Several prospective randomized studies have shown that the treatment of chronic myeloid leukemia with interferon-α (IFN-α) prolongs the survival by comparison with conventional chemotherapy. However, although IFN-α can induce cytogenetic responses, true complete remissions are rarely achieved and information on the long-term effects of IFN-α treatment is limited. For that purpose, we updated and analyzed a prospective comparative trial of IFN-α and conventional chemotherapy that was initiated in 1986. The first analysis of the trial was already published, and showed a survival advantage for IFN-α (NEnglJ Med12:820, 1994). The observation period of living patients now ranges between 95 and 129 months and we examined the long-term effects of IFN-α treatment, always by comparison with conventional chemotherapy and according to the intention-to-treat principle. The patients who were submitted to allogeneic bone marrow transplantation (BMT) in chronic phase (38 of 322 or 12%) were censored at the date of BMT. Seventy-three of the original 284 nontransplanted patients were alive, 56 (30%) in the IFN-α arm and 17 (18%) in the chemotherapy arm. Forty-one patients overall (14%) were still receiving IFN-α. In the IFN-α arm 9 patients were in continuous complete cytogenetic remission and 11 were in major or minor cytogenetic remission. Median and 10-year survival of low-risk patients were 104 months (95% CI, 85 to 127 months) and 47% (95% CI, 36% to 59%) in IFN-α arm versus 64 months (95% CI, 49 to 98 months) and 30% (95% CI, 16% to 44%) in chemotherapy arm (P = .03). Median and ten-year survival of non-low-risk patients were 69 months (95% CI, 56 to 76 months) and 16% (95% CI, 8% to 24%) in IFN-α arm versus 46 months (95% CI, 39 to 61 months) and 5% (95% CI, 0% to 11%) in chemotherapy arm (P = .006). A low Sokal’s risk, hematologic response, and cytogenetic response were associated with a longer survival. No major or unusual side effects were recorded after the 5th year of IFN-α treatment. Fourteen patients died in chronic phase, 9 (4%) in IFN-α arm and 5 (5%) in chemotherapy arm, mainly of cardiovascular accidents (6 cases) and of other cancers (5 cases). We conclude that a policy of chronic treatment with IFN-α maintained a significant survival advantage over conventional chemotherapy on a long-term basis and irrespective of the risk. However, the great majority of the long-term survivors were in the low-risk group. The question of treatment discontinuation was not addressed in this study.

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evaluated after 8 and 14 months and yearly thereafter, based on a minimum of 10 evaluable metaphases, and was defined according to the percentage of Ph negative metaphases as none, minimal (1% to 32% Ph neg), minor (33% to 65% Ph neg), major (66% to 99% Ph neg), and complete (100% Ph neg). The hematologic response was defined as complete if blood counts were normal (hemoglobin > 110 g/L, platelet < 500 × 10^9/L, WBC < 10 × 10^9/L), if the differential leukocyte count did not contain immature cells, and if the spleen was not palpable. The formulation of Sokal et al 13 was used to categorize the patients by risk.

Statistical analysis. Survival was calculated according to the method of Kaplan and Meier 14 from the date of randomization to the date of death or last contact. Follow-up information was available on all patients. At last contact (June 1997), the follow-up of living patients ranged between 95 and 129 months (median, 112 months). During the chronic phase, 38 patients underwent allogeneic bone marrow transplantation (BMT) (12%) and 6 patients were autografted (2%). Allogeneic BMT was allowed by the protocol, whereas autografts were protocol violations. For that reason, all survival calculations and comparisons were made including, excluding, or censoring the patients who were submitted to transplant. The results were always identical, and the survival data that are reported hereforth include all randomized patients, with censoring for allogeneic transplant. The time to the progression to accelerated or blastic phase was calculated from randomization, with censoring for allogeneic BMT and for death in chronic phase. Analyses and comparisons were made by the chi-square test and Student’s t-test, and log-rank analysis at specific time points was performed whenever appropriate.

RESULTS

Patients’ status. The status of the patients who were not transplanted is shown in Table 1. In the IFN-α arm 56 of 188 patients (30%) were alive and 16 of these patients (8%) maintained a complete or a major cytogenetic remission. In the chemotherapy arm 17 of 96 patients (18%) were alive, with a minor cytogenetic response in one case.

