Treatment of Chronic Myeloid Leukemia With Allogeneic Bone Marrow Transplantation After Preparation With BuCy2


One hundred fifteen patients with chronic myelocytic leukemia (CML) were administered busulphan 4 mg/kg for 4 days and cyclophosphamide 60 mg/kg on each of 2 days (BuCy2) followed by allogeneic bone marrow transplantation from histocompatible sibling donors. For 62 patients in chronic phase, 26 in accelerated phase, and 27 in blast transformation, the actuarial survival at 3 years was 58%, 41%, and 25%, respectively. Actuarial probability of relapse was 3%, 12%, and 27%, respectively. Only two patients in chronic phase showed a transient cytogenetic relapse and one of these died from subsequent transplant-related complications, whereas the other remains cytogenetically normal 697 days posttransplant. Patients who were transplanted within 1 year of diagnosis in chronic phase had a survival of 70% compared with 40% when transplanted beyond 1 year from diagnosis. This significant difference in survival was due to transplant-related complications and was correlated with previous exposure to high doses of busulphan. This study indicates that BuCy2 is a useful conditioning regimen for marrow transplantation in patients with CML and results in similar survival statistics and transplant-related mortality as would be expected with conditioning regimens containing total body irradiation. It is possible that relapse after BuCy2 may be lower than expected with regimens containing total body irradiation, but larger analyses are required.

THE PROGNOSIS for patients with chronic myeloid leukemia (CML) has not changed substantially during the past 60 years when patients are treated with conventional therapy.1,2 Marginal improvement has been obtained with high-dose chemotherapy3-8 and promising results have been seen in recent years with interferon,9 but it is not clear whether this treatment will result in long-term cures. During the past decade, allogeneic bone marrow transplantation (BMT) after high-dose chemotherapy and total body irradiation (TBI) has resulted in cures of at least 50% in patients transplanted in chronic phase. Results in patients with blast transformation show leukemia-free survival of only 20%.6,9

Santos et al10 reported an irradiation-free regimen consisting of 4 mg/kg of oral busulphan (Bu) for 4 days followed by 50 mg/kg of intravenous cyclophosphamide (Cy) for 4 days, and this was associated with low relapse but a relatively high incidence of transplant-related mortality. A pilot study11 suggested that reduction of Cy dose to 120 mg/kg administered over 2 days (BuCy2) might be associated with a lower incidence of treatment-related complications. This analysis presents the results of 115 patients with CML who were conditioned with BuCy2 and underwent allogeneic BMT at four transplant centers.

MATERIALS AND METHODS

Patient characteristics. Discussion with colleagues from Ohio during an International Meeting resulted in a decision to evaluate the use of BuCy2 as a conditioning regimen in consecutive patients suffering from acute leukemia and CML. A formal phase II trial was not established. A previous publication12 described the results for acute myelocytic leukemia.

All patients in this group had Philadelphia chromosome-positive CML. Their ages ranged from 12 to 58 years, with a median of 35 years. There were 68 males and 47 females. Transplants were performed in chronic phase in 62 patients, in accelerated phase in 26, and in blast transformation in 27. Acceleration was defined as a transition phase associated with increasing leukocyte or platelet count and/or increasing splenomegaly despite chemotherapy, increase of blast cells in the marrow greater than 10% but less than 30%, significant basophilia greater than 20%, development of additional cytogenetic abnormalities, persistent fever, and/or bone pain with an unsatisfactory explanation. Blast crisis was defined as greater than 30% blasts in the marrow aspirate associated with hematologic and constitutional changes. Fifty-six patients underwent transplantation at Ohio State University Hospitals (OSU and Columbus), 27 at Hahnemann University (Philadelphia, PA), 17 at St Vincent's Hospital (Sydney, Australia), and 15 at the Alfred Hospital (Melbourne, Australia). All patients who underwent conditioning with the preparative regimen between March 8, 1984 and August 1, 1990 are reported. Informed consent was obtained from each patient through the Institutional Review Boards of the participating centers. All patients in this study had received prior treatment with hydroxyurea and/or Bu. The time from diagnosis to transplant was 2 to 113 months (median, 9.5 months) in the chronic phase patients; 1 to 84 months (median, 23 months) in the accelerated group; and 1 to 123 months (median, 12 months) in the blast transformation group.

