To assess the influence of pretransplant cytoreductive therapy with special reference to interferon-α (IFN-α) treatment and/or busulfan therapy between 1 and 129 months (median, 15 months) pretransplant. Using the categorized treatment duration with each pretransplant cytoreductive agent as a measure for individual patient exposure to each agent, prolonged (>12 months) IFN-α administration was identified as the sole significant pretransplant therapy-related predictor of transplant outcome by proportional hazards regression analysis. The adjusted risk ratio (RR) of transplant-related mortality (TRM) was 2.5-fold higher (95% confidence limits [95% CL], 1.4 to 4.5; \( P < .004 \)) compared with other pretransplant therapy and this was mainly attributable to a 3.1-fold higher RR (95% CL, 1.4 to 6.4; \( P < .005 \)) of fatal posttransplant infections after prolonged IFN-α treatment pretransplant. Marrow graft failure developed exclusively among 7 of 30 patients (23%) with donors other than HLA-identical family members and was further restricted to patients who had been previously exposed to IFN-α. The probability of graft failure was 49% ± 28% in 17 patients pretreated with IFN-α compared with 0% for the other 13 patients with mismatched family or unrelated donors (\( P < .008 \)). In addition, a significant delay in neutrophil and platelet count reconstitution was observed among patients with donors other than HLA-identical family members after pretransplant IFN-α exposure. No influence of pretransplant cytoreductive therapy on either acute and chronic graft-versus-host disease or leukemic relapse was detected in this study. As a consequence of its adverse effect on TRM, prolonged pretransplant IFN-α treatment was independently associated with a 2.5-fold lower likelihood (95% CL, 1.4 to 4.5; \( P < .003 \)) of 5-year overall survival and with a 2.3-fold lower likelihood (95% CL, 1.3 to 4.2; \( P < .004 \)) of 5-year disease-free survival posttransplant after adjustment for other significant prognostic factors in multivariate analysis. In conclusion, the present study strongly suggests that prolonged pretransplant IFN-α administration in patients with chronic-phase \( Ph^1 \)-positive CML may be associated with an increased risk of fatal transplant-related complications and an inferior outcome after allogeneic BMT. Future analyses on transplant results in chronic-phase CML patients should carefully evaluate the impact of treatment duration or, if applicable, of the cumulative doses of IFN-α and other cytoreductive agents administered pretransplant.

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these factors include certain patient and donor characteristics, such as patient and/or donor age, gender and histocompatibility matching, the type of immunopharmaceutical prophylaxis to prevent acute graft-versus-host disease (GVHD), and the time interval from diagnosis to transplant. Recently, a retrospective analysis from the International Bone Marrow Transplant Registry (IBMTR) showed that pretransplant cytoreductive therapy with busulfan adversely affects transplant outcome as compared to hydroxyurea.21 Biologic effects of IFN-α include inhibition of hemopoietic cell and marrow fibroblasts growth, enhanced expression of major histocompatibility antigens, and an increase in the activity of lymphocytes mediating antigen-specific and non-specific cytotoxicity.24-28 These and other biologic features of IFN-α may interfere with different steps of the marrow transplant procedure. One recent retrospective univariate analysis from the M.D. Anderson Cancer Center did not find an effect of prior IFN-α on transplant outcome in CML patients, who received transplants from HLA-identical family donors.29 In considering the rapidly growing number of transplant candidates, who have been exposed to IFN-α, further and more comprehensive studies are required to determine whether IFN-α may affect transplant outcome. This report focuses on the influence of pretransplant cytoreductive agents with special reference to IFN-α therapy on major endpoints of allogeneic BMT in 133 consecutive patients with chronic-phase Ph'-chromosome-positive CML in a single referral-based marrow transplant center. Multivariate regression technique including well-defined prognostic factors for these endpoints was used in the present analysis to determine whether the type or duration of pretransplant therapy may independently influence transplant outcome.

