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, 186 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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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 Eleven additional IFN patients received free therapy, because reran-
terred, representing about 10% of the estimated number of CML cases in West Germany over a 7.5-year period. The IFN arm was started 2.9 years later in June 1986. For the following reasons, 80 patients did not fulfill the inclusion criteria: no chronic phase (n = 5); no treatment required and not treated during the recruitment period (n = 10); pretreatment with cytostatics, IFN, or splenic irradiation (n = 6); lack of informed consent (patients declined to have randomized therapy or their data included in a data bank, n = 38); second neoplasia before registration (n = 10); and other reasons that made the feasibility of therapy according to protocol a priori unlikely (patients on visit from overseas, unsurmountable language problems, psychiatric conditions; n = 11). A total of 622 patients were random-
ized. Two patients had neither initial nor follow-up documentations (1 randomization error, 1 unauthorized randomization). Of the 622 randomized patients, 620 were eligible for evaluation. In 16 patients the diagnosis of CML was retracted by the physicians and/or rejected by the Central Review Committee (by treatment group: 4 IFN, 7 busulfan, and 5 HU patients). Of these patients, 10 had cytogenetic analyses that were all Ph-. Of the 604 CML patients that were randomized and eligible for evaluation, 34 (5%) could not be evaluated cytogenetically or molecularly, either because of death before a successful analysis (n = 18) or due to technical and/or compliance problems (n = 16). Of the 570 patients with known Ph status, 57 (10%) were bcr/abl- and/or Ph-negative. Of the 513 Ph- and/or bcr/abl-positive patients, 133 had been randomized to receive IFN, 186 busulfan, and 194 HU. The lower number of IFN patients is due to the later start of randomization for this treatment group. Eight randomized Ph+ patients had exclusion criteria (3 IFN, 2 busulfan, and 3 HU patients); 5 patients were not in chronic phase (accelerated or blastic phase: 2 IFN, 1 busulfan, and 2 HU patients), 1 patient had contraindications for IFN treatment, 1 patient declined to receive HU, and 1 patient had organic mental syndrome. These patients were included in the intention-to-treat analysis. The median observa-
tion time for the 513 patients is 3.0 years (range, 0.1-9.8; 2.9 for IFN, 2.8 for busulfan, and 3.4 for HU patients).

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 anal-
lysis, and bone marrow cytology and histology. Review panels con-
trolled 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 includ-
ing 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 $5 \times 10^8$ IU/m^2 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 therape-
getic 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, Gelsenzh-Wychlen, Germany) and 2b (Intron A; Essex, Munich, Ger-
many) 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. 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.

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Survival was analyzed with the Kaplan-Meier estimator and logrank test.20 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.

**Survival after discontinuation of IFN.** In an attempt to determine what happens to patients after IFN is discontinued due to various reasons, we analyzed those 65 patients in whom IFN was discontinued before blast crisis due to IFN resistance (including because of IFN antibodies), toxicity,
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 randomized to HU tend to have a somewhat better survival than those randomized 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 Fig 4. After correction 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 (\( \approx 2 \) follow-up) analyses. Thus, 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