Treatment discontinuation and adjustment. The number of the patients who discontinued the assigned treatment and went off protocol before progression was 114 of 218 (52%) in the IFN-α arm and 37 of 104 (35%) in the chemotherapy arm. The difference was due to the fact that 39 patients (18%) discontinued IFN-α because of the side effects that are listed in Table 2. The classic flu-like syndrome including fatigue, fever, musculo-skeletal pain, and headache covered 37% of discontinuations, either early or late. Anorexia, nausea, and diarrhea came second, but only during the first 3 years of treatment. Neurologic side effects like depression, amnesia, lethargia, psychosis, reversible coma in one case, and polyneuropathy, mainly sensorial, developed during the first 5 years of treatment and were the third cause of treatment discontinuation.

In the IFN-α arm 84 patients overall (38%) also received chemotherapy before progression to accelerated or blastic phase, either because IFN-α was discontinued for side effects (39 cases) or because it was believed that IFN-α was unable to control the disease (45 cases). In the chemotherapy arm, no option was provided for crossing the treatment to IFN-α, but IFN-α was actually administered to 8 patients, 2 to 70 months after randomization. The overall survival of these 8 patients was long, ranging from 96 to 129 months (median, 106 months), with 2 of 8 alive at last contact.

The dose of IFN-α that was originally scheduled for this study was 9 mIU daily (corresponding to 63 mIU weekly) for 8 months, to be maintained thereafter at maximum tolerated dose if any cytogenetic response was obtained. During the first year, the mean IFN-α weekly dose was significantly higher in the patients who achieved any degree of cytogenetic response than in the others (Table 3). Thereafter, in the majority of the nonresponders the dose was decreased to 9 mIU weekly, as it was prescribed by the protocol. In the responders the dose was also adapted, according to tolerance, and from the 5th year on was about 20 mIU weekly (Table 3).

BMT. The option for allogeneic BMT from an HLA-compatible family donor was always open and was actually
used during the chronic phase in 33 patients, 2 to 65 months after registration (median, 15 months). In another 5 patients an allogeneic BMT was performed later (42 to 107 months after registration) from a matched unrelated or a partially matched related donor. In summary, 38 of 322 patients of any age (12%) and of 172 patients less than 51 years old (22%) received an allogeneic BMT during the chronic phase. Sixteen of the 38 transplanted patients (42%) died of transplant or transplant-related complications, two are alive with leukemia, and the remaining 20 (53%) are alive and in hematologic remission. Two additional patients, both in the IFN-α arm, were transplanted in blastic phase and died of transplant. Six patients (4 in the IFN-α arm and 2 in the chemotherapy arm) were autografted in chronic phase. Three of them died of leukemia and three are alive with leukemia. Ten patients (6 in the IFN-α arm and 4 in the chemotherapy arm) were autografted in accelerated or blastic phase. Seven died of transplant or leukemia, and three are alive with leukemia.

**Survival and progression.** The median survival of the 218 patients who were assigned to IFN-α and of the 104 patients who were assigned to chemotherapy was 76 months and 52 months, respectively (95% CI, 69 to 86 months and 43 to 66 months, log-rank test, \( P = .002 \)) (Fig 1). The proportion of the patients who were projected to be alive after 10 years was 29% (95% CI, 23% to 36%) in IFN-α arm and 17% (95% CI, 9% to 25%) in chemotherapy arm. Figure 1 also shows the rate of the progression from chronic to accelerated or blastic phase. The median time from diagnosis to progression was 74 months with IFN-α and 46 months for chemotherapy (log-rank test, \( P = .0005 \)).

Figure 2 shows the survival and the progression from chronic to accelerated or blastic phase of Sokal’s low-risk patients as a function of treatment. Figure 3 shows the same for Sokal’s intermediate- and high-risk patients. The difference was significant both in low-risk patients (\( P = .03 \) for survival and \( .02 \) for progression) and in intermediate- and high-risk patients (\( P = .006 \) for survival and \( .002 \) for progression).

