Choice of Pretransplant Treatment and Timing of Transplants for Chronic Myelogenous Leukemia in Chronic Phase


We analyzed the outcome of 450 HLA-identical sibling bone marrow transplants for chronic myelogenous leukemia (CML) in chronic phase performed between 1985 and 1990 and reported to the International Bone Marrow Transplant Registry (IBMTR). All patients received either hydroxyurea (n = 292) or busulfan (n = 158) to treat their CML before transplant. The median interval between diagnosis and transplant was 10 months (range, 1 to 191). Patients treated with hydroxyurea had a higher probability (95% confidence interval) of leukemia-free survival (LFS) at 3 years than those treated with busulfan (61% [51% to 70%] v 45% [36% to 55%], P < .0003). Probability of LFS was also higher in patients transplanted within 1 year of diagnosis (61% [53 to 68%] v 47% [38% to 57%], P < .0001). After adjustment for patient and transplant covariables in a multivariate analysis, prior chemotherapy and duration of disease pretransplant were independent associated with LFS. These data support the use of hydroxyurea rather than busulfan and transplant within 1 year of diagnosis for patients with CML and an HLA-identical sibling.

ONE MARROW transplantation (BMT) is increasingly used to treat chronic myelogenous leukemia (CML). For patients under 50 years of age transplanted in chronic phase from HLA-identical sibling donors, the probability of long-term disease-free survival is 60% to 80%. Results of transplant in advanced phases of CML are less favorable. Thus, although treatment-related mortality (TRM) is substantial and occasional relapses occur, patients are usually advised to undergo transplantation while in chronic phase.

Optimal treatment for patients before transplant is controversial. Busulfan and hydroxyurea are both used. Since busulfan administered over prolonged periods can damage the lungs and other organs, hydroxyurea is generally regarded as safer, but there are few data showing that this is so. We therefore studied the effects of initial treatment with one or the other of these two cytotoxic drugs on transplant outcome.

MATERIALS AND METHODS

Patients. The International Bone Marrow Transplant Registry (IBMTR) received detailed reports on 1,266 patients receiving bone marrow transplants from HLA-identical siblings between 1985 and 1990 for Philadelphia chromosome-positive CML in chronic phase. Chronic phase was defined by previously published criteria. The analysis was restricted to 450 patients treated with either busulfan or hydroxyurea before transplant. Patients treated with both drugs, with other cytotoxic drugs, or with interferon were excluded. Most patients received either cyclophosphamide and total-body irradiation or busulfan for pretransplant conditioning and cyclosporine A (CSA), methotrexate (MTX), or both to prevent graft-versus-host disease (GVHD). Patients receiving T-cell-depleted bone marrow were excluded. Patient, disease, and treatment details are listed in Table 1. Twenty-four of 450 patients (5%) were included in a previously published IBMTR study.

Statistical methods. The primary end point examined was treatment failure, defined as relapse or TRM. Relapse was based on standard hematologic and clinical criteria. TRM was defined as death in continuing complete remission. Actuarial probabilities of leukemia-free survival (LFS), relapse, TRM, and survival were calculated using standard life-table methods. Univariate analyses of the effects of disease duration and prior treatment on outcome were performed using the Lee-Desu statistic.

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results. Prognostic variables considered were hemoglobin, leucocyte and platelet counts at diagnosis, spleen size pretransplant, splenectomy pretransplant, myelofibrosis, Karnofsky performance score, race, donor/recipient sex match, donor/recipient cytomegalovirus (CMV) antibody status, conditioning regimen, GVHD prophylaxis, and year of transplant. Variables not significantly associated with treatment failure were removed from the model singly until only those significant at the \( P < .05 \) level remained.

### Table 2. Three-Year Probabilities (95% confidence interval) of TRM, LFS, and Survival After HLA-Identical Sibling Bone Marrow Transplants for CML in First Chronic Phase According to Disease Duration and Before Treatment

<table>
<thead>
<tr>
<th>Disease Duration (mo) and Prior Treatment</th>
<th>Probability of TRM (95% CI)</th>
<th>Probability of Relapse (95% CI)</th>
<th>Probability of LFS (95% CI)</th>
<th>Probability of Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12, hydroxyurea</td>
<td>208</td>
<td>29% (16%-46%)</td>
<td>9% (2%-35%)</td>
<td>65% (47%-80%)</td>
</tr>
<tr>
<td>≥12, hydroxyurea</td>
<td>84</td>
<td>38% (19%-62%)</td>
<td>13% (3%-45%)</td>
<td>54% (30%-76%)</td>
</tr>
<tr>
<td>&lt;12, busulfan</td>
<td>62</td>
<td>44% (21%-69%)</td>
<td>9% (1%-50%)</td>
<td>51% (27%-75%)</td>
</tr>
<tr>
<td>≥12, busulfan</td>
<td>96</td>
<td>53% (33%-72%)</td>
<td>14% (3%-51%)</td>
<td>41% (21%-64%)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