<table>
<thead>
<tr>
<th>Table 1. Initial Patient Characteristics (Mean ± SD)</th>
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<tr>
<td>Treatment of Ph+ Patients* (n = 513)</td>
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<tr>
<td><strong>Age (yr)/median (range)</strong></td>
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<tr>
<td>IFN (n = 133)</td>
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<tr>
<td>47.4 ± 14.9/47 (18-85)</td>
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<tr>
<td>Bu (n = 188)</td>
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<tr>
<td>43.5 ± 15.4/49 (17-84)</td>
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<td>HU (n = 194)</td>
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<tr>
<td>46.9 ± 15.3/47 (15-84)</td>
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<tr>
<td><strong>Sex (% male)</strong></td>
</tr>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>66.2</td>
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<tr>
<td>Bu</td>
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<tr>
<td>63.8</td>
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<tr>
<td>HU</td>
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<tr>
<td>50.5</td>
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<tr>
<td><strong>Symptoms due to organomegaly (%)</strong></td>
</tr>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>89.6</td>
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<tr>
<td>Bu</td>
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<td>86.4</td>
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<tr>
<td>HU</td>
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<tr>
<td>66.2</td>
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<tr>
<td><strong>Liver size (cm in MCL)</strong></td>
</tr>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>12.7 ± 2.3</td>
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<tr>
<td>Bu</td>
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<tr>
<td>12.3 ± 2.4</td>
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<tr>
<td>HU</td>
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<tr>
<td>12.6 ± 2.7</td>
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<tr>
<td><strong>Spleen size (cm below costal margin)</strong></td>
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<tr>
<td>IFN</td>
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<tr>
<td>505 ± 368/412 (94-2,400)</td>
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<tr>
<td>Bu</td>
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<tr>
<td>480 ± 369/309 (52-3,400)</td>
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<tr>
<td>HU</td>
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<tr>
<td>506 ± 364/410 (10-2,658)</td>
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<tr>
<td><strong>Karnofsky index (%)</strong></td>
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<tr>
<td>IFN</td>
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<tr>
<td>89.6 ± 11.3</td>
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<tr>
<td>Bu</td>
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<tr>
<td>87.6 ± 13</td>
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<tr>
<td>HU</td>
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<tr>
<td>89.3 ± 10</td>
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<tr>
<td><strong>Splenomegaly (%)</strong></td>
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<td>IFN</td>
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<tr>
<td>4.9</td>
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<tr>
<td>Bu</td>
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<td>5.2</td>
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<td>HU</td>
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<tr>
<td>4.6</td>
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<tr>
<td><strong>LDH (U/L, normal &lt;240)/median (range)</strong></td>
</tr>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>804 ± 364/735 (140-3,048)</td>
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<tr>
<td>Bu</td>
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<tr>
<td>751 ± 472/682 (166-3,570)</td>
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<tr>
<td>HU</td>
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<tr>
<td>741 ± 346/673 (161-2,471)</td>
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<tr>
<td><strong>No. of cytogenetic responses</strong></td>
</tr>
<tr>
<td>IFN</td>
</tr>
<tr>
<td>3.4 ± 0.7/2.0 (0.4-35)</td>
</tr>
<tr>
<td>Bu</td>
</tr>
<tr>
<td>2.9 ± 3.4/2.0 (0.1-19)</td>
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<tr>
<td>HU</td>
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<tr>
<td>3.2 ± 4.1/2.0 (0-27)</td>
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<tr>
<td><strong>Sokal's risk groups</strong></td>
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<tr>
<td>Low (%)</td>
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<tr>
<td>27.1</td>
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<tr>
<td>Intermediate (%)</td>
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<tr>
<td>35.3</td>
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<tr>
<td>High (%)</td>
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<td>37.6</td>
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Unless noted, all features recorded in 96% to 100% of patients. Abbreviations: Bu, busulfan; MCL, medioclavicular line; LDH, lactate dehydrogenase; ALP, alkaline leukocyte phosphatase; BM, bone marrow.

* Seven Ph-negative, bcr/abl-positive cases and two Ph-undetermined, bcr/abl-positive cases included.

† Features recorded in 93% (liver size), 87% (ALP), and 83% (quantitative BM cytology) of patients.
A IFN vs. Busulfan

B IFN vs. Hydroxyurea

Fig 2. Survival of Ph- or bcr/abl-positive CML patients: (A) IFN vs. busulfan, (B) IFN vs. HU.

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/m²/d corresponded well to the $5 \times 10^6$ IU/m²/d outlined in the protocol. During the following 60 months, it declined to about $2 \times 10^6$ IU/m²/d.
Correlation of survival with WBC counts. We previously proposed 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 ≤10 × 10^9/L at 6 months after start of therapy had longer median survival times than those with WBC counts above 10 × 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.
chiatric, and dermatologic symptoms. These reactions were responsible for discontinuation of IFN in 24 patients (18%) and represented the major problem with IFN therapy. All adverse reactions, however, were reversible after cessation of therapy or regressed in the course of continued IFN therapy. Baseline levels of adverse effects were reached 12 to 30 months after start of IFN therapy.

Adverse reactions to busulfan and HU were less frequent and mainly consisted of cytopenias and bone marrow aplasia (busulfan only), minor gastrointestinal (nausea) or dermatologic problems (skin atrophy), and drug fever (HU only). They were responsible for discontinuation of busulfan in 19 patients (10.2%; mainly cytopenias) and of HU in one patient (0.5%; drug fever).

Prognostic evaluation. Cytogenetic remissions and survival analysis indicate that IFN alters the natural course of CML. This consideration is also supported by a change of prognostic parameters. All previous prognostic evaluations have involved patients who were treated by 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.