**PATIENTS AND METHODS**

**Patients.** Between May 1982 and November 1993, a total of 135 consecutive patients with Ph'-positive CML in first chronic phase underwent allogeneic BMT in the marrow transplant program at the University Hospital of Essen after written informed consent had been obtained for all aspects of the procedure. Candidate patients were offered marrow transplantation if a mutual medical consent regarding the transplant indication had been reached between the referring and transplant physicians. Busulfan and hydroxyurea therapy pretransplant was generally performed using conventional dosages of these agents in the study population. The majority of patients pretreated by IFN-α had participated in different trials of recombinant human IFN-α2B performed at the University Hospital of Essen.30,31 In none of these patients had a durable major cytogenetic remission been achieved before BMT. Patients were classified as being preexposed to IFN-α if they had received 3 to 7 weekly IFN-α applications for a minimum of 4 consecutive weeks before BMT. At admission to transplant, the diagnosis and disease stage were verified by hematologic and cytogenetic examinations in all patients. Two patients in whom a busulfan-based preparative regimen was performed were excluded from the analysis.

**Marrow transplant characteristics.** The remaining eligible 133 patients received a combined radiochemotherapeutic preparative regimen consisting of single-dose or fractionated total body irradiation (TBI) preceeded or followed by 60 mg/kg intravenous (IV) cyclophosphamide on each of 2 consecutive days. Details of the different TBI regimens used in this study have been previously described.32 In short, 18 patients received single-dose TBI at a dose of 8.6 Gy delivered either by a linear accelerator (13 patients) or by a telecobalt source (5 patients). One hundred fifteen patients were treated with a fractionated TBI regimen consisting of one daily fraction of 2.5 Gy on 4 consecutive days to a cumulative dose of 10 Gy. In patients treated with this regimen, shielding of the lungs was performed to reduce the lung dose to 8 Gy. Fractionated TBI was delivered by a linear accelerator in 9 patients and by a telecobalt source in 106 patients.

One hundred three patients received marrow grafts from HLA-A,B,DR genotypically or phenotypically identical family donors. In 15 patients, the family marrow donor had a single serologic HLA-class I or II disparity with regard to GVHD. Fifteen patients received transplants from unrelated marrow donors who were HLA-A,B,DR-phenotypically matched in 14 patients and 1-antigen mismatched in 1 patient.

To prevent acute GVHD, 30 patients received single-agent IV methotrexate (MTX) according to the standard Seattle regimen.33 In 83 patients, short-course MTX in conjunction with continuous IV cyclosporine (CsA) has been used, as previously published.34 Fourteen patients were treated with a combination of a monoclonal antibody directed to a constant epitope of the αβ-T-cell receptor and CsA. The remaining 6 patients received continuous IV CsA only.

The assessment and grading of acute and chronic GVHD followed the commonly accepted clinical criteria as proposed by Glucksberg et al.35 and Thomas et al.36 Supportive care measures remained nearly identical during the time period covered by this analysis and have been reported in detail.37

**Statistical analysis.** Evaluation of potential prognostic disease features at diagnosis and of previous cytoreductive therapy was based on medical chart review. Sokal’s score was calculated from the published algorithm using patient sex, spleen size, the percentage of circulating blasts, platelet count, and hematocrit as variables.38 As a measure for the exposure to pretransplant cytoreductive agents, the duration of treatment with a given agent was determined. In patients who had received intermittent cytoreductive therapy, the treatment time intervals for each agent were added. Univariate analyses involving the treatment duration with pretransplant cytoreductive agents were performed on a two-level classification comparing patients who were treated for up to 12 months or for a longer time period with these agents. Clinical endpoints in univariate analysis were the times to reach absolute neutrophil counts greater than 0.5 × 10^9/L and greater than 1.0 × 10^9/L, self-sustaining platelet counts greater than 20.0 × 10^9/L and greater than 50.0 × 10^9/L, the times to acute and chronic GVHD, leukemic recurrence, treatment-related death, infectious and noninfectious death, DFS, and survival. Normal graft function was assumed if patients achieved transplant-derived absolute neutrophil counts greater than 0.5 × 10^9/L and self-sustaining platelet counts greater than 20.0 × 10^9/L up to 30 days after BMT. Primary graft failure was diagnosed if these thresholds were not reached until day 30 together with severe hypocellularity on marrow biopsies taken at that time. Secondary graft failure was assumed if cell counts permanently declined below these thresholds after day 30 and severe marrow hypocellularity developed without evidence for infectious causes (especially cytomegalovirus (CMV) disease). Evaluations on acute GVHD included patients who survived at least 14 days after BMT and were performed on a two-level classification of the clinical grades of severity (patients with grades 0-I versus those with grades II-IV). Patients with primary graft failure were excluded from these evaluations. Analyses involving chronic GVHD were based on patients who survived longer than 70 days after BMT. Diagnosis of leukemic recurrence followed hematologic and cytogenetic criteria. Cytogenetic remissions after BMT were defined as less than 30% Ph'-positive marrow metaphases (with a minimum of 20 metaphases analyzed) on repeated cytoge-
nectic analyses. Patients who did not exceed this threshold on repeated examinations and did not progress to hematologic relapse were thus regarded as relapse-free survivors. Transplant-related mortality (TRM) was defined as death from any cause other than relapse after BMT. Patients were regarded as disease-free survivors if they survived in continuous hematologic and cytogenetic remission after BMT.

