve a complete hematologic response compared to 4 of 36 who did (60% vs 11%, $P < 0.05$). In the latter group three had no cytogenetic response, and one had a minimal cytogenetic response with a decrease of Philadelphia-positive metaphases to 85% for 3 months only.

The patterns of blastic crisis and response to chemotherapy differed from previous experience. Six of the 13 patients had lymphoid blastic crisis, three had undifferentiated, and four had myeloid blast crisis morphologies. Five of the six patients who had lymphoid blast crisis achieved remission and entered a second chronic phase lasting for a median of three months (range 2 to 11+ months) with vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD).

Toxicity. Early and late patterns of host toxic reactions were observed among patients treated with IFN-α (Table 6). Forty-seven of the 51 patients (92%) experienced early toxic reactions, most of which consisted of fever, chills, fatigue, anorexia, and muscle and bone pains. Severe early toxic reactions were unusual and did not require interruption of treatment in any patient. Other toxicities such as insomnia, excessive sweating, nervousness, postnasal drip, and mild depression were unusual. The toxic effects usually lasted for a median of three days (range one to 12 days), improved gradually with therapy, and were manageable with antipyretic and analgesic medications.

The majority of patients tolerated chronic therapy well, with 76% maintaining an average performance status of 0 (Zubrod scale) and continuing their normal activities. Twelve patients (24%) had mild chronic symptoms with an average performance status of 1 to 2. Overall, six patients (12%) had treatment discontinued because of late toxicities.

Serious late toxic reactions included myalgias; bone and joint pains; severe fatigue, weight loss, and decreased performance; neurotoxicity; and immune-mediated thrombocytopenia (Table 6). The myalgias that occurred at some point during therapy in 17 patients were generally diffuse. Patients usually responded to a decrease in interferon dosage and to analgesics. Bone pains occurred most frequently in the proximal upper and lower extremities, pelvis, and ribs. Temporary discontinuation of therapy and administration of analgesics and steroids allowed therapy to be resumed in eight of the 12 patients who had severe pains. Chronic severe fatigue, anorexia, weight loss, and poor performance were observed in four patients.

Neurotoxicity was manifested in several patterns, some of which have been reported.23 Central nervous system (CNS) manifestations consisted of apathy or agitation, insomnia, withdrawal, bland affect, lack of interest, decreased attention span and short-term memory, and depression. These occurred mildly in nine patients, improving with methylphenidate in six, and severely in three patients, requiring treatment interruption. One of the two patients who showed parkinson-like signs and symptoms had concomitant severe depression, which led to discontinuation of therapy.

Among the four patients who developed immune-mediated thrombocytopenia with platelet counts lower than 50,000/91.
 µL, platelet recovery was noted in two patients after discontinuation of interferon and institution of steroids; the other two patients underwent splenectomy for persistent thrombocytopenia with subsequent recovery of platelet counts. Other less common chronic toxic reactions included mild hair loss (18%), diarrhea (12%), headaches (14%), anorexia (10%), disturbed liver function (6%), postnasal drip (6%), cough, lung infiltrates, and impotence (2% each).

The incidence of severe toxic reactions increased with development of resistant disease. Five patients were taken off study because of resistant disease and increasing toxicity, which consisted of muscle or bone pains in four and neurotoxicity in one patient.

Survival. After a median follow-up period of 37 months, 40 patients (78%) are alive, 36 being in chronic phase disease (25 of them on IFN-α therapy) and four in second chronic phase. The median overall survival has not been reached, and the projected three-year survival is 76% (Fig 2).

Relative yearly hazard rates for death were 6% during the first, 9% during the second, and 9% during the third year of study. The projected 3-year survival was 94% for patients with complete hematologic remission and 45% for those with partial hematologic remission or resistant disease. Only two of the 36 patients who achieved complete hematologic remission on IFN-α therapy have died, compared to 9 of the 15 patients who did not (6% v 60%; P < 0.01).

As with remission induction, different patterns of survival were observed in different risk categories: the 3-year survival...
growth and differentiation of normal and CML myeloid cell progenitor cells in vitro and to induce granulocytopenia among treated patients. The excessive myeloid proliferative activities were shown to suppress the Philadelphia chromosome-positive cells to less than 35%, and 10% to 30% manifesting 100% diploid metaphases. These “true” complete and partial remissions were transient in all patients. This demonstrates the existence of cells with a normal karyotype in the marrow of patients with CML that could repopulate the patient’s marrow after eradication of the leukemic clones. In contrast to the results of intensive chemotherapy, suppression of the Philadelphia chromosome-positive clones with IFN-α was slow to occur, progressive in nature, and long-lasting in a substantial number of our patients (Table 4). Suppression of the Philadelphia chromosome was also more pronounced among low-risk patients. The dramatic but transient cytogenetic response patterns with intensive chemotherapy and the slowly developing but persistent ones with IFN-α may be enhanced and maintained by the use of a combined modality approach.