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\(^3\)). On the basis of conditional power calculations,\(^9\) 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 others\(^3\) 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 \(30 \times 10^9/\text{L}\))\(^9\) 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.\(^3\) In addition, the protocol strictly required monotherapies in all treatment arms. In the advent
Fig 7. Survival of patients according to WBC counts ≤10 × 10^9/L v above 10 × 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 al²⁷ and Simon and Makuch.²⁸
of therapy resistance or intolerability, the randomized therapy was changed to an alternative therapy (crossover for busulfan and HU, rerandomization for IFN patients). It appears possible that the combination of IFN with HU in patients with insufficient response to IFN alone might confer a survival advantage. In 1991, we opened a second study to analyze this point.

The superiority of IFN to busulfan, but not to HU, raises several therapeutic and biologic questions. First, we had to rule out that the survival advantage of IFN is due to technical reasons such as an unequal distribution of prognostic factors. As can be seen in Table 1, no statistically significant differences are observed between the randomization groups at baseline. The proportion of low-risk patients according to Sokal’s criteria is lower in our study than in Sokal’s original publication and in other series, excluding the possibility that our data are due to the selection of a prognostically favorable patient group. In addition, we had to examine whether our busulfan group was treated suboptimally. The median survival of 45.4 months, however, compares well with numbers reported by Canellos et al. As the IFN arm started 2.9 years after the chemotherapy arms and a superiority of IFN patients for survival time was observed, it was necessary 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

### Table 3. Timing and Causes of Permanent Treatment Termination

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<tr>
<th>Cases with treatment termination (%)</th>
<th>Total</th>
<th>Protocol Violation</th>
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<tr>
<td>IFN (n = 133)</td>
<td>111 (83.5)</td>
<td>14 (10.5)</td>
<td>164 (80.1)</td>
<td>16 (8.6)</td>
<td>167 (86.1)</td>
<td>15 (7.7)</td>
<td>442 (86.2)</td>
<td>45 (8.8)</td>
</tr>
<tr>
<td>Time of termination (%)</td>
<td>Never received</td>
<td>randomized therapy</td>
<td>6 (5.4)</td>
<td>5</td>
<td>4 (2.4)</td>
<td>4</td>
<td>4 (2.4)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Early (&lt;3 mo)</td>
<td>28 (25.2)</td>
<td>2</td>
<td>7 (4.3)</td>
<td>1</td>
<td>8 (4.8)</td>
<td>3</td>
<td>43 (9.7)</td>
</tr>
<tr>
<td></td>
<td>Intermediate (3-24 mo)</td>
<td>57 (51.4)</td>
<td>4</td>
<td>77 (47.0)</td>
<td>9</td>
<td>78 (46.7)</td>
<td>8</td>
<td>212 (48.0)</td>
</tr>
<tr>
<td></td>
<td>Late (&gt;24 mo)</td>
<td>20 (18.0)</td>
<td>3</td>
<td>76 (46.3)</td>
<td>2</td>
<td>77 (46.1)</td>
<td>0</td>
<td>173 (39.1)</td>
</tr>
<tr>
<td>Causes of termination (%)</td>
<td>Therapy resistance</td>
<td>55 (41.4)</td>
<td>4 (4)*</td>
<td>(15 IFN-AB pos.)</td>
<td>110 (59.1)</td>
<td>10 (2)*</td>
<td>128 (66.0)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Adverse effects</td>
<td>24 (18.0)</td>
<td>19 (10.2)</td>
<td>1 (0.5)</td>
<td>33 (6.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMT</td>
<td>20 (15.0)*</td>
<td>21 (11.3)*</td>
<td>26 (13.4)*</td>
<td>67 (13.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient rejection</td>
<td>10 (7.5)</td>
<td>12 (6.5)</td>
<td>12 (2)*</td>
<td>11 (5.7)</td>
<td>11 (4)*</td>
<td>33 (6.4)</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Second neoplasia</td>
<td>2 (1)*</td>
<td>2 (0.1)</td>
<td>1 (0.5)</td>
<td>5 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are as of February 28, 1994.

Abbreviation: BMT, bone marrow transplantation.

* Patients never received randomized therapy.

† The remaining BMTs were after prior discontinuation of randomized therapy.
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.31 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.31-33,39 Of 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.40,41 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.9-12,44,45 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 HU-treated patients as well. Tolerability, however, is lowest in the IFN treatment group and, thus, so 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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