Donor characteristics. All donors were siblings of the recipient; 113 were HLA-A, -B, and -DR identical on serotyping, one patient was an identical twin, and one was a one HLA antigen mismatch. Their cells were mutually nonreactive in the mixed lymphocyte culture. Informed consent was received from all donors. Donor marrow cell dose ranged from 0.33 to 8.6 × 10^8 (median, 3.6 × 10^8) cells/kg of recipient.

Conditioning. All patients received 4 mg/kg of oral Bu daily for 4 days. Cy 60 mg/kg was administered by intravenous (IV) infusion on each of the next 2 days. The infusion of Cy was accompanied by 6 L of fluid per 24 hours. Marrow was infused from the donor 24 to 48 hours after completion of Cy infusion. During conditioning, all patients received either phenytoin or lorazepam to prevent seizures.

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Graft-versus-host disease (GVHD) prophylaxis. Seventy-six patients received cyclosporin (CSP) and methylprednisolone (MP) as prophylaxis against GVHD. This regimen has been previously described.13 The rest received CSP and short methotrexate (MTX) as described by Storb et al.14 although some of these received reduced doses of MTX. Two patients received CSP alone or CSP and T-cell depletion using the monoclonal antibody (MoAb) MuLy 1 as previously described.15 Clinical acute GVHD was graded according to the criteria of Glucksberg et al16 and chronic GVHD was graded according to the criteria of Shulman et al.17

Other posttransplant measures. All patients received acyclovir 200 mg 8th hourly orally as prophylaxis against herpes simplex starting on the day after the transplant. All patients received weekly infusions of intravenous gamma globulin 0.4 g/kg as prophylaxis against infection and GVHD. No patients received hematopoietic growth factors postgrafting.

Statistical methods. The statistical analysis was undertaken on April 4, 1992 and the date of the last follow-up was March 1, 1992. The Mann-Whitney U-test was used to test for engraftment differences by GVHD prophylaxis. The Kaplan-Meier product limit method18 was used to estimate survival and leukemia-free survival (LFS), as well as the incidence of GVHD, interstitial pneumonitis, and relapse incorporating the log-rank test to assess differences between groups. The relationship between time from diagnosis to transplant and Bu dose was estimated using Pearson's correlation.

RESULTS

Engraftment. Four patients died prematurely from sepsis before day 35 and were not evaluable for engraftment. Engraftment was defined as recovery of granulocytes to $0.5 \times 10^9$/L for 2 consecutive days. Of the remaining 111 patients, 110 engrafted satisfactorily. The one patient who failed to engraft had a very large spleen and marrow fibrosis pretransplant and died on day 50. The granulocyte counts decreased below $0.5 \times 10^9$/L at a median of 6 days (range, 0 to 8 days) after infusion of BM. The median time to engraftment was 18 days, with a range of 7 to 38 days. The median time to reach a sustained platelet count of $\geq 40 \times 10^9$/L was 20 days (range, 8 to 76 days). Patients receiving CSP and MP experienced a significantly shorter duration of neutropenia median of 11 days (range, 1 to 32 days) compared with those receiving CSP and MTX, with a median of 16 days (range, 7 to 37 days) ($P < .004$). A more rapid return of platelets to $\geq 40 \times 10^9$/L was noted in the patients receiving CSP + MP, with a median of 19 days (range, 8 to 53 days), than in those receiving CSP + MTX, with a median of 24 days (range, 12 to 76 days). This difference was significant at $P < .003$.