**Deaths in chronic phase.** Fourteen patients died in chronic phase; nine of them had been assigned to IFN-α (4%) and five had been assigned to chemotherapy (5%) (Table 4). The deaths occurred either early (3 to 14 months after diagnosis), and were due to infection, cardiac disease, or gastric bleeding; or late (32 to 99 months after diagnosis), and were due to cardiac or vascular disease, or to other cancers. Fatal cardiovascular events were slightly more frequent in IFN-α patients (5 of 218 or 2.3%) than in chemotherapy patients (1 of 104 or 1%). Cancers were slightly more frequent in chemotherapy patients (4 of 104 or 4%) than in IFN-α patients (2 of 218 or 1%). Among the nine IFN-α patients who died in chronic phase, four were in stable complete or major cytogenetic remission.

**Prognostic factors.** Prognostic factors for survival were examined in all the patients and in those who had been randomized to receive IFN-α (Table 5). In all the patients, many factors were associated with survival, but by multivariate analysis only treatment arm remained statistically very significant, together with age, spleen, and Sokal’s score. In the patients who had been assigned to IFN-α the survival was significantly influenced by Sokal’s score, hematologic response, and cytogenetic response. Figure 4 shows a landmark survival analysis of the patients who were assigned to IFN-α according to hematologic response.
logic response and to cytogenetic response. Both responses were associated with a substantial and very significant prolongation of survival.

**Cytogenetic response in IFN-α arm.** A cytogenetic response (Ph neg metaphases, 33% to 100%) was obtained in 70 of 218 cases (32%). The best cytogenetic response was complete (Ph neg, 100%) in 23 cases (10%), was major (Ph neg, 66% to 99%) in 23 cases (10%), and was minor (Ph neg, 33% to 65%) in the remaining 24 cases (11%). The time to achieve the first response ranged from less than 1 year to 7 years (median, 1 year), but the time to achieve the best response was even longer, with a median of 2 years. That was mainly due to the fact that the majority of the complete cytogenetic responses were detected rather late (4 after 1 year, 6 after 2 years, 5 after 3 years, and 8 after 5 years or more). Though many cytogenetic responses were first recorded after more than 1 year, many responders (48 of 70, 68%) received their first response within the first year of treatment, and other 14 patients (20%) were found to have some Ph neg metaphases within the same period. Only 8 of 70 cases (11%) did not show any Ph neg metaphases after the first year of treatment. One of these patients achieved a complete and stable response later, whereas the other 7 achieved only a major or a minor response, and that response was unstable and transient. Table 6 shows the course and the fate of 70 patients who achieved a cytogenetic response. Seven of them (10%) were submitted to allogeneic BMT. Of the remaining 63 patients, 4 died in chronic phase (6%), 34 (54%) are alive and in chronic phase, and the remaining 25 (40%) progressed to accelerated or blastic phase and died of leukemia or related complications. The proportion of the cases with progression was negatively related with the quality of the cytogenetic response (13% for complete response, 39% for major response, and 68% for minor response, P = .005) (Table 6). In the 10 patients who progressed to accelerated or blastic phase after a complete or a major cytogenetic response, two modalities of progression were observed: in 5 cases the loss of the cytogenetic response was rapidly followed by an acute blast crisis, with a lymphoid phenotype in 4 of 5 cases; in the other 5 cases, the time from cytogenetic response loss to progression was much longer, ranging between 17 and 73 months, progression to blastic phase was slow, and the terminal phenotype was myeloid.

**DISCUSSION**

The main purpose of this updated report of the Italian study is to provide information on the long-term effects of a policy of chronic IFN-α treatment. The first point was to evaluate the effects of IFN-α on long-term survival, and more clearly to answer the question if the survival benefit over conventional chemotherapy would continue in the long term. This point was not settled in prior reports because the difference between conventional chemotherapy and IFN-α does not concern the cure rate, but the cytogenetic response rate. In this study complete and major cytogenetic responses occurred in 46 of 218 patients (21%) and only 9 patients (4%) were still in complete cytogenetic remission after more than 8 years. Al-
though some of these patients were found to be sometimes also in molecular remission, as defined by nonquantitative reverse transcriptase polymerase chain reaction, and although some cases of molecular remission were described by others, in the great majority of the patients leukemia cannot be cleared off by current IFN-α treatment. Therefore, this study cannot provide evidence that IFN-α can cure CML, but shows that the survival benefit of IFN-α over conventional chemotherapy did not die out and was maintained in the long term either in the low-risk patients or in the patients with a higher risk. However, whereas the relative benefit of IFN-α over chemotherapy was independent of the risk, the absolute benefit was not, because nearly all the long survivors were in the low-risk group.