### RESULTS

**Influence of prior treatment before BMT.** Patients were divided into two groups according to whether they received busulfan or hydroxyurea as treatment for chronic-phase CML. TRM was significantly higher, while LFS and overall survival were significantly lower in patients treated previously with busulfan versus those treated previously with hydroxyurea (Table 2 and Fig 1). Results were similar whether or not busulfan was used for conditioning.

**Influence of disease duration before BMT.** Patients were divided into two groups according to whether BMT was performed within or after 1 year from diagnosis. TRM and relapse were significantly lower and LFS and survival significantly higher in patients transplanted within 1 year of diagnosis (Table 2 and Fig 1).

**Influence of prior treatment and disease duration.** When details of prior treatment and duration of CML were considered together in multivariate analysis, both were independent predictors of outcome (Fig 1). Their effect was not changed by including other prognostic variables in the regression models, including patient age, donor-recipient sex-match, donor-recipient CMV status, splenectomy, conditioning regimen, GVHD prophylaxis, or year of transplant. TRM (relative risk, 1.6; \( P < .01 \)), treatment failure (relative risk, 1.5; \( P < .02 \)), and overall mortality (relative risk, 1.7; \( P < .005 \)) were all higher in patients treated with busulfan pretransplant, regardless of the interval between diagnosis and transplant. An interval between diagnosis and transplant greater than 1 year increased the risk of TRM (relative risk, 1.5; \( P < .02 \)), relapse (relative risk, 2.7; \( P < .05 \)), treatment failure (relative risk, 1.7; \( P < .003 \)), and overall mortality (relative risk, 1.5; \( P < .02 \)) regardless of prior treatment. Primary causes of treatment failure are listed in Table 3. One hundred forty-two of 148 nonrelapse deaths were in the first year posttransplant. Of the six nonrelapse deaths occurring more than 1 year after transplant, four were related to complications of extensive chronic GVHD (three from infection and one from bronchiolitis obliterans), one was from cardiac arrhythmia in the setting of pulmonary infection, and one from sepsis in the absence of GVHD.

### DISCUSSION

This analysis shows that patients treated with busulfan have a lower probability of survival after transplant than those treated with hydroxyurea. It also supports the conclusion of earlier reports\(^1,2\) that the interval from diagnosis to
transplant influences the probability of TRM and survival posttransplant. In contrast to an earlier report, a longer interval between diagnosis and transplant had a negative impact both in patients receiving busulfan and those receiving hydroxyurea for pretransplant therapy. The finding also contrasts with an earlier IBMTR study that failed to find an association between disease duration and transplant outcome. This difference may result from differences in GVHD prophylaxis between the two studies. In the current study, better outcome after early versus late transplants was most striking in patients receiving combined MTX and CsA, which was used in 60% of patients. Fewer than 5% of patients in the previous study received this regimen. Another new finding of the current study is the trend for increased relapse in patients transplanted more than 1 year after diagnosis.

The increase in TRM after treatment with busulfan may reflect damage to various organs, especially lungs. The well-known increased incidence of pneumonitis in nontransplanted patients receiving large amounts of busulfan is consistent with this hypothesis. Although the risk of noninfectious interstitial pneumonitis was somewhat higher in patients treated with busulfan, there was not a significant difference in the causes of treatment failure (Table 3).

The increase in treatment failure in patients transplanted more than 1 year after diagnosis may also reflect cumulative toxicity of cytotoxic drugs, either busulfan or hydroxyurea, since it results primarily from nonrelapse deaths. It would be interesting to compare survival of patients in this analysis with survival after transplant in patients who receive little or no treatment with cytotoxic drugs before transplant; however, these patients are rare. Whether prior treatment with interferon influences transplant outcome is unknown.

The results of this study support the recommendation that patients with CML in chronic phase be treated with hydroxyurea rather than busulfan before transplant and that transplants should be performed relatively early after diagnosis.

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REFERENCES


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