Comparisons between continuous covariates were performed by the two-tailed Wilcoxon rank-score test across strata. Differences between discrete covariates were compared by the two-tailed Fisher's exact test. Time to event estimates (± standard errors) were calculated by the product-limit method with right-censoring of subjects at the last time point at which they were at risk for a given event. For testing the homogeneity of time to event distributions across strata, the log-rank test was used. Features involved in all univariate and multivariate analyses were Sokal's score, disease duration before transplant, type and duration of each previous cytoreductive therapy, overall treatment duration, patient/donor age (per decade) and gender match, graft source (HLA-A,B,DR-identical family donors vs other donors), graft size, female donor sensitization status for male recipients, patient and donor CMV serology pretransplant, spleen status and myelofibrosis pretransplant, type of conditioning regimen, prophylaxis to prevent acute GVHD, and time interval of transplant (1982 to 1985, 1986 to 1989, or 1990 to 1993).

The independence of covariates with significance levels less than 5% in univariate analysis was tested by proportional hazards general linear model (PHGLM) analyses using forward and backward selection processes. After termination of model building, adjusted covariates with significance levels less than 5% in the models were only regarded significant if they were included by the forward selection process and were likewise not removed by the backward selection process. To account for interactions of GVHD with TRM, leukemic relapse, DFS, and survival, the duration to the development of acute or chronic GVHD was defined by a time-dependent covariate function in PHGLM-analyses examining these endpoints. Other covariates representing time intervals were analyzed on a two-level classification in multivariate analysis (≤12 months and >12 months). Maximal partial-likelihood estimates and estimates of conditional risk ratios (RR) and their 95% confidence limits (95% CI) were derived from regression analyses after adjustment for all significant covariates in the models. Demographic and treatment characteristics of the study population are summarized in Table 1.

RESULTS

Engraftment. All 133 patients survived for at least 20 days after BMT and were thus evaluable for engraftment. Primary or secondary marrow graft failure occurred exclusively among 7 of 30 patients (23%) with donors other than HLA-identical family members and was further restricted to patients who had been previously exposed to IFN-α. The probability of graft failure was 49% ± 28% in 17 patients pretreated with IFN-α, compared with 0% for the other 13 patients with mismatched family or unrelated donors (P < .008). In all but 1 of the patients who developed marrow graft failure in this study, the duration of pretransplant IFN-α administration exceeded 12 months.

The kinetics of neutrophil and platelet count reconstitution according to pretransplant therapy and graft source is depicted in Fig 1. When analyzing the entire study population, no differences in the duration to attain the respective endpoints of reconstitution were detected between patients with or without IFN-α pretransplant (data not shown). This was also true among patients with HLA-identical family donors (Fig 1). However, in patients with donors other than HLA-identical family members, the time to reaching these endpoints was significantly delayed for patients pretreated by IFN-α compared with those who had not been previously exposed to this agent (Fig 1).