The cost and scarcity of the partially pure human IFN-α material have been a significant problem in the conduct of large-scale clinical trials; this has been avoided recently through the availability of the pure recombinant alpha interferons. It has been argued that response to IFN-α or its toxicity may be partly attributed to the impurities of this partially purified form of interferon alpha. However, our recent preliminary experience with the pure recombinant alpha A interferon has demonstrated similar response and toxicity patterns. Of the first 17 patients treated, 13 (76%) achieved a complete hematologic remission, and six (35%) had evidence of suppression of the Philadelphia chromosome. The chronic course of CML disease requires long-term follow-up to evaluate treatment benefit. One important question is whether IFN-α therapy will change overall patient prognosis. In this CML population, the yearly risk of death of 6% to 9% in the first three years compares favorably with the expected yearly mortality of 25% after the second year of follow-up for patients treated with single-agent therapy with myleran or hydroxyurea. The 76% projected survival at 3 years is also encouraging in comparison with the 3-year survival rate of 53% among a historic control group of 155 patients from our institution who were treated with hydroxyurea or myleran and with the 3-year survival percentage range of 35% to 65% in other reports. The yearly incidence of blast crisis ranged from 5% to 1% in the first 3 years (Fig 3) and is lower than previously reported. Interestingly, the majority of patients who developed blastic crisis manifested lymphoid or undifferentiated cellular morphologic characteristics. This contrasts with the reported 60% to 75% incidence of myeloid blast crisis morphology reported in CML. This raises the possible advantage of additive chemotherapy in suppressing involved lymphoid cells. Finally, response to IFN-α seems to be a good parameter for predicting long-term prognosis. The 3-year survival rate was 94% for patients having a complete hematologic response and 45% for the remaining population.

The study of prognostic factors and risk categories in CML is useful in several ways, including therapeutic strategy planning. Early intensive chemotherapy was shown previously to benefit mainly patients in the intermediate- and high-risk groups, the 76% projected survival among low-risk patients. The cost and scarcity of the partially pure human IFN-α material have been a significant problem in the conduct of large-scale clinical trials; this has been avoided recently through the availability of the pure recombinant alpha interferons. It has been argued that response to IFN-α or its toxicity may be partly attributed to the impurities of this partially purified form of interferon alpha. However, our recent preliminary experience with the pure recombinant alpha A interferon has demonstrated similar response and toxicity patterns. Of the first 17 patients treated, 13 (76%) achieved a complete hematologic remission, and six (35%) had evidence of suppression of the Philadelphia chromosome.

The administration of human leukocyte IFN-α in the current study resulted in complete hematologic remission in the majority of patients. Therapy affected the peripheral blood, bone marrow, and spleen. The process of response was gradual, requiring a median of 14 weeks of therapy to achieve a complete hematologic remission and a median of 9 months to observe initial Philadelphia chromosome suppression. Changes were seen first in the peripheral blood, while bone marrow changes appeared late. A cyclic pattern of clinical response was observed in about one quarter of patients, possibly due to preservation of a partial feedback mechanism.

Since our study used strict criteria in defining complete hematologic remission, the complete hematologic response rate of 71% is not comparable to response rates reported for myleran or hydroxyurea. Studies with these agents often did not require disappearance of palpable splenomegaly or complete normalization of the peripheral differential counts.

Most interesting was the gradual suppression of the Philadelphia chromosome among responding patients. Previous studies with intensive combination chemotherapy resulted in significant suppression of the Philadelphia chromosome, with 30% to 60% of patients showing a decrease of Philadelphia chromosome-positive cells to less than 35%, and 10% to 30% manifesting 100% diploid metaphases. These “true” complete and partial remissions were transient in all patients. This demonstrates the existence of cells with a normal karyotype in the marrow of patients with CML that could repopulate the patient’s marrow after eradication of the leukemic clones. In contrast to the results of intensive chemotherapy, suppression of the Philadelphia chromosome-positive clones with IFN-α was slow to occur, progressive in nature, and long-lasting in a substantial number of our patients (Table 4). Suppression of the Philadelphia chromosome was also more pronounced among low-risk patients. The dramatic but transient cytogenetic response patterns with intensive chemotherapy and the slowly developing but persistent ones with IFN-α may be enhanced and maintained by the use of a combined modality approach.

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high-risk prognostic categories. The present analysis demonstrates a substantial benefit of IFN-α therapy among intermediate- and low-risk patients. The combined use of intensive chemotherapy and interferons in a common treatment program may improve the outcome of all risk categories.

The acute toxic reactions to IFN-α were moderate. Chronic toxicities were treatment-limiting in 12% of patients. Serious toxicities included skeletal, muscular, and joint pains, neurotoxicity, and immune-mediated thrombocytopenia. Of interest was the simultaneous development of severe toxicity and resistant disease in a number of patients, raising the possibility of the release of certain factors from granulocytes that could induce inflammation in the musculoskeletal system.

In summary, this study showed IFN-α to induce hematologic remission in a majority of patients with chronic-phase CML. There were marked associated changes in the blood and bone marrow including suppression of the Philadelphia chromosome-positive clones. The unique biologic activity of IFN-α in CML opens possibilities for studies with interferons alone and in combination with intensive chemotherapy in an attempt to delay the onset of blast crisis and to improve survival in this patient population.

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