Randomized Comparison of Interferon-α With Busulfan and Hydroxyurea in Chronic Myelogenous Leukemia


As curative bone marrow transplantation is available only to a minority of patients with chronic myelogenous leukemia (CML), drug therapy remains of central interest. Several nonrandomized studies have suggested that interferon-alpha (IFN) may prolong survival in CML. In a randomized multicenter study the influence of IFN versus busulfan or hydroxyurea (HU) on survival of Philadelphia-positive (Ph+) CML was examined. A total of 513 Ph+ patients were randomized for treatment as follows: 135 for IFN, 166 for busulfan, and 194 for HU. IFN-treated CML patients have a significant survival advantage over busulfan-treated (P = .008), but not over HU-treated patients (P = .44). The longer survival is due to slower progression to blast crisis. Median survival of IFN-treated patients is 5.5 years (5-year survival, 59%; 95% confidence interval (CI), 48%-70%), of busulfan-treated patients, 3.8 years (5-year survival, 32%; CI, 24%-40%), and of HU-treated patients, 4.7 years (5-year survival, 44%; CI, 36%-53%). Patients who continue on IFN survive longer than those in whom IFN is discontinued before blast crisis (P = .007). Complete hematologic IFN-responders have a survival advantage over partial responders or nonresponders (P = .02). Cytogenetic IFN-responders have no significant survival advantage over nonresponders (P = .2). Patients who attain white blood cell (WBC) counts of 10 × 10^9/L or less have a survival advantage in the IFN (P = .007) and HU (P = .05) groups. Whereas toxicity in the IFN group was considerably higher than in the busulfan or HU groups, long-lasting cytopenias necessitating discontinuation of therapy as observed with busulfan have not been seen with IFN or HU. The problems of conventional prognostic scores (Sokal's score, Score 1) that we observed in IFN-treated patients support the idea that IFN changes the natural course of CML. We conclude that, with regard to survival of CML in the chronic phase, IFN is superior to busulfan and as effective as HU. Whether and to what extent IFN is superior to HU appears to depend, at least in part, on the degree of WBC suppression by HU-therapy and on the risk profile of the patients.

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In contrast with therapeutic progress in treating acute leukemias, survival of chronic myelogenous leukemia (CML) is not much better today than 70 years ago. The principle mode of treatment has been palliative chemotherapy for the past 40 years, mostly with busulfan and hydroxyurea (HU). The randomized comparison of these two agents has been a previous goal of our study group. As curative bone marrow transplantation can be offered only to a minority of patients with chronic myelogenous leukemia (CML), drug therapy remains of special interest. Since its introduction in 1983, a promising substance appeared to be interferon-α (IFN), as it showed not only good efficacy in the chronic phase of CML, but also induced cytogenetic remissions and possibly prolonged survival. The use of IFN seems limited by the high rate of adverse reactions and by the fact that the hematologic response rate was lower with IFN than with HU or busulfan. In 1986, the German CML Study Group, therefore, decided to expand its study and to compare IFN with conventional chemotherapies in a randomized trial with regard to survival, hematologic and cytogenetic responses, toxic effects, course of the disease after discontinuation of IFN, and prognostic parameters at diagnosis and in the course of disease.

MATERIALS AND METHODS

Study design and definitions. The study outline is shown in Fig 1. Checkpoints were as follows: (1) resistance or intolerable adverse effects to the first therapy, with crossover of drugs in the chemotherapy arms or rerandomization to busulfan or HU in the IFN arm; (2) resistance to the second therapy; (3) diagnosis of blast crisis; and (4) death. Blast crisis was diagnosed if blasts and promyelocytes were more than 30% of peripheral white blood cells (WBCs) or more than 50% of nucleated cells in the bone marrow. Complete hematologic remission was defined as normal WBC count with normal differential (WBCs less than 10 × 10^9/L, bands and metamyelocytes ≤5%), normal platelet count, no CML-related symptoms, and normal spleen size (11 to 12 cm maximal diameter or nonpalpable). A partial hematologic remission was defined as a more than 50% decrease of WBC count or a WBC count ≤20 × 10^9/L. Patients with bone marrow transplantations were censored as lost-to-follow up at the time of transplantation.