Acute GVHD. Forty-five of 129 evaluable patients (35%) developed grades II-IV acute GVHD. No significant influence of pretransplant therapy on the probabilities of grades II-IV acute GVHD was detectable in this study (34% ± 14% for IFN-α-treated patients vs 37% ± 10% for the other patient subset). Multivariate analysis identified three
Fig 1. Product-limit estimates of the time to reach the endpoints of hematologic reconstitution from the day of transplantation (day 0). (A) Absolute neutrophil counts greater than 0.5 x 10^9/L. (B) Absolute neutrophil counts greater than 1.0 x 10^9/L. (C) Self-sustaining platelet counts greater than 20.0 x 10^9/L. (D) Self-sustaining platelet counts greater than 50.0 x 10^9/L. Patients were categorized according to pretransplant IFN-α administration and graft source (1: no IFN-α, HLA-identical family donors; 2: IFN-α, HLA-identical family donors; 3: no IFN-α, mismatched family or unrelated donors; 4: IFN-α, mismatched family or unrelated donors). The indicated significances were derived from testing the differences in the time to events distribution functions between patients in groups 3 and 4 by the log-rank test. No significant differences were detected between patients in groups 1 and 2.

independent prognostic factors for the development of grades II-IV acute GVHD in the following order of significance: marrow donors other than HLA-identical family members compared with HLA-identical family donors (RR, 2.6; P < .009), female marrow donors for male recipients compared with other gender combinations (RR, 2.0; P < .02), and prophylaxis of acute GVHD other than the combination of sMTX and CsA compared with sMTX and CsA (RR, 2.0; P = .03).

Chronic GVHD. One hundred six of the 133 patients (80%) survived more than 70 days with functioning grafts and were therefore considered evaluable for chronic GVHD. With a median onset on day 176 (range, 73 to 530 days) posttransplant, 61 of these 106 patients (58%) developed chronic GVHD. The probabilities of chronic GVHD were not significantly different between patients with or without IFN-α pretransplant (72% ± 16% v 55% ± 12%). In multivariate analysis, only grades II-IV acute GVHD predicted the development of chronic GVHD (RR, 4.3; P < .0001).

Transplant-related mortality. Fifty-five of the 133 patients (41%) have died from causes related to the transplant procedure. The primary causes of transplant-related death categorized according to pretransplant IFN-α exposure are summarized in Table 2. The influence of treatment duration on TRM was further analyzed according to categorized causes of death and to posttransplant time periods (Table 3). The overall probability of TRM was significantly higher for the 27 patients treated with IFN-α for more than 12 months...
as compared with the 23 patients who received IFN-α for shorter time periods (P < .009; Table 3). In contrast, no significant influence of treatment duration on TRM was detectable in the 83 patients exclusively pretreated by hydroxyurea and/or busulfan. Although the probabilities of fatal infectious complications within the first 120 days after BMT were nearly identical for the four patient subgroups, patients pretreated with IFN-α for more than 12 months had a significantly higher probability of fatal infections in the later posttransplant period compared with those who were treated for shorter time periods with IFN-α (P < .03; Table 3). As described for the overall probability of TRM, the treatment duration with hydroxyurea and/or busulfan did not significantly affect the probabilities of either infectious or noninfectious TRM during the different posttransplant time periods (Table 3). The probability of TRM in the 103 patients with HLA-identical family donors appeared lower as opposed to this estimate in patients with alternative donors (38% ± 5% v 53% ± 9%), but this difference was not significant. Including the entire study population in regression model building, three factors remained significant with regard to TRM after adjustment for the other significant prognostic covariates: acute GVHD, prophylaxis of acute GVHD, and the duration of IFN-α treatment (Table 4). Multivariate analysis on fatal posttransplant infections as an endpoint identified the same three independent prognostic factors in the following order of significance: acute GVHD (RR, 4.7; P < .0001), duration of IFN-α treatment (RR, 3.1; P < .005), and prophylaxis of acute GVHD (RR, 2.4; P < .02).

Relapse. The projected 5-year relapse estimate was 17% ± 10% for the entire study population. Ten of the 11 relapses (91%) in this study occurred within the first 4 years, whereas a single patient relapsed at 6 years posttransplant. None of the prognostic covariates included in the analysis affected the probability of relapse. The 5-year relapse estimates were 23% ± 11% for patients pretreated by IFN-α and 15% ± 12% for patients who only received hydroxyurea and/or busulfan pretransplant.

