We studied the clinical course of 130 chronic myeloid leuke-
mia (CML) patients (89 males and 41 females) in the
European Bone Marrow Transplantation Group (EBMT)
registry who received transplants before January 1, 1988
and who subsequently had evidence of recurrent leukemia.
All patients had received a pretransplant conditioning regi-
men including total body irradiation (TBI). The first evi-
dence of relapse was cytogenetic only in 74 (57%) patients
while no patient who relapsed in advanced phase (AP or
BC) survived more than 3.5 years from relapse (P <
.0001). The actuarial survival of patients relapsing before
6 months, between 6 and 12 months, and later than 12
months after transplant was 27%, 26%, and 45%, respec-
tively (P < .002). Among patients with cytogenetic re-
lapse, partial or complete disappearance of Ph-positive
cells occurred in 40% of untreated patients and in 42% of
those treated with interferon (IFN). However, IFN therapy
significantly delayed progression toward hematologic dis-
ease. Cytogenetic responses were observed in 25% of pa-
tients who received IFN for relapse into CP, while only one
minor cytogenetic response was reported in patients on
conventional chemotherapy. For patients presenting with
cytogenetic relapse as well as for those in hematologic re-
lapse, IFN therapy significantly improved the 2-year proba-
bility of survival. However, long-term survival for IFN-
treated patients in either group was not different from
long-term survival in comparable patients not receiving
IFN therapy. Twenty-nine patients of this series under-
went a second bone marrow transplant (BMT) and the pro-
jected survival at 4 years after the second transplant is
28%. In multivariate Cox regression analysis, four factors
remained significantly associated with survival: disease
phase at relapse (P < .0001), duration of time interval
from BMT to relapse (P = .0001), interferon therapy at
relapse (P = .0024), and patient sex (P = .0032). This
retrospective study provides evidence that some patients
who relapse after BMT may benefit from treatment with
IFN; a second BMT may offer the chance of cure. Data
from this analysis may be useful in designing future pro-
spective trials on posttransplant CML relapse.

HLOGENEIC bone marrow transplant (BMT) is
currently the only curative treatment for patients with
chronic myeloid leukemia (CML), but therapeutic success is
still sometimes limited by disease recurrence. Indeed, the
4-year probability of hematologic relapse for CML patients
in first chronic phase (CP) undergoing unmanipulated allo-
genetic BMT is 10% to 20%.1-3 The relapse rate increases to
40% to 60% for patients transplanted in advanced phase1,3,4
and for those grafted during CP who receive T-cell-depleted
marrow.3,5,6

The incidence of cytogenetic relapse after BMT is more
difficult to establish. The frequency and reliability of cytoge-
netic examinations vary greatly among different centers
and, in some cases, the recurrence of Ph-positive cells in
bone marrow has been recognized as only "transient."7,12 So
far no factor can predict whether cytogenetic evidence of the
Ph chromosome in a small proportion of marrow meta-
phases will be followed by hematologic disease or whether
the Ph-positive cells will disappear spontaneously.

The outcome for CML patients with hematologic relapse
is also uncertain. Not all necessarily die within a short time,
but, at present, no exhaustive analysis on survival is avail-
able. Furthermore, the therapeutic approach to hematolo-
gic relapse is not standardized, but depends on disease
phase and center policy.

For this reason we have analyzed the patterns of CML
relapse and the outcome according to therapeutic manage-
ment in a large series of patients after BMT. In this analysis
we were specifically interested in evaluating the influence
on survival of interferon (IFN) treatment. The aim of our

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Outcome for Patients Who Relapse After Allogeneic Bone Marrow
Transplantation for Chronic Myeloid Leukemia

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tino Hospital, Genoa, Italy; the Institute of Hematology, Univer-
sity of Perugia, Italy; the Royal Free Hospital, London, UK, the
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3211
PATIENTS AND METHODS

We conducted a retrospective analysis on behalf of the European Bone Marrow Transplantation Group (EBMT) Chronic Leukemia Working Party. All patients reported to the EBMT registry with Ph-positive relapse after allogeneic transplant for CML were considered. The study was restricted to patients transplanted from an HLA-identical sibling before January 1, 1988, who received a conditioning regimen including total body irradiation (TBI). The minimum follow-up time was 4 years. The closing date of analysis was December 1992.