Patients. All patients with newly diagnosed, not pretreated CML in the chronic phase were registered. They were randomized if they fulfilled at least one of the following six criteria: unexplained fatigue, weight loss of more than 10% in 6 months, fever of more than 38.5°C on 5 consecutive days, organomegaly-related symptoms, leukocytosis of more than 50 × 10^9/L, and/or thrombocytosis of more than 1 × 10^11/L. There was no age limit. According to the study protocol, cytogenetic results were not required for randomization in order to recruit as many patients with the clinical diagnosis of CML as possible. Philadelphia-negative (Ph−) patients or patients with unknown Ph status were excluded later and analyzed separately.

From July 1983 to January 1991, 702 CML patients were regis-
Forty-four busulfan patients were crossed over to HU, and 29 HU patients were crossed over to busulfan.

As of February 28, 1994, 148 patients are still under study (54 IFN patients, 44 busulfan patients, and 50 HU patients). The median observation time of these patients is 4.4 years (4.2 years for IFN, 4.4 years for busulfan, and 4.6 years for HU patients). The data from the busulfan and the HU arms were updated from the original publication on these two arms.

The present report is based on the 513 randomized, Ph- and/or bcr/abl-positive CML patients on an intention-to-treat basis.

Diagnostic investigations. Pretherapeutic diagnostic evaluation consisted of history, physical examination, complete blood cell count including reticulocytes, alkaline leukocyte phosphatase (ALP), serum lactate dehydrogenase (LDH), chromosome and molecular analysis, and bone marrow cytology and histology. Review panels controlled the quality of bone marrow cytology and histology and chromosome analyses.

Follow-up investigations were documented every 6 or 12 months and at disease progression (checkpoints 1, 2, and 3). Investigations at 6-month intervals included inquiry about symptoms (fever, fatigue, side effects of drugs), physical examination (spleen size, extra-medullary manifestations, weight), complete blood cell count including reticulocytes, and LDH. Investigations at 12-month intervals included chromosome analysis and bone marrow cytology and histology. In addition, the annual dosages of the respective drugs were determined. IFN patients were also documented 1 and 2 months after start of therapy and at hematologic remission.

Therapy. IFN was administered in a dosage of $5 \times 10^7$ IU/m²/d, subcutaneously (SC). Treatment goal was to give the maximal tolerable dose with WBC counts of $2 \times 10^9$ to $4 \times 10^9$/L and to reach hematologic remission. The dosage was reduced in the event of intolerable adverse effects and increased (if tolerated) if no therapeutic effect was observed after 12 weeks. IFN was discontinued if therapy resistance was observed (no partial or complete hematologic remission within 4 months) or in the presence of intolerable adverse effects. In this study, IFN 2a (Roferon A; Hoffmann-La Roche, Gensach-Wyhlen, Germany) and 2b (Intron A; Essex, Munich, Germany) were used. Each participating center was allowed to decide which IFN it preferred when the first patient was randomized but had to adhere to this decision for the rest of the study. Ninety patients (67.7%) were treated with IFN 2a, 43 (32.3%) with IFN 2b. Busulfan (0.1 mg/kg/d) was given intermittently (discontinuation at WBC count less than $20 \times 10^9$/L, resumption at $50 \times 10^9$/L) as published previously. HU (40 mg/kg/d adjusted up or down to the nearest pill) was given continuously with the goal of normal WBC counts.
(range, $5 \times 10^9$ to $15 \times 10^9/\text{L}$). The protocol excluded the combination of IFN with chemotherapy during the chronic phase.