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>IFN-α Dose (mIU/m²/d)</th>
<th>Duration of IFN-α Treatment (mo)</th>
<th>Time from D/C IFN-α to Death (mo)</th>
<th>Overall Survival (mo)</th>
<th>Age at Death (yr)</th>
<th>Causes of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α</td>
<td>4.0</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>45</td>
<td>Infection, acute, nonidentified</td>
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<td>2</td>
<td>6</td>
<td>8</td>
<td>63</td>
<td>Cardiac, congestive heart failure</td>
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<tr>
<td>IFN-α</td>
<td>1.2</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td>69</td>
<td>Cardiac, congestive heart failure</td>
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<td>10</td>
<td>0</td>
<td>10</td>
<td>66</td>
<td>Gastric bleeding, liver cirrhosis at necropsy</td>
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<tr>
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<td>99</td>
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<td>91</td>
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<td>IFN-α</td>
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<td>IFN-α</td>
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<td>—</td>
<td>—</td>
<td>64</td>
<td>63</td>
<td>Vascular, cerebral, undefined</td>
</tr>
<tr>
<td>CHT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>65</td>
<td>Cancer, pharingeal</td>
</tr>
<tr>
<td>CHT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>38</td>
<td>59</td>
<td>Cancer, pancreatic</td>
</tr>
<tr>
<td>CHT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>67</td>
<td>61</td>
<td>Cancer, bronchogenic</td>
</tr>
</tbody>
</table>

Fourteen patients died in chronic phase, nine in the IFN-α arm and five in the chemotherapy arm. Abbreviations: CHT, chemotherapy; D/C, discontinuation of.

The model was applied to all cases, with the exclusion of 16 patients who were transplanted or were shifted to other treatments within the first 8 months. For IFN-α arm, the model was applied to the 162 patients (74% of total) who were alive and in chronic phase after 24 months, to avoid the bias related with time-dependent variables like hematologic and cytogenetic response (landmark analysis at 24 months).

*Hematologic response was evaluated after 8 months.
†Cytogenetic response was defined as a percentage of Ph neg metaphases ≥33% and was evaluated within 24 months, with examinations at 8, 14, and 24 months.
and 4). The second point was to evaluate the long-term compliance and the long-term side effects of chronic IFN-α treatment. Late treatment-related toxicity was neither more frequent nor different from early toxicity (Table 2). In particular, no more cases of neurologic toxicity were observed. However, it should be noticed that the number of cases “at risk” after 6 years was only 54 and that the mean dose that was administered after that time was 3 mIU daily. Eight patients (4%) died in chronic phase. In one case death was attributed to treatment-related pancytopenia. In the other 7 cases, a direct responsibility of treatment could not be established, but based on the causes of death (Table 4), special attention should be paid to the chronic administration of IFN-α to patients with established risk factors for cardiac or vascular disease. The development of other cancers was of concern, but the proportion was not different in the two treatment arms (1% with IFN-α and 4% with conventional chemotherapy).

This study was planned in 1985 and was started in 1986 with the aim of evaluating if IFN-α would prolong the survival over conventional chemotherapy. The design was not conceived with the purpose of answering other questions like the prediction, the kinetic, and the duration of the response. However, because these questions are important, the data were examined retrospectively and the results suggested that the cytogenetic response to IFN-α was predicted by Sokal’s risk and by hematologic response, and that the great majority of the cytogenetic responses were achieved within 1 year of treatment, though in many cases the responses improved significantly with time. The results also suggested that when the best cytogenetic response was only minor (Ph neg, 33% to 65%), the response was unstable and of a short duration, whereas the median duration of complete and major responses (Ph neg, ≥66% to 100%) was of about 60 months. These data fit with the observations from the M.D. Anderson Hospital trial.19,20,21