Seventeen European centers contributed patients to the study; additional data for 130 patients were collected by questionnaire. Detailed information was asked for about the type of relapse, therapy for relapse, response to therapy, second transplant, and clinical outcome.

Of the 130 patients included in this analysis, 89 were male and 41 female; the median age was 33 (range, 12 to 42) years. At BMT, 88 (68%) patients were in first CP, 8 (6%) in second CP, 29 (22%) in accelerated phase (AP), and 5 (4%) in blast crisis (BC).

For graft-versus-host disease (GVHD) prophylaxis, 86 (65%) patients received T-cell-depleted marrow, with or without cyclosporine (CSA); 27 (22%) received CSA alone, 3 (2%) received methotrexate (MTX) alone, and 14 (11%) were treated with a combination of CSA and MTX.

The phase of disease at time of the first BMT as at time of relapse was defined according to the International Bone Marrow Transplant Registry (IBMTR) criteria. Both hematologic and cytogenetic relapses were included. A minimum of 20 metaphases was required in the cytogenetic evaluation; the presence of any Ph-positive cells detected after engraftment was then considered to represent cytogenetic relapse.

Criteria for response to therapy were defined as follows: (1) hematologic response: normalization of peripheral blood counts and disappearance of clinical signs of disease; (2) no cytogenetic response: no reduction of Ph-positive cells from initial level; (3) minor cytogenetic response: 40% reduction of Ph-positive cells from initial level; (4) partial cytogenetic response: <50% reduction of Ph-positive cells from initial level; (5) complete cytogenetic remission: disappearance of all Ph-positive cells; and (6) molecular remission: negativity of bcr rearrangement by Southern blotting.
Acute and chronic GVHD were classified according to Seattle criteria. Only those patients surviving more than 100 days after BMT were considered evaluable for chronic GVHD.

**STATISTICAL METHODS**

Means, medians, standard errors, and standard deviations were calculated by the Biomedical Package (BMDP) and Statistical Analysis System (SAS) programs and compared by $x^2$ analysis and unpaired Student's t-test for differences between groups. Actuarial survival and remission curves were prepared by the method of Kaplan and Meier and differences between curves were calculated with the generalized Wilcoxon test. All analyses were prepared and calculated for all subgroups from diagnosis, from time of first BMT and from time of relapse after BMT. As no substantial differences were found when the actuarial curves were calculated from these different time points, only the last ones are reported.

Variables known to influence outcome (patient sex, age, T-cell depletion, GVHD, time from BMT to relapse, disease stage at relapse, and second transplant) were tested in univariate analysis and those at $P < .05$ level were evaluated in partial multivariate models using Cox proportional hazards regression. Those variables found significant were then included in the final model.

**RESULTS**

For the 130 patients the first evidence of relapse after BMT was cytogenetic in 74 (57%) patients and hematologic in 56 (43%). Cytogenetic and hematologic relapses were diagnosed at a median of 287 (range, 60 to 1,891) and 380 (range, 74 to 2,577) days after BMT, respectively.

Although 20 of 42 (48%) patients transplanted in advanced stage (second CP, AP, BC) subsequently relapsed into a more benign phase of disease, for all patients, disease phase at relapse was significantly correlated with that at time of BMT ($P < .0001$).

The use of T-cell depletion and the presence of acute and/or chronic GVHD did not affect the nature of the relapse, ie, cytogenetic versus hematologic. However, the number of karyotypic examinations performed posttransplant was significantly higher in patients reported as having cytogenetic relapse compared with those with hematologic relapse ($P < .05$, data not shown).