**Cytogenetics.** For follow-up analyses at least 25 metaphases were analyzed whenever possible. For evaluation of cytogenetic response, analyses with less than five metaphases were discarded, analyses with 5 to 10 metaphases were used only when supported by follow-up analyses. Complete cytogenetic remission was defined as absence of any Ph+ mitosis. A major cytogenetic response was defined as 1% to 35%, a minor cytogenetic response as 36% to 65%, and a minimal response as 66% to 95% Ph+ positivity.

**Molecular analyses.** The bcr/abl status was determined by the Southern blot and polymerase chain reaction (PCR) techniques according to published procedures. Seves of 24 (29%) molecularly analyzed Ph+ patients and two patients that could not be cytogenetically evaluated were bcr/abl-positive and were included in the analyses of Ph+ patients (five IFN, one busulfan, and three HU patients).

**IFN antibodies.** Sera were screened pretherapeutically and at 6-month intervals for IFN antibodies. The IFN antibodies were determined by a standard enzyme immunoassay (EIA). The results were examined independently by a second laboratory using coded samples. Antibody titers and their neutralizing capacities were determined and correlated with IFN responsiveness of patients.

**Documentation.** After diagnosis and randomization, all data were documented in an initial case record form. During the course of the study, follow-up forms were completed. Whenever a checkpoint was reached, a separate follow-up form was filed. After a patient had died or was lost to follow up, a final documentation form was filed.

**Biostatistics.** Sample size was estimated according to George and Desu. Assuming $\alpha = 0.05$ (two-sided) and $\beta = 0.20$, 518 Ph+ CML patients (130 IFN, 194 each with busulfan and HU) are three independent variables: circulating eosinophils (greater than 2%), peripheral blasts (greater than 0.7959 extramedullary manifestations = 0.064), and neutrophils ($0.0116 \text{age} - 43.4 + 0.0345 \text{platelets}\text{700} = 0.563 + 0.0878 \text{organomegaly related symptoms} = 0.35 + 0.7959 \text{extramedullary manifestations} = 0.064$) - 0.0121. The IFN score uses three independent variables: circulating eosinophils (greater than 2%), extramedullary nonlastic manifestations (mostly of skin and lymph nodes), and circulating erythroblasts (greater than 9). No factor denotes low, one factor intermediate, and two or more factors high-risk patients. All analyses were performed by the Biometric Center with the program package SAS.

The correction for the graphic presentation of time-dependent variables was performed according to Simon and Makuch. A univariate survival analysis and a graphical realization of the effect of time-dependent covariates (eg, cytogenetic response during IFN therapy) using the product limit method of Kaplan-Meier is biased, as patients who eventually become responders must live long enough to achieve a response (time to response), whereas a patient who dies before the first response is counted as a nonresponder. To correct for this bias, Simon and Makuch modified the Kaplan-Meier estimator. The main idea of this procedure is to take into account the time to response. The Mantel-Byar test was used to compare survival times of responders and nonresponders.

Conditional power analysis was performed according to Andersen to compute the probability of the likely future outcome of the trial conditionally on the data already accumulated up to the time of the analysis. The relative risk of HU versus IFN was .69, indicating a benefit for IFN. Assuming a stable relative risk, the conditional power for achieving a statistically significant result ($\alpha = 0.01$) is .42 after two more years of observation. As there are currently only 54 IFN and 50 HU patients still at risk, major deviations of the relative risk = .69 are not very likely in the near future. But even a large variation in relative risk of ±.10 would result in a change of ±.03 in power only, making the probability of a statistically significant result within 2 years very small.

**Ethics.** The protocol followed the Declaration of Helsinki and was approved by the ethics committees of the Universities of Munich and Ulm, Germany. Informed consent was obtained from all patients.

**RESULTS**

**Patient characteristics.** The initial characteristics of the 513 randomized, Ph- and/or bcr/abl-positive CML patients are shown in Table 1. They are distributed evenly in the three randomization groups. The grouping of patients into the three Sokal risk groups is similar in all treatment groups.