GVHD. The actuarial incidence of grade II-IV AGVHD was 32% (95% confidence interval [CI], 26% to 38%). There was no significant difference in the incidence of grade II-IV AGVHD in those patients receiving CSP + MP (29%) as compared with those receiving CSP + MTX (38%). This result is illustrated in Fig 1. Chronic CGVHD, limited or diffuse,16 was noted in 67% of evaluable patients. Of these, 87% had a Karnofsky score greater than 70% at 6 months and 74% had a Karnofsky score greater than 70% at 1 year.
**Figure 4. Hematologic relapse by disease stage (chronic phase versus blast significant, \( P < .003 \).**

**Figure 5. Survival in first chronic phase by time from diagnosis to transplant (\( P < .015 \)).**

**Figure 6. Survival in first chronic phase related to prior Bu therapy (\( P < .002 \)).**

**Figure 7. Bu dose by time from diagnosis to transplant (all patients).**

**IP.** The actuarial incidence of IP was 12% (95% CI, 9% to 14%) (Fig 2). The majority of patients afflicted with this complication underwent lung biopsies and the cause was identified as cytomegalovirus in 67%, drug related or idiopathic in 26%, and adenovirus in 7%. The case mortality was 80% (12 IP deaths, 2 AGVHD deaths, and 1 recovered). Thirty-one recipients were cytomegalovirus (CMV) negative and 28 of these received CMV-negative blood products and only one developed CMV IP. Three received some CMV-positive blood products and two of these developed CMV IP. Twenty-one patients who were CMV negative received CMV-positive BM and 63 patients were CMV positive and received either CMV-positive or CMV-negative BM. All of this latter group of 84 patients received CMV-positive blood products and seven developed CMV IP.

**Other complications.** VOD was diagnosed on the clinical and laboratory findings of tender hepatomegaly, ascites, jaundice, and abnormal liver function tests, and was found in 11 of 111 patients (9.9%) who were evaluable in that they had been observed for at least 42 days after transplant. There was no significant difference in the incidence of VOD in patients transplanted in chronic phase (4 of 61, 6.6%), accelerated phase (2 of 23, 8.7%), or blast crisis (5 of 26, 19.2%). While VOD contributed to death in some patients, it was not the sole cause of death in any patient. There was a very low correlation of VOD with AGVHD II-IV (\( r < .042 \)). Of the 11 patients who had VOD, 7 had no AGVHD II-IV and 4 had AGVHD II-IV. Hemorrhagic cystitis associated with macroscopic hematuria was noted in 6 of 56 patients in chronic phase, 3 of 22 in accelerated phase, and 3 of 24 in blast transformation. This represents an overall incidence of 11.8% in evaluable patients who were observed for at least 84 days after transplantation.

**Survival and relapse.** Survival by disease stage (Fig 3) was 58% in chronic phase (95% CI, 46% to 70%), 41% in accelerated phase (95% CI, 19% to 63%), and 25% in blast transformation (95% CI, 6% to 43%). LFS, excluding transient cytogenetic relapse, was 58% in CP (95% CI, 46% to 70%), 41% in accelerated phase (95% CI, 19% to 63%), and 25% in blast transformation (95% CI, 6% to 43%). Hematologic relapse was very low: 2.6% (95% CI, 2% to 3.4%), 12% (95% CI, 6% to 19%), and 27% (95% CI, 10% to 43%).
to 43%) in chronic, accelerated, and blast phase of the disease, respectively (Fig 4). Cytogenetic relapse only was seen in two patients in chronic phase. In both, the return of the Philadelphia chromosome was transient, disappearing on subsequent karyotyping. One of these patients died from disease, respectively (Fig 4).

In chronic phase patients there is a striking difference in survival when the time from diagnosis to transplant is considered. Figure 5 shows the actuarial survival in patients transplanted within the first year of diagnosis compared with those transplanted beyond 1 year from diagnosis. Survival in the early transplants is 70%, compared with 40% in the late transplants ($P < .015$). A similar, but not so marked, difference is noted when survival is assessed in relation to previous exposure to Bu. Those patients receiving no previous Bu or less than 100 mg had a survival of 65% compared with those previously receiving high doses of Bu with a survival of 27% ($P < .002$) (Fig 6). Overall, there was a significant correlation ($r = .793, P < .005$) between time to transplant and exposure to Bu (Fig 7). Those patients who did not receive Bu were treated with hydroxyurea, although accurate data on doses was not available. In this group, there was no significant difference in survival for those patients transplanted less than 1 year from diagnosis compared with those treated beyond 1 year from diagnosis (Fig 8).