At the date of analysis, 69 patients have died and 61 are alive. The 6-year probability of survival from relapse is 36% (95% confidence interval [CI]: 31% to 42%) with a significantly higher proportion of survivors among females (53% [95% CI: 44% to 62%]) than in male patients (30% [95% CI: 24% to 36%]) ($P < .002$) (Fig 1). This difference in favor of female patients also remains highly significant when 29 patients (19 males and 10 females) undergoing a second BMT are excluded (data not shown).

The 6-year actuarial survival calculated by disease phase from the first evidence of relapse is 52% (95% CI, 45% to 59%) for the patients with cytogenetic relapse and 30% (95% CI, 17% to 43%) for patients in hematologic CP, while no patient relapsing in advanced phase (AP and BC) survived more than 3.5 years from relapse. This difference is highly significant ($P < .0001$).

The first evidence of relapse after BMT was detected before 6 months in 39 patients, between 6 and 12 months in 34, and later than 12 months in 57. For these three groups of patients, the actuarial survival at 6 years from relapse is 27% (95% CI, 15% to 39%), 26% (95% CI, 16% to 36%) and 45% (95% CI, 34% to 56%) ($P < .002$), respectively (Fig 2).

Outcome of patients with cytogenetic relapse. Of 74 patients with cytogenetic relapse, 49 were male and 25 female. As for the total of all patients, the 6-year actuarial survival is better for female than male patients: 69% (95% CI, 58% to 80%) for the former and 46% (95% CI, 38% to 54%) for the latter ($P < .002$).

The cytogenetic relapse occurred less than 6 months from BMT in 26 patients, between 6 and 12 months in 21 patients, and later than 12 months in 27 patients. For the three patient groups the 6-year probability of survival is 43% (95% CI, 33% to 53%), 42% (95% CI, 28% to 56%) and 61% (95% CI, 42% to 80%), respectively ($P < .03$).

Of 74 patients, 50 were not treated, while the remaining

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**Table 1. Characteristics of Patients With Cytogenetic Relapse**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Yes IFN</th>
<th>No IFN</th>
<th>P</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td>No. of patients</td>
<td>24</td>
<td>50</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Age (mean ± SD [y])</td>
<td>30.04 ± 9</td>
<td>28.96 ± 8</td>
<td>NS</td>
<td>29.5 ± 9</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>11</td>
<td>38</td>
<td>49</td>
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<tr>
<td>F</td>
<td>13</td>
<td>12</td>
<td>.01</td>
<td>25</td>
</tr>
<tr>
<td>Disease phase at BMT</td>
<td>1st CP</td>
<td>23</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>2nd CP</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Accelerated</td>
<td>1</td>
<td>11</td>
<td>.1</td>
<td>12</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>0</td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>T-cell depletion</td>
<td>Yes</td>
<td>22</td>
<td>31</td>
<td>.008</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>19</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Time from BMT to relapse (mo)</td>
<td>≤6</td>
<td>10</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>&gt;6 ≤12</td>
<td>8</td>
<td>13</td>
<td>NS</td>
<td>21</td>
</tr>
<tr>
<td>≥12</td>
<td>6</td>
<td>21</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Percentage of Ph positive cells (mean ± SD)</td>
<td>38.54 ± 34</td>
<td>40.56 ± 32</td>
<td>NS</td>
<td>39.56 ± 33</td>
</tr>
<tr>
<td>Cyclosporine prophylaxis (56 patients)</td>
<td>3</td>
<td>12</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Relapse on CSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse off CSA</td>
<td>14</td>
<td>27</td>
<td>NS</td>
<td>41</td>
</tr>
</tbody>
</table>