Ninety patients (17.5%) received bone marrow transplants (32 in the IFN arm, 25 in the busulfan arm, and 33 in the HU arm) and were censored. A total of 275 patients died, 195 in blast crisis (39 IFN, 83 busulfan, and 73 HU patients) and 35 of other CML-related causes (marasm, infection, or hemorrhage mostly due to cytopenia and bone marrow aplasia, which were in part busulfan-associated). Twenty-five patients died of CML-independent causes. In 20 patients, the cause of death was unknown.

**Survival.** The median interval from diagnosis to randomization and start of therapy was 5 days. Three years after the last patient was randomized, the median survival is 66 months in the IFN group, 45.4 months in the busulfan group, and 56.2 months in the HU group. The 5-year survival rate of IFN-treated patients is 59% [95% confidence interval (CI), 48%-70%]; of busulfan-treated patients, 32% (CI, 24%-40%); and of HU-treated patients, 44% (CI, 36%-53%). The difference between busulfan- and IFN-treated Ph+ patients is significant at $P = .008$ (Fig 2A). The survival advantage of IFN over busulfan is recognized in all Sokal prognostic subgroups. The prolongation of survival by IFN is explained by a prolongation of the chronic phase with a slower progression to blast crisis: at 5 years, 59% of IFN, 31% of busulfan, and 44% of HU patients were alive and free of blast crisis.

The difference between IFN- and HU-treated patients is not significant ($P = .44$; Fig 2B). We analyzed whether a prolongation of observation time for 2 more years could result in a statistically significant result using conditional power calculations (see Materials and Methods). On the basis of these calculations and the number of patients still at risk, we conclude that the current results with regard to survival will not change within 2 more years’ observation time.
poor compliance, or other reasons. We found that these patients have a survival disadvantage (median survival, 52.5 months) as compared with those 61 patients who have continued on IFN according to protocol until blast crisis or are still continuing (median survival not reached at 72 months, *P* = .007; Fig 3). The early time of discontinuation (median, 4.9 months) and the good disease control by subsequent HU or busulfan treatment make subclinical manifestations of accelerated phase as a reason for IFN resistance in the majority of cases unlikely. Patients rerandomized to HU tend to have a somewhat better survival than those rerandomized to busulfan, as 60% of the 30 patients with secondary HU and 46% of the 24 patients with secondary busulfan are still alive, but this difference is not significant.

Hematologic responses. Table 2 shows that the rates for complete and partial hematologic remissions are similar in the three treatment groups. A difference is observed for the no-response rate, which is higher in the IFN than in the chemotherapy groups. As all analyses follow the intention-to-treat principle, patients who have never received randomized therapy due to various reasons are included in the no-response group (six IFN, four busulfan, and four HU patients). Duration of hematologic remissions and times to hematologic response are shown in Table 2. For the median time to response (6.5 months), complete hematologic IFN responders have a significant survival advantage (median survival not reached at 72 months) over partial responders or nonresponders (median survival, 65 months; *P* = .02; Fig 5A). Complete hematologic remissions preceded complete or major cytogenetic responses in all patients.

Cytogenetic responses. Of 133 IFN-treated patients, 84 (63%) had at least two cytogenetic evaluations during the course of treatment and therefore were eligible for analysis of cytogenetic response (Table 2). The average number of cytogenetic analyses of all IFN patients was 2.3; that of IFN patients eligible for cytogenetic evaluation, 3 (= 2 follow-up) analyses. Thus far, 15 patients (18% of those eligible for evaluation, 11.3% of all IFN patients) showed a cytogenetic response, with six of these (7.2% of patients eligible for evaluation) having complete cytogenetic remissions at least
once during the observation period, and five of these presently continuing. Complete cytogenetic remissions were first observed from 6 to 30 months after start of IFN treatment. Two patients have been in complete cytogenetic and/or hematologic remission for more than 2 years after cessation of all therapy. One of these turned bcr/abl-negative by PCR 41 months after the first cytogenetic response. In total, the 15 cytogenetic IFN responders do not show a significant survival advantage over the 69 nonresponders (P = .2; Fig 5B) after correction for the median time to response (Simon-Makuch method\(^{26\text{R}}\)). Thus far, however, none of the patients with complete or major responses has died, suggesting that the patients in this subgroup have a survival advantage. Without the 15 cytogenetic IFN responders, the survival advantage of IFN over busulfan is not significant (P = .08). In contrast with the IFN-treated patients, cytogenetic responses were observed less frequently in the busulfan- and HU-treated patients (Table 2). Whereas the number of cytogenetic analyses is similar to that of the IFN-treated patients (2.1 and 2.2 analyses per busulfan- and HU-treated patient, respectively), cytogenetic responses were observed in only four (3.5%) and six (5%) patients, respectively, with only one complete remission after additional intensive chemotherapy because of blast crisis.