**Causes of death in the first year.** The transplant-related mortality was quite high in this group of patients. The causes of death include late graft failure/rejection (2), relapse (3), AGVHD (6), IP (7), CGVHD + infection (12), sepsis (15), others (8); including 1 suicide, 1 accident, 3 adult respiratory distress syndrome, 2 gastrointestinal hemorrhage, and 1 airways obstruction.

In the patients transplanted in chronic phase, the differences in survival between those transplanted early compared with those transplanted late appear to be related to differences in IP, AGVHD, and infection (Fig 9).

**Risk factors for LFS.** Using a Cox multivariate analysis, a number of risk factors were analyzed to determine a relationship, if any, between these factors and success or failure of the transplant. The factors analyzed are documented under statistical methods. This analysis showed that the significant factors relating to a poor result include delay from diagnosis to transplant ($>1$ year), previous treatment with Bu, AGVHD (II-IV), blast crisis, VOD, and a male patient with a female donor (Table 1).

**Discussion**

This report includes a large series of patients transplanted for various stages of CML with a irradiation-free regimen. The patients were all adults in a relatively old age group and the survival is at least as good as that reported after conditioning with TBI.8 The striking feature of this group is the very low relapse rate not only in patients transplanted in chronic phase, but in those transplanted with more advance disease. Previous publications6-8 have reported relapses from 7% to 30% when patients are transplanted in chronic phase and from 42% to 80% when transplants are undertaken in advance disease. The incidence of VOD and hemorrhagic cystitis was not as high as reported previously.20 AGVHD was not severe in these patients and was in the range previously reported with combinations of immunosuppressive drugs.

Previously, the Seattle Group have published a large series of patients transplanted for CML and have shown a survival advantage for those transplanted early, within 1 year of diagnosis.6 An even larger series was analyzed by the International Bone Marrow Transplant Registry (IBMTR)9 and the difference in the early transplants was not demonstrated. Subsequent analyses (IBMTR, unpublished observations) showed a survival advantage in early transplants.
Table 1. Multivariate Cox Regression Analysis on the Risk of Relapse or Death

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>( P ) Value</th>
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<tbody>
<tr>
<td>VOD (no/yes)</td>
<td>3.7</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>AGVHD II-IV (no/yes)</td>
<td>2.9</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Time from diagnosis to BMT (&lt; 1 yr / &gt; 1 yr)</td>
<td>2.7</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Male patient, female donor (no/yes)</td>
<td>2.5</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Previous Bu therapy (no/yes)</td>
<td>2.2</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Blast crisis (no/yes)</td>
<td>2.0</td>
<td>&lt;.02</td>
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but not as marked as shown by Seattle. In this group, there is a clearcut advantage in survival when patients are transplanted within 1 year of diagnosis and this appears to be related to less exposure to Bu previously, as this survival advantage was not shown in a subgroup of patients who had been treated on hydroxyurea. The toxicity of the BuCy2 regimen was higher in patients with CML previously treated with Bu, but in those patients transplanted early and not exposed to Bu previously it was of the same order as reported in acute myeloblastic leukemia.12

BuCy2 is very easy to administer and would seem to be as effective as irradiation-containing regimens, although this may be subsequently confirmed with randomized trials in the future and further analysis from the IBMTR. A significant advance might be the availability of a parenteral preparation of Bu, as the bioavailability of oral doses has been shown to be quite variable from patient to patient. Unexpectedly high levels may be associated with toxicity, while lower levels may reduce antileukemic effectiveness.21-23

It appears clear from this study and others using TBI that early transplantation in CML is likely to result in much lower transplant-related mortality and subsequent improvement in long-term cure rate. More data are required to study the relationship of previous drug treatment to survival after transplantation. New approaches to reduce interstitial pneumonitis will lead to even better results.24

The selection of the most effective conditioning regimen for advanced disease remains a dilemma, as early toxicity is a problem with both TBI- and Bu-containing regimens and relapse remains higher than in those patients transplanted early in the disease process.

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Treatment of chronic myeloid leukemia with allogeneic bone marrow transplantation after preparation with BuCy2

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