---

**Table 2. Response to Therapy of Patients With Cytogenetic Relapse**

<table>
<thead>
<tr>
<th>Response</th>
<th>IFN</th>
<th>No IFN</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>3</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Partial</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Complete</td>
<td>4 (16%)</td>
<td>10 (20%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (42%)</td>
<td>20 (40%)</td>
<td>30 (40%)</td>
</tr>
<tr>
<td>Failure with progression to Chronic phase</td>
<td>11</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>2</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>14 (58%)</td>
<td>30 (60%)</td>
<td>44 (60%)</td>
</tr>
<tr>
<td>Months from cytogenetic to hematologic relapse</td>
<td>Median</td>
<td>15</td>
<td>3.3</td>
</tr>
<tr>
<td>Range</td>
<td>3-46</td>
<td>1-66</td>
<td>1-66</td>
</tr>
</tbody>
</table>
24 received IFN therapy, usually α-IFN. The characteristics of the two groups of patients are shown in Table 1. The only significant differences were the higher number of female patients and of recipients of T-cell-depleted bone marrow in the group treated with IFN. IFN was administered at a median starting dose of 3 (range, 0.5 to 5) × 10^6 U/m^2 for a median of 3 (range, 3 to 7) days per week. However, in this retrospective analysis, dose adjustments and the total dose of IFN administered could not be assessed.

Ten of the 24 (42%) patients receiving IFN were responders. The cytogenetic response was minor in three patients, partial in three, and complete in four (Table 2). The complete cytogenetic remission was confirmed by Southern analysis for bcr rearrangement. Fourteen (58%) IFN-treated patients did not respond and progressed to hematologic disease (11 to CP and 3 to AP) at a median time of 15 (range, 3 to 46) months from cytogenetic relapse.

Of the 50 patients with cytogenetic relapse who were untreated, 20 (40%) showed a spontaneous reduction in the proportion of Ph-positive metaphases, which was minor in 10 patients and complete in 10 patients. The characteristics of these 20 patients were not substantially different from those of 10 patients whose cytogenetic response was observed during IFN therapy (data not shown). Thirty (60%) patients progressed to hematologic disease (16 to CP and 14 to AP) at a median time of 3.3 (range, 1 to 66) months from cytogenetic relapse.

The probability of progression to hematologic disease was significantly (P < .02) delayed among IFN-treated patients (Fig 3). The 2-year probability of survival of 24 patients receiving IFN for cytogenetic relapse is significantly higher than that of 32 patients to whom IFN therapy was never administered, and also than that of 18 patients receiving IFN only at the time of hematologic progression (Fig 4).
Cytogenetic response

The mean percentage of Ph-positive cells decreased (Tables 3 and 4), the difference was found with regard to the patient characteristics. Comparing these patients with the 44 in whom the number of Ph-positive metaphases remained constant, no difference was found.

These results also remain consistent when patients who received a second transplant are excluded from the analysis (data not shown). However, at 6 years, actuarial survival is no longer different.

Thirty patients, 20 untreated and 10 treated with IFN, showed a reduction in the proportion of Ph-positive metaphases. Comparing these patients with the 44 in whom the number of Ph-positive metaphases remained constant, no difference was found with regard to the patient characteristics. However, the mean percentage of Ph-positive cells detectable at relapse was lower in the former (31% ± 5% vs 47% ± 5%; P = .04).

Outcome of patients with hemato logic relapse. Fifty-six patients relapsed with primary hematologic recurrence of disease: 27 (48%) in CP, 11 (20%) in AP, and 18 (32%) in BC.

To evaluate patient characteristics and response to therapy (Tables 3 and 4), the 56 patients with primary hematologic relapse and the 30 patients with cytogenetic relapse, who did not receive IFN and therefore did not receive IFN and then progressed to hematologic disease, were considered together. The patient group not receiving IFN included a higher number of patients in advanced phase, but no other difference was found.

The median starting dose of IFN was 5 (range, 0.5 to 10) × 10⁶ U/m² and the median number of treatment days per week was 5 (range, 3 to 7).

Of 43 patients in CP, 28 received IFN, either as single therapy or in association with hydroxyurea, and 15 received conventional chemotherapy only. Seven of 28 (25%) IFN-treated patients obtained a cytogenetic response: one minor, two partial, and four complete. In contrast, only one minor response (6%) was reported with conventional chemotherapy (P = .007).

Twelve patients in advanced phase (8 AP and 4 BC) received IFN after or in combination with chemotherapy. Two of them achieved a cytogenetic response: one minor and one partial. No cytogenetic response was observed among the 31 patients not treated with IFN (7 AP and 24 BC).