**Dosage requirement.** Drug dosages are shown in Fig 6A. The IFN dosage required to maintain hematologic remission and/or WBC counts of $2 \times 10^9/L$ to $4 \times 10^9/L$, or tolerated, decreased during the course of treatment. During the first 4 weeks the IFN dosage of $4.85 \times 10^6$ IU/m\(^2/d\) corresponded well to the $5 \times 10^6$ IU/m\(^2/d\) outlined in the protocol. During the following 60 months, it declined to about $2 \times 10^6$ IU/m\(^2/d\).
Correlation of survival with WBC counts. We previously proposed\(^1\) that one reason for the survival advantage of HU-treated over busulfan-treated patients might have been better control of the leukemic cell mass as reflected by lower WBC counts in patients treated with HU. Therefore, we also analyzed WBC counts in IFN-treated patients during the first 60 months of treatment and compared them with those in busulfan- and HU-treated patients (Fig 6B). The proportions of patients with normal or subnormal WBC counts were considerably higher in the IFN (33% to 60%) and HU groups (27% to 40%) than in the busulfan group (10% to 24%).

Patients with WBC counts $\leq 10 \times 10^9/L$ at 6 months after start of therapy had longer median survival times than those with WBC counts above $10 \times 10^9/L$ (Fig 7). These differences were significant in the IFN ($P = .007$) and HU groups ($P = .05$), but not in the busulfan group ($P = .07$).

**IFN therapy and treatment termination.** The mean duration of IFN treatment for the 127 patients who received IFN was 1.8 years. The main reasons for termination of IFN treatment were lack (or loss) of recognizable therapeutic efficacy and intolerable adverse reactions (Table 3). IFN-specific problems are reflected by the higher early treatment discontinuation rate (25.2% in the IFN vs 4.3% in the busulfan group and 4.8% in the HU group). In 14 instances (10.5%) the termination or omission of IFN treatment represented protocol violations, as compared with 16 instances (8.6%) in the busulfan arm and 15 instances (7.7%) in the HU arm. At present, 22 IFN, 22 busulfan, and 27 HU patients continue therapy according to protocol (41%, 50%, and 55%, respectively, of patients still in study). The median duration of IFN therapy for the 22 patients still on IFN is 4.2 years (range, 2.1 to 7.3 years). No differences in efficacy have been observed between IFN 2a and IFN 2b.

**IFN antibodies.** IFN antibodies were detected in 25 of 105 patients eligible for evaluation (23.8%), 18 of whom (72%) had neutralizing antibodies. Of these patients, 15 (60% of antibody-positive, 14.3% of patients eligible for evaluation) developed secondary IFN resistance. In comparison, secondary IFN resistance was detected in only 13 of 80 antibody-negative patients (16.3%). The data show that clinically relevant IFN antibodies may occur in 10% to 15% of IFN-treated CML patients. IFN antibodies developed with both IFN preparations.