DFS. With a median follow-up of 59 months (range, 14 to 148 months), 67 of the 133 patients (50%) remain alive and in continuous remission, resulting in a DFS estimate of 49% ± 5% at 5 years posttransplant. The 5-year DFS estimates were not significantly different between patients with or without pretransplant IFN-α (42% ± 8 v 53% ± 6%). When considering the duration of pretransplant cytoreductive therapy, the 5-year DFS estimate declined from 59% ± 11% for patients with IFN-α for ≤12 months to 26% ± 11% for those with IFN-α for more than 2 months (P < .02). In contrast, no significant influence of treatment duration on DFS was detectable in patients who had not been previously exposed to IFN-α; their 5-year DFS estimate was 48% ± 7% if treatment duration was ≤12 months and 59% ± 9% if therapy exceeded 12 months posttransplant. The adverse influence of prolonged pretransplant IFN-α administration on DFS resulted from a similar reduction of these estimates in the 33 patients with HLA-identical family donors (64% ± 12% v 33% ± 14%; P = .05) and in the 17 patients with alternative donors (50% ± 25% v 23% ± 12%). When analyzing the entire study population, patients with marrow donors other than HLA-identical family members achieved a 5-year DFS estimate comparable to that of patients with HLA-identical family donors (46% ± 9% v 50% ± 5%; Table 4).

Table 3. Probabilities (± SE) of TRM From Infectious and Noninfectious Causes Within and After 120 Days Posttransplant According to Treatment Group and Duration of Pretransplant Therapy

<table>
<thead>
<tr>
<th>Treatment Duration and Prior Therapy</th>
<th>Probability of TRM Within 120 d (%)</th>
<th>Probability of TRM After 120 d (%)</th>
<th>Overall Probability of TRM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infectious</td>
<td>Noninfectious</td>
<td>Subtotal</td>
</tr>
<tr>
<td>≤12, - IFN-α</td>
<td>47</td>
<td>14 ± 5</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>&gt;12, - IFN-α</td>
<td>36</td>
<td>15 ± 6</td>
<td>6 ± 4</td>
</tr>
<tr>
<td>≤12, + IFN-α</td>
<td>23</td>
<td>17 ± 8</td>
<td>0</td>
</tr>
<tr>
<td>&gt;12, + IFN-α</td>
<td>27</td>
<td>19 ± 9</td>
<td>22 ± 8</td>
</tr>
</tbody>
</table>

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this estimate was found between patients with or without IFN-α pretransplant (48% ± 7% vs 59% ± 5%). However, in patients exposed to IFN-α for more than 12 months, the 5-year survival estimate was significantly reduced as opposed to patients with a shorter IFN-α exposure (69% ± 10% vs 22% ± 11%; P < .006; Fig 2). This adverse effect of treatment duration on overall survival could not be shown in the 83 patients exclusively treated with hydroxyurea and/or busulfan pretransplant. Their 5-year survival estimate was 55% ± 7% if treatment duration was ≤12 months and 62% ± 8% if pretransplant treatment exceeded 12 months (Fig 2). Prolonged IFN-α administration similarly affected the overall survival of patients with HLA-identical family donors and of those with alternative donors. In the first subset of patients, the 5-year survival estimate decreased from 73% ± 10% if IFN-α treatment did not exceed 12 months to 31% ± 16% after prolonged IFN-α exposure (P < .05). The corresponding estimates for patients with alternative donors were 50% ± 25% and 23% ± 12%, respectively. Donors other than HLA-identical family members alone had no significant adverse influence on overall survival as compared with HLA-identical family donors (46% ± 9% vs 57% ± 5%) in this study (Table 4). As described for the endpoints of 5-year DFS and TRM, the same three independent predictors were identified for the overall survival of the study population by multivariate analysis (Table 4).