The 6-year actuarial survival of patients who relapsed in CP is 30% (95% CI, 17% to 43%), significantly higher (P < .0001) than that of patients relapsing in advanced phase (Fig 5). For both groups, IFN therapy improved the 2-year probability of survival. As observed in patients with cytogenetic relapse, this effect disappeared on a longer follow-up (Figs 6 and 7). The difference in favor of IFN-treated patients is still significant when patients undergoing a second BMT are excluded (data not shown).

Second transplant. Twenty-nine patients (19 males and 10 females), 16 in CP and 13 in AP of disease, were submitted to a second transplant at a median of 34.9 (range, 7.6 to 62.3) months from first BMT. In each case, bone marrow donors were the same as for the first transplant.

Most patients were prepared with a conditioning regimen including busulfan alone or associated with cyclophosphamide. As GVHD prophylaxis, 22 patients received CSA, combined with a short course of MTX in 9 patients, 4 patients were transplanted with T-cell-depleted marrow, and 1 patient received MTX alone; 2 patients did not receive any prevention for GVHD.

Engraftment, defined as recovery of granulocytes to >0.5 × 10⁹/L, was reached in all patients at a median of 19 (range, 8 to 35) days after transplant. Only 5 (17%) patients experienced advanced grade (II-IV) of acute GVHD, while

| Table 3. Characteristics of Patients With Hematologic Relapse |
|------------------|------------------|------------------|------------------|
|                  | Yes IFN | No IFN | P     |
| No. of patients  | 40      | 48     | 86    |
| Age (mean ± SD)  | 31.30 ± 8 | 28.93 ± 9 | NS    |
|                  | 30.11 ± 8 |            |       |
| Sex              | M       | F      |       |
|                  | 33      | 36     | 69    |
|                  | 7       | 10     | 17    |
| Disease phase at BMT |
| 1st CP          | 28      | 23     | 51    |
| 2nd CP          | 0       | 9      | 9     |
| Accelerated     | 11      | 12     | .023  |
| Blast crisis    | 1       | 2      | 3     |
| T-cell depletion | Yes     | 28     | 25    | 53    |
|                  | No      | 12     | 21    | 33    |
| Time from BMT to relapse (mo) |
| ≤6               | 8       | 16     | 24    |
| >6 ≤ 12         | 13      | 9      | NS    |
| >12              | 19      | 21     | 40    |
| Disease phase at relapse |
| Chronic phase   | 28      | 15     | 43    |
| Accelerated     | 8       | 7      | .0001 |
| Blast crisis    | 4       | 24     | 28    |
| Cyclosporine prophylaxis (70 patients) |
| Relapse on CSA  | 10      | 9      | 19    |
| Relapse off CSA | 24      | 27     | NS    |
|                   | 51      |        |       |

The 6-year actuarial survival of patients who relapsed in CP is 30% (95% CI, 17% to 43%), significantly higher (P < .0001) than that of patients relapsing in advanced phase (Fig 5). For both groups, IFN therapy improved the 2-year probability of survival. As observed in patients with cytogenetic relapse, this effect disappeared on a longer follow-up (Figs 6 and 7). The difference in favor of IFN-treated patients is still significant when patients undergoing a second BMT are excluded (data not shown).
chronic GVHD developed in 5 of 16 (31%) evaluable patients.

At a median follow-up of 3 (range, 0 to 24) months from second BMT, 19 (65.5%) patients (12 males and 7 females) have died: 10 of 16 (62.5%) who were transplanted in CP and 9 of 13 (69.3%) transplanted in AP. The 4-year probability of survival for all 29 transplanted patients is 28% (95% CI, 16% to 40%) with 10 patients (9 in complete remission and 1 in relapse) surviving between 1 and 48 months from second BMT. Four of 10 survivors have a second complete remission interval longer than the time from first BMT to relapse. Surviving patients underwent second BMT at a mean of 43.5 ± 16 months from the first transplant. In comparison, patients who died received the second BMT at a mean of 24 ± 14 months after the first BMT (P = .002).