**Adverse effects.** The adverse reactions to IFN were analyzed by World Health Organization standard grading and mainly consisted of flu-like gastrointestinal, neurologic/psy-
Fig 4. Duration of and time to hematologic response. (A) Duration according to treatment group. The median duration of any hematologic remission (partial or complete) was 3.15 years for busulfan patients, 4.6 years for HU patients, and 4.8 years for IFN patients. (B,C) IFN group only: Distribution of times to (B) first (partial or complete response) and (C) complete response. The median time to first response was approximately 2.5 months for the 110 responders, to complete remission approximately 6.5 months for the 41 complete responders.
IFN VERSUS BUSULFAN OR HYDROXYUREA IN CML

A Complete Hematological Responders vs Partial and Nonresponders

- Responders: n=41
- Nonresponders: n=92
- p=0.02

B Cytogenetic Responders vs Nonresponders

- Responders: n=16
- Nonresponders: n=69
- p=0.2

Fig 5. (A) Survival of complete hematologic IFN-responders vs partial responders and nonresponders (median time to response, 6.5 months). (B) Survival of cytogenetic IFN-responders vs nonresponders (median time to response, 14.7 months). The analyses are corrected for the median times to hematologic or cytogenetic response, respectively, and presented according to the method of Simon and Makuch. Only those patients still alive at 6.5 or 14.7 months, respectively, are shown. Significance was analyzed by the Mantel-Byar test.

Chronic myeloid leukemia (CML) is a malignant disease of hematopoietic stem cells that is characterized by the Philadelphia chromosome (Ph; 9; 22). This chromosomal rearrangement results in the constitutive expression of the BCR-ABL tyrosine kinase, which is thought to be the key event in the biology of CML. The disease is usually divided into three phases: chronic, accelerated, and blast crisis phases. The natural history of CML is characterized by a steady progression from the chronic phase to blast crisis, with a median survival of 10 years from diagnosis in the absence of treatment.

The most important result of the present study is the prolongation of survival by IFN as compared with a standard chemotherapy, mostly with busulfan or hydroxyurea. When Sokal's prognostic score was applied to our busulfan- and hydroxyurea-treated patients (n = 373), prediction of survival of prognostic subgroups was good (P = .0001), in close agreement with that of Sokal's original publication. When it was applied to our IFN-treated patients (n = 129), the prognostic prediction was much poorer (P = .02) with no prognostic separation between low- and intermediate-risk groups. The same was true when we used Score 1. We have, therefore, searched for parameters of prognostic relevance for IFN-treated CML patients and found that our IFN score (see Materials and Methods) is of good prognostic discrimination if applied to our IFN patients (n = 125; P = .003).

DISCUSSION

The most important result of the present study is the prolongation of survival by IFN as compared with a standard...
busulfan regimen. Because our analysis followed the intention-to-treat principle and because six patients randomized for IFN, in fact, never received IFN and for nine other patients IFN therapy was terminated without obvious reason, our survival data may underestimate the true benefit of IFN. The 59% 5-year survival rate and 66-month median survival time of our IFN patients as shown in Fig 2, however, are close to the data reported in other studies for nonrandomized and randomized patients.30-32

A second interesting result is that the median survival after IFN therapy (66 months) is not significantly better than that observed after HU therapy (56-58 months). On the basis of conditional power calculations,29 we conclude that the current results with regard to survival time will not change with a further observation time of 2 years. We cannot rule out that after a prolonged observation period a small proportion of IFN patients, perhaps those with cytogenetic responses, will have a relevant survival advantage over HU as well.