**DISCUSSION**

The observation that various species of IFN-α have the potential to induce lasting cytogenetic remissions in a sub-group of patients with chronic-phase Ph1-positive CML has prompted a large number of clinical trials investigating the usefulness of IFN-α for the treatment of chronic-phase CML. Despite the limited knowledge regarding the pharmacologic mechanisms by which IFN-α induces the currently unpredictable cytogenetic responses in chronic-phase CML, this cytokine holds promise to become standard therapy for patients with newly diagnosed CML. In considering the rapidly increasing use of IFN-α even in CML patients who are potential candidates for allogeneic BMT, it appears important to determine whether the pleiotropic biologic effects of this cytokine may interfere with the marrow transplant procedure. In vitro properties of IFN-α on hematopoietic progenitor and marrow stroma cells include growth inhibition, modulation of adhesion molecule expression, and release of growth-regulating cytokines and receptors. Furthermore, IFN-α is capable of enhancing the expression of major (and possibly minor) histocompatibility antigens and of activating lymphocytes mediating antigen-specific and nonspecific cytotoxicity. These and possibly other as yet undefined biologic features of IFN-α may have consequences for different clinical aspects of marrow transplantation, such as donor cell engraftment, transplant-related toxic complications, GVHD, and reconstitution of the immune system posttransplant.

One recent clinical report from Giralt et al suggested that pretransplant IFN-α treatment did not adversely affect the outcome of patients who received marrow transplants from HLA-identical sibling donors in first chronic phase or...
in advanced disease stages of CML. In the present analysis on a larger population of patients treated by allogeneic BMT in the first chronic phase of CML, a strong adverse effect of prolonged (ie, >12 months) pretransplant IFN-α administration on transplant outcome has been observed that was mainly attributable to an increased risk of graft failure and fatal infections posttransplant. This resulted in a significantly higher overall TRM and in an inferior survival of patients exposed to IFN-α for more than 12 months pretransplant. Besides the size of the patient series and center-specific influences, there are several other distinctions between the above-cited report and the present analysis. We included patients who received marrow grafts from partially matched family or unrelated donors. This appears to be justified by the fact that donors other than HLA-identical family members alone did not contribute to the increased hazard of TRM and the lower likelihood of survival in our series. Furthermore, we evaluated the duration of treatment with each pretransplant cytoreductive agent as a measure for individual patient exposure to each agent, whereas, in the other report, patients were merely grouped according to therapy with or without IFN-α. The classification of treatment duration at 12 months was chosen in the present analysis because this treatment duration is required to assess IFN-α–induced cytogenetic responses with a sufficient degree of certainty. Thus, it can be expected that the majority of transplant candidates who participated in initial trials of IFN-α and were primary or secondary nonresponders to this agent will have been exposed for more than 12 months. We additionally performed proportional hazards regression analysis including other potential prognostic factors to determine whether type and duration of pretransplant treatment independently predicted transplant outcome. In contrast, the cited report contained only univariate analysis without appropriate statistical consideration of interactions between prognostic factors. The overall survival estimates in the previous report and this report showed nearly identical results for patients with IFN-α (56% ± 10% at 3 years v 48% ± 7% at 5 years) or without IFN-α (66% ± 13% at 3 years v 59% ± 5% at 5 years) pretransplant. It might thus be speculated that the adverse influence of prolonged pretransplant IFN-α administration on transplant outcome became detectable through the larger patient number and the different analytical approach in the present study.

Neither disease duration nor overall treatment duration pretransplant had an influence on transplant outcome in this analysis. With regard to pretransplant disease duration, this appears contrary to one recent IBMTR study and reports from single institutions. However, this difference might be explained by the comparatively small fraction of patients (26%) in the present report who underwent transplantation within 12 months from diagnosis and the resulting low power to detect an effect of disease duration on outcome. In contrast, 40% of patients in the IBMTR analysis were grafted within the first 6 months from diagnosis, and it appears highly probable that the favorable influence of the shorter time interval between diagnosis and transplant on transplant outcome in this analysis was biased by patients with a comparably low exposure to pretransplant cytoreductive agents. Furthermore, the IBMTR study did not account for the duration of pretransplant treatment, but simply categorized patients according to the type of the administered cytoreductive agent.