Multivariate analysis. In the final model of the Cox multivariate analysis of survival, four variables remained significant: (1) patient sex: female versus male; (2) IFN therapy at relapse: no IFN versus IFN at hematologic relapse; (3) time interval from BMT to relapse: <6 versus ≥6 < 12 versus ≥12 months; and (4) disease phase at relapse: cytogenetic versus CP versus AP (Table 5).

**DISCUSSION**

This report is a retrospective multicenter study of relapse of CML after BMT and includes a large series of patients transplanted before 1988 with a follow-up of at least 4 years. Patient outcome was analyzed according to prior transplant procedure, pretransplant patient characteristics, type of relapse, and therapy.

As observed in other series, the disease phase at hematologic relapse was different in some patients from that for which the patients were transplanted. However, in most
cases the disease phase at BMT was the same as that at relapse, so it was not included in the final model of multivariate analysis. As expected, the disease phase at relapse was the most significant prognostic factor for survival.

The second variable that particularly influenced survival was the interval time between BMT and leukemic recurrence; the later the relapse occurred, the longer patients survived. All patients in this series had received basically the same conditioning regimen (cyclophosphamide plus TBI), so it seems unlikely that the time of relapse depends on the degree of pretransplant leukemic suppression. Moreover, no correlation was found between time of relapse and disease phase. Indeed, the effect of time interval in influencing survival was also observed among patients with cytogenetic relapse. This correlation suggests that survival of patients with relapse after BMT is related to the intrinsic proliferative potential of the leukemic clone and its capacity to expand toward a more severe hematologic and clinical stage.

In both univariate and multivariate analyses, females had a more favorable prognostic factor for survival. In several reports on CML patients not undergoing BMT, survival of female patients is higher than that of males. However, in multivariate analysis, the patient sex is never identified as an important prognostic factor. The significance of this observation in our analysis remains unexplained.

The potential of IFN therapy in CML patients with relapse after T-cell–depleted or unmanipulated BMT has been reported. Our study confirms in a large series that a substantial dose of IFN and cytogenetic response. Among patients who relapsed in CP, the percentage of cytogenetic responders is not substantially different from that reported for patients treated with IFN in late CP.

In comparison, a higher proportion of patients with cytogenetic relapse responded to IFN. However, the influence of IFN in patients with cytogenetic relapse after BMT is more difficult to assess. Several patients not given any therapy for their cytogenetic relapse showed a spontaneous reduction or disappearance of Ph-positive cells. In addition, in the posttransplant setting the optimal dose schedule of IFN is not defined. In two previous studies, patients with only cytogenetic or hematologic relapse did not tolerate a daily dose of IFN beyond 3 × 10⁶ U/m² or 1.6 × 10⁶ U/m², respectively. Unfortunately, our retrospective data did not allow us to study a possible correlation between the total administered dose of IFN and cytogenetic response.

Criteria to define cytogenetic relapse after BMT are not presently established. Therefore, in our series, the presence of any evaluable percentage of Ph-positive cells detected at any time after engraftment was considered to represent cytogenetic relapse. This might not necessarily be correct; a transient reemergence of Ph-positive cells or their persistence in serially studied karyotypes without progression toward hematologic relapse have been reported.

Evaluation of the cytogenetic relapse may depend on several factors. Indeed, Ph-positive metaphases have been more frequently observed within 100 days after BMT, when such cells can still be considered a residual of mature recipient cells surviving the pretransplant conditioning regimen and definitively disappearing thereafter.

In some cases Ph-positive cells have been detected later on, but often in percentage <10% among normal donor hematopoiesis. In fact, a proportion >25% of Ph-positive metaphases and a condition of mixed chimerism have been found to be related with an increased risk of hematologic relapse. In our study, all patients with >40% of Ph-positive cells eventually progressed to hematologic relapse.