The absence of a survival advantage of IFN over HU in contrast to observations by others33 can be explained by the superior survival of our HU patients (in spite of higher proportions of intermediate- and high-risk patients), which is probably due to stringent treatment criteria with a higher degree of WBC suppression by HU (treatment goal: normal WBC counts, in contrast with less than \(30 \times 10^9/L\))33 and by the observation that intermediate- and high-risk patients, which comprise 73% of our study population (Table 1), do not respond as well to IFN.31 In addition, the protocol strictly required monotherapies in all treatment arms. In the advent
Fig 7. Survival of patients according to WBC counts $\leq 10 \times 10^9/L$ vs above $10 \times 10^9/L$ at 6 months after start of therapy with (a) IFN, (b) HU, and (c) busulfan. The curves are corrected for the time to reach the 6-month interval according to the methods of Anderson et al.\textsuperscript{27} and Simon and Makuch.\textsuperscript{26}
ences are observed between the randomization groups at publication and in other series, excluding the possibility of reasons such as an unequal distribution of prognostic factors. It appears possible that the combination of IFN with HU in a favorable patient group. In addition, we had to examine busulfan and HU, rerandomization for median survival of Sokal’s criteria is lower in our study than in Sokal’s original whether our busulfan group was treated suboptimally. The necessity to rule out that reasons related to this delay are responsible for the survival difference. We compared patients randomized before 1986 with those randomized later. There was no significant difference between the groups either in initial patient characteristics (prognostic factors) or in survival time of these patients. The same difference for survival time between the treatment groups could be observed for both time periods taking into account different sample size and duration of observation time. Therefore, we conclude that the survival difference is the result of the different therapies.

Second, possible reasons for the superiority of IFN to busulfan but not HU have to be considered. Analyzing the superiority of HU to busulfan, we proposed that a decrease of tumor mass and/or a slowing of the granulocyte proliferation rate might decrease the rate of progression to blast crisis. According to this hypothesis, the number of clonal cells of the mitotic pool at risk for transformation is one factor determining progress to blast crisis. If this hypothesis is true, the more efficient reduction of WBC counts, which probably reflect tumor cell mass, by HU might partially account for the survival advantage. As IFN also prolongs survival time and reduces WBC counts more efficiently than busulfan and similar to HU (Fig 6B); and as patients with normal or subnormal WBC counts have a survival advantage in the IFN and HU groups, we suggest that one reason for the superiority of IFN may be the more efficient reduction of WBC counts, possibly by a nonselective growth inhibitory effect.

Another reason may be a more specific effect of IFN on CML. The segregation of the slopes of the busulfan and IFN survival curves starting from year 2 after diagnosis indicates that IFN changes the course of CML. This is further supported by more frequent and better cytogenetic remissions under IFN therapy than under conventional chemotherapy and by differences in prognostic parameters between IFN- and chemotherapy-treated patients as observed in this study and also by others. Therefore, we suggest that the favorable effect of IFN on survival in CML may be due to better reduction of WBC counts similar to that observed after HU therapy, as well as other not yet completely understood mechanism(s) inhibiting the Ph+ cell clone more specifically, such as interference with cytokine production, tumor suppressing activities, and/or cytoplasmic tyrosine kinase(s) and transcription factors.

A further result of this study is information on the course of the disease after discontinuation of IFN. Discontinuation of IFN and the necessity to change therapy appears to be an unfavorable factor as patients who continue on IFN have a

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<th>Table 3. Timing and Causes of Permanent Treatment Termination</th>
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<td><strong>IFN (n = 133)</strong></td>
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<td><strong>Cases with treatment termination (%)</strong></td>
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<td>Abbreviation: BMT, bone marrow transplantation.</td>
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<td>* Patients never received randomized therapy.</td>
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<td>† The remaining BMTs were after prior discontinuation of randomized therapy.</td>
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survival advantage over those who were changed to other drugs. Therefore, it appears possible that continuation of IFN, albeit in low dosage, might confer a survival advantage.

Another result of interest is the recognition of prognostic factors for IFN-treated CML patients both at diagnosis and in the course of the disease. Our IFN score appears to identify CML patients according to their response to IFN therapy and may represent a useful tool for selecting patients upon diagnosis. The usefulness of this score, however, must be confirmed independently in other patient populations.

Hematologic and cytogenetic remissions are time-dependent factors of prognostic interest. Taking the time to remission into account, hematologic remission is of favorable prognostic relevance. Cytogenetic remissions may be of prognostic relevance only if they are complete or major.