The clinical degree of severity and the pharmacologic prophylaxis of acute GVHD were the other two independent predictors of transplant outcome in this series. For chronic-
phase CML patients, both prognostic factors are in agreement with single institution and registry analyses.\textsuperscript{15-20,22,49}

That IFN-\(\alpha\) treatment may adversely affect the growth of marrow fibroblasts and hematopoietic cells in long-term liquid cultures of allograft recipients with CML has been previously reported by others.\textsuperscript{25} In our series, delayed posttransplant hematopoietic recovery was associated with donors other than HLA-identical family members, if the recipients had been exposed to IFN-\(\alpha\) pretransplant. In addition, all 7 graft failures in this study occurred in this subset of patients. This finding together with the documented in vitro properties of IFN-\(\alpha\) on marrow stroma cells challenges the question whether prolonged treatment with pharmacologic dosages of IFN-\(\alpha\) may result in lasting or irreversible alterations of the marrow microenvironment.\textsuperscript{24,25,44,47} Although prolonged IFN-\(\alpha\) exposure adversely affected the outcome of both HLA-identical family donor transplants and transplants from alternative donors, this currently unresolved issue may be particularly important for patients who carry a higher risk for a disturbed hematopoietic recovery posttransplant because of other reasons, such as recipients of T-cell–depleted grafts or patients with partially matched family or unrelated marrow donors.

Similar to the report from Giralt et al,\textsuperscript{29} we observed no influence of previous IFN-\(\alpha\) administration on the occurrence of either moderate to severe acute GVHD or chronic GVHD. Because the immune system of marrow transplant recipients has been largely destroyed by the conditioning regimen at the time of transplantation, it appears unlikely that modulating properties of posttransplant IFN-\(\alpha\) treatment on host lymphocytes and antigen-presenting cells may play a critical role in the pathogenesis of GVHD. The significant prognostic factors for acute and chronic GVHD in this study are in keeping with most previous analyses on these conditions.\textsuperscript{21,22,50-53}

Although mortality rates from transplant-related complications in the early posttransplant period were similar for the different patient subsets in this analysis, patients with prolonged IFN-\(\alpha\) treatment had a significantly increased risk to die from late infectious complications in comparison to patients whose treatment duration with IFN-\(\alpha\) did not exceed 12 months pretransplant. In multivariate analysis, this adverse effect of prolonged IFN-\(\alpha\) administration could be clearly separated from other significant prognostic factors of TRM. The underlying mechanisms for the sustained susceptibility to infections in patients with prolonged pretransplant IFN-\(\alpha\) treatment observed in this study are not clear. Whether this reflects an impaired capacity of hematopoietic cells to respond to infectious agents as a consequence of lasting alterations of the marrow microenvironment or other currently undefined long-term effects of prolonged IFN-\(\alpha\) administration deserves further investigations.

In considering the antileukemic activity of IFN-\(\alpha\) in chronic-phase CML, it might be postulated that lowering of the leukemic burden pretransplant results in a reduced risk of disease recurrence posttransplant. All patients in this study had active disease at the time of transplantation, and we were unable to detect a beneficial effect of pretransplant IFN-\(\alpha\) on the risk of disease recurrence. Due to the favorable appearing long-term results of IFN-\(\alpha\) treatment in the subset of patients, which achieves complete or major cytogenetic remissions, it is currently not advisable to investigate the impact of cytogenetic remissions obtained by pretransplant IFN-\(\alpha\) administration on the risk of relapse after allogeneic BMT.\textsuperscript{24,27,12,13} Therefore, this important question will not be answered in the nearer future.

In conclusion the present study strongly suggests that prolonged pretransplant IFN-\(\alpha\) administration in patients with chronic-phase CML is associated with a higher risk of transplant-related complications and an inferior outcome after allogeneic marrow transplantation. This raises the question whether prolonged courses of IFN-\(\alpha\) treatment are justifiable in potential transplant candidates, who do not attain favorable cytogenetic responses within 12 months of IFN-\(\alpha\) treatment. Future analyses on transplant results in chronic-phase CML patients should carefully evaluate the impact of treatment duration or, if applicable, of the cumulative doses of IFN-\(\alpha\) and other cytoreductive agents administered pretransplant. Such studies will contribute to the identification of the most appropriate pretransplant treatment in different prognostic subgroups of chronic-phase CML patients.

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2990 BEELEN ET AL


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Prolonged administration of interferon-alpha in patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia before allogeneic bone marrow transplantation may adversely affect transplant outcome

DW Beelen, U Graeven, AH Elmaagacli, N Niederle, O Kloke, B Opalka and UW Schaefer