Furthermore, the evolution of the cytogenetic pattern is clearly influenced by the regimen used to prevent GVHD. CML patients receiving T-cell–depleted marrow are at highest risk of relapse. Therefore, Ph-positive metaphases, even if first detected in a minor proportion of cells, frequently increase to a greater percentage within a few

<table>
<thead>
<tr>
<th>Variables</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sex</td>
<td>F</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>2.4044 (1.2633-4.5767)</td>
</tr>
<tr>
<td>Interferon therapy at relapse</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Yes at cytogenetic</td>
<td>0.6586 (0.4895-0.8859)</td>
<td>.0024</td>
</tr>
<tr>
<td>Yes at hematologic</td>
<td>0.4337 (0.2396-0.7849)</td>
<td></td>
</tr>
<tr>
<td>Time from BMT to relapse (mo)</td>
<td>&lt;6</td>
<td>1</td>
</tr>
<tr>
<td>≥6 &lt; 12</td>
<td>0.6256 (0.4849-0.8069)</td>
<td>.0001</td>
</tr>
<tr>
<td>≥12</td>
<td>0.3913 (0.2362-0.6512)</td>
<td></td>
</tr>
<tr>
<td>Disease phase at relapse</td>
<td>Chronic</td>
<td>2.5373 (1.8613-3.4587)</td>
</tr>
<tr>
<td>Advanced (AP; BC)</td>
<td>6.4379 (3.4646-11.9628)</td>
<td></td>
</tr>
</tbody>
</table>
months and then deteriorate to overt hematologic relapse in the majority of patients.

In contrast, procedures that modify the immune status of transplanted patients may contribute to increase the heterogeneity of the cytogenetic pattern. Reversion to normal donor hematopoiesis has been reported after CSA discontinuation in patients with only cytogenetic or hematologic relapse. In our study, a lower percentage of Ph-positive metaphases detected at cytogenetic relapse was the only characteristic significantly related to subsequent reduction or disappearance of Ph-positive cells. No other factor, including IFN therapy, was found to influence the cytogenetic response. Nevertheless, IFN therapy significantly delayed the progression toward hematologic disease, and such an effect becomes much more consistent when the significantly higher number of recipients of T-cell-depleted marrow among IFN-treated patients is considered.

The delayed progression to hematologic disease increased the probability of survival, which was significantly higher at 2 years for patients treated with IFN at the time of cytogenetic relapse than for patients who never received IFN or for those treated at hematologic progression. Such observation suggests that, for patients in cytogenetic relapse, the “wait and see” policy is not advisable and IFN therapy should be given as soon as cytogenetic relapse is confirmed.

The beneficial effect of IFN therapy on 2-year survival was even observed for patients relapsing either in chronic or advanced phase of disease. However, IFN failed to cure patients. Most of them later progressed to more advanced stages of disease and died.

In line with other experiences, the results from this study confirm that second BMT has to be considered a high-risk therapeutic procedure. However, the transplant-related mortality was significantly lower for patients submitted to second BMT at a longer interval from the first transplant. The effectiveness of IFN in controlling disease progression could delay second BMT for patients not achieving a persistent cytogenetic response.

The best therapy for patients with relapse after BMT needs to be defined. Encouraging, though preliminary, results have been recently reported by the use of donor buffy-coat infusion, alone or in association with α-IFN, in the treatment of CML patients relapsing either hematologically or cytogenetically after BMT. In a recent European survey (J. Kolb, personal communication), 27 of 32 (84%) CML patients achieved a complete cytogenetic remission following donor buffy-coat infusion for leukemic recurrence. However, acute GYHD > 1 grade and marrow aplasia developed in 34% and 31% of patients, respectively, with an overall mortality rate of 22%. Donor buffy-coat infusion seems highly effective in treating CML patients in relapse after BMT, but the risk of related complications and mortality has to be taken into account.

The results of our retrospective study on a large patient series clearly show that long-term survival and, possibly, cure of CML patients who relapse after BMT can still be obtained. The analysis identified IFN therapy as an independent factor positively influencing survival. In designing any future prospective study on posttransplant CML relapse, a therapeutic approach with IFN is advisable. However, its effect is not sustained. Alternative treatments, such as donor buffy-coat infusion or second BMT, should be considered for patients not achieving a complete cytogenetic remission.

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