The average number of 2.3 cytogenetic analyses per IFN-treated patient corresponds to about one cytogenetic follow-up analysis per patient in 2 years (half the frequency required by the protocol) and reflects the reluctance of most patients and doctors to have bone marrow analyses performed repeatedly. Due to the low frequency of follow-up analyses, the number of cytogenetic responses probably underestimates the true response rate, because transient responses are missed. Nevertheless, six patients with a complete cytogenetic remission at least once during IFN treatment were observed. In this context, the low rate of good-risk patients in this study has to be remembered, as cytogenetic responses are less frequent in intermediate- and high-risk patients.

The number of cytogenetic responses has been increasing with continuing cytogenetic analyses, and we expect to obtain, in due time and in consideration of the risk profile of our patients, a similar cytogenetic response rate to others. If special interest is the elimination of the Ph clone in one of our patients 41 months after the first cytogenetic response, as demonstrated by bcr/abl negativity in PCR. PCR negativity in bone marrow transplant recipients is considered indicative of Ph eradication and cure and has been reported in IFN-treated patients only in very few cases after prolonged observation times. It remains to be seen how frequently such an event occurs if more IFN-treated complete cytogenetic responders have been observed long enough. As the probability of the detection of cytogenetic remissions increases with duration of survival, it cannot be ruled out that cytogenetic responders represent an a priori subgroup of CML patients of particularly good prognosis.

A relevant aspect of this study is the application of IFN therapy to an unselected group of CML patients. Most reports published thus far comprise patients preselected by age, mobility, general fitness, or other parameters. In this study, all eligible patients were randomized. Our oldest patient was 85 years old. IFN-related benefits and problems as reported in this study, therefore, are probably representative for CML patients in general hematologic practice.

Several problems with IFN therapy have been encountered and should caution the deliberate use of IFN in all CML patients. First, the rate of adverse drug effects is by far the highest among available drug treatments. The adverse effects in our patients correspond well to observations by others. We cannot state that IFN is tolerated better in younger patients, because IFN had to be terminated because of intolerable adverse effects in young patients as well (data not shown). The average age at diagnosis of the 22 patients still continuing on IFN (47.8 years) is not lower than that of the total IFN group (47.4 years). Severe late toxicity has not been reported in our patients thus far, but in view of observations by others, the observation period in our patients may not be long enough for definite analysis. Long-lasting cytopenias necessitating discontinuation of therapy as observed with busulfan have not been seen either with IFN or with HU.

A second problem with IFN therapy is the need for regular injections, which requires considerable patient compliance and fitness. Particularly in older patients, the necessity of regular injections caused problems.

Third, the considerable costs of IFN have to be considered. Whereas the costs per day of HU or busulfan range from $1.00 to $3.00 per day, the initial treatment costs of IFN amount to about $100.00 per day. Although the requirement of IFN in our study dropped by about 60% during the first 4 years of treatment, the costs of IFN therapy remain about 50-fold greater than that of conventional chemotherapy.

The appearance of high-titered, neutralizing IFN antibodies followed by IFN resistance indicates that secondary IFN resistance after initial responsiveness to IFN may be due to IFN antibodies. According to the IFN manufacturers, antigenicity of IFN may be influenced by the preparation procedure and the galenic of IFN that was changed in the meantime. IFN resistance due to IFN antibodies did not influence responsiveness to subsequent chemotherapy.

Protocol violations with regard to randomized therapy were more frequent in the IFN group than in the busulfan and HU groups (10.5% vs. 8.6% vs. 7.7%, respectively; Table 3), but the difference is not significant. In this context, one must consider that our IFN arm was started in June 1986, when little experience was available on IFN treatment, and most physicians involved had no prior experience with IFN therapy. This may explain why in a number of cases the physicians decided to discontinue IFN treatment against the protocol and earlier than they would now.

In conclusion, it appears that, in the future, first-line therapy for CML will include IFN, HU, and allogeneic bone marrow transplantation. Complete and major cytogenetic IFN responders may have a survival advantage over HUtreated patients as well. Tolerability, however, is lowest in the IFN treatment group and, thus, may be the quality of life. The optimal choice for the individual patient, therefore, remains to be determined and may be facilitated by prognostic subgrouping.

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APPENDIX

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