The treatment protocol prescribed a daily IFN-α dose of 9 mIU, corresponding to 63 mIU weekly to be administered for at least 14 months and indefinitely in the case of any cytogenetic response. The doses that were actually administered ranged widely, with a mean value decreasing from 50 mIU weekly during the first year to about 20 mIU weekly from the 5th year and continuing for the remainder of the study. These data are the result of a treatment policy that was targeted to the maximum tolerated dose and do not answer the questions regarding whether lower doses of IFN-α can be more cost-effective and if the treatment should be continued forever or could be discontinued once a durable complete or major cytogenetic response has been achieved, as suggested by the observations from M.D. Anderson Hospital.12,19,21

Evaluating and discussing the long-term effect of IFN-α treatment raises two main problems. The first problem is how to improve the cytogenetic response rate and how to prolong survival even more. The addition of low-dose arabinosyl cytosine was shown to be effective in one study and is currently being tested by our group. The second problem concerns the relationship with BMT. Autologous BMT can help to improve survival but there is no evidence of a cure and although it is conceivable that the longer the time from diagnosis, the worse the results, pretreating with IFN-α does not prevent from successful autografting. Pretreating with IFN-α does not prevent from allogeneic BMT either, although delaying the transplant would probably increase transplant-related mortality. One study raised the suspicion that IFN-α treatment may specifically adversely affect transplant outcome, but more studies showed that this was not the case. Allogeneic BMT from an HLA-identical sibling is currently considered as the first therapeutic option in the management of CML for patients under the age of 60, and CML is the first in the list of the indications for an allogeneic transplant from a matched unrelated donor. This is conceivable because allogeneic BMT is the only procedure that can cure CML. However, CML is no longer a rapidly fatal disease and about 50% of the cases present with low-risk features. In this study, the 10-year survival of the low-risk patients who were assigned to IFN-α is 47% (95% CI, 36% to 59%) for all of the 91 patients and 64% (95% CI, 47% to 80%) for the 36 patients who achieved a cytogenetic response. It should not be overlooked that these are not the best results that can be obtained at a single specialized center, but rather, are the results of a nationwide multicenter study that pioneered the introduction of IFN-α in Italy.

APPENDIX

The active members of the group for this study were: N. Testoni, M.D. Zamagni, G. Martinnelli: University of Bologna; D. Damiani, M. Michieli: University of Udine; A. Zaccaria, Ospedale Ravenna; G. Specchia, V. Liso: University of Bari; M. Lazzarino, C. Bernasconi: University of Pavia; E. Montefusco, G. Alimena, F. Mandelli: University La Sapienza, Roma; P. Leoni, S. Rupoli, M. Candela: University of Ancona; A. Nosari, L. Gargantini: Ospedale Niguarda Ca’Granda, Milano; I. Majolo, S. Tringali: Ospedale Cervello, Palermo; A.M. Liberati, F. Grignani, A. Tabilio, M. Martelli: University of Perugia; F.

<table>
<thead>
<tr>
<th>Table 6. IFN-α Arm. Disease Course and Evolution of the Patients Who Achieved a Cytogenetic Response (Ph neg metaphases ≥ 33%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best Cytogenetic Response (Ph neg metaphases)</td>
</tr>
<tr>
<td>No. of cases</td>
</tr>
<tr>
<td>Allogeneic BMT</td>
</tr>
<tr>
<td>Remaining</td>
</tr>
<tr>
<td>Dead, accelerated or blastic phase</td>
</tr>
<tr>
<td>Dead, chronic phase</td>
</tr>
<tr>
<td>Alive, chronic phase</td>
</tr>
<tr>
<td>Discontinued IFN-α before progression</td>
</tr>
</tbody>
</table>

The proportion of the patients who progressed and died in accelerated or blastic phase was significantly related with the cytogenetic response (P = .005, chi-square test).
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Long-Term Follow-Up of the Italian Trial of Interferon-? Versus Conventional Chemotherapy in Chronic Myeloid Leukemia

The Italian Cooperative Study Group on Chronic Myeloid Leukemia*