Marrow Transplantation for Chronic Myeloid Leukemia: A Randomized Study Comparing Cyclophosphamide and Total Body Irradiation With Busulfan and Cyclophosphamide


A prospective randomized study was conducted comparing two conditioning regimens for the treatment of patients with chronic myeloid leukemia in chronic phase by marrow transplantation from HLA identical siblings. Sixty-nine patients received 60 mg/kg of cyclophosphamide on each of 2 successive days (BU-CY). In 1987, Tutschka reported the use of a conditioning regimen consisting of busulfan (BU; 16 mg/kg administered over 4 days) followed by 60 mg/kg CY on each of 2 successive days (BU-CY). There was no significant difference between the BU-CY and the BU-CY groups in the 3-year probabilities of survival (0.80 for both), relapse (0.13 for both), or event-free survival (CY-TBI, 0.68; BU-CY, 0.71) or in speed of engraftment or incidence of venocclusive disease of the liver. The 4-year probabilities of survival and event-free survival for patients transplanted within 1 year of diagnosis were 0.86 and 0.72, respectively, for each group. Significantly more patients in the CY-TBI group experienced major creatinine elevations. There was significantly more acute graft-versus-host disease in the CY-TBI group. Fewer days, positive blood cultures, hospitalizations, and inpatient hospital days were significantly more common in the CY-TBI group than in the BU-CY group. In conclusion, the BU-CY regimen was better tolerated than, and associated with survival and relapse probabilities that compare favorably with, the CY-TBI regimen.

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bodies. Chronic GVHD was treated with prednisone alone or in combination with CSP.

**Tissue Typing Studies**

All donor-recipient pairs were HLA genotypically identical siblings as shown by serologic typing for HLA-A, B, DR, and DQ, testing in mixed lymphocyte culture assays and more recently supplemented by typing for DRB alleles by the hybridization of sequence-specific oligonucleotide probes to polymerase chain reaction amplified DNA.

**Relapse**

All patients were scheduled to have marrow samples examined by cytogenetic analysis on days 21, 56, and 84, then every 6 months for 2 years, and then annually. Relapse was defined as the detection of Ph-positive metaphases in the marrow after day 50 posttransplant. Relapse was further categorized as transient when Ph-positive metaphases cleared from the marrow and remained undetectable without definitive therapeutic intervention. Otherwise, relapses were defined as persistent. Clinical relapse was defined when hematologic or clinical changes characteristic of CML first recurred after transplantation.

**Infection**

A day of fever was defined as 24 hours during which the patient had a recorded temperature greater than 38.3°C. Throat swabs and samples of blood and urine were cultured weekly for the presence of cytomegalovirus (CMV). Interstitial pneumonia (IP) was diagnosed by bronchoalveolar lavage, open lung biopsy, or autopsy. Various infectious disease prophylaxis strategies were used during this study including isolation in laminar air flow rooms; the prophylactic use of systemic antibiotics, fluconazole, acyclovir, ganciclovir; and the use of screened or filtered blood products. Screened blood products were used for all CMV-seronegative recipients with seronegative donors until mid 1989 when all such patients received either screened or filtered blood products. Acyclovir for CMV prophylaxis was administered to all patients before, and to none after, 1991. However, it was administered for prophylaxis to all herpes simplex virus-seropositive patients. Ganciclovir was administered to all CMV-seropositive recipients either for excretion (until 1988), then at either engraftment or at the first development of antigenemia. Fluconazole was not used until 1990 when 50% of allogeneic recipients were randomized to receive it, and subsequently, all allogeneic patients received it. There were no stratifications that affected the allocation of these approaches in the arms of the current study, between which they were evenly distributed. Ceftazidime was used for systemic prophylaxis against infection in 21 patients in the CY-TBI group and in 13 patients in the BU-CY group. CEFTAZIDIME (P = .12, Fisher).

**Causes of Death**

Deaths after persistent posttransplant relapse were categorized as caused by leukemia, irrespective of the proximate cause. Deaths in the absence of persistent relapse were categorized as nonrelapse mortality. Infection was listed as the cause of death when a bacterial, viral, or fungal infection other than IP was the proximate cause of death in patients who had not relapsed. Infections were further categorized according to their association with or without GVHD. Deaths caused by IP formed a separate category.

**Informed Consent**

Risks of the treatment protocols were explained fully to the patients, donors, and relatives. Informed consent was obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

**Statistical Analysis**

The statistical design was based on the assumption that the relapse probability would be 20% for patients treated with CY-TBI. For an 80% power of detecting a decrease to 5%, 60 patients would be needed in each arm of the study.

Normally distributed means were compared using the standard two-sample t test, and nonnormal distributions were compared with the two-sample Wilcoxon test. Other comparisons of proportion were performed with the two-tailed Fisher's exact test.

The endpoints of engraftment analysis were the first days on which patients achieved 3 consecutive days with granulocyte counts of at least 0.1, 0.5, and 1.0 × 10⁹/L or 7 consecutive days with platelet counts of 20 × 10⁹/L without platelet transfusions.

The endpoints of survival analysis were duration of remission (from transplantation until persistent relapse, censored by death or end of follow-up) and relapse-free survival (from transplantation until relapse or death, censored by the end of follow-up). Patients were considered to be at risk for transplant-related mortality from the day of marrow infusion until relapse or the end of follow-up. The distributions of the probabilities of surviving, remaining in remission, dying from causes other than relapse, and developing persistent relapse were estimated by the method of Kaplan and Meier, and levels of statistical significance were calculated by the log-rank statistic. Durations of follow-up were calculated to the latest date of contact with each patient, and events were recorded through November 1993. No adjustments for multiple comparisons were made in calculating the reported P values.

**RESULTS**

**Patient Characteristics**

Table 1 presents the hematologic characteristics at the time of diagnosis and at the time of transplant, as well as those associated with preparation for transplant. The two groups were comparable with respect to factors believed to be associated with prognosis for patients receiving conventional care. All Ph chromosomes involved the standard t(9;22)(q34;q11) translocation. Seven patients (3 treated with BU-CY and 4 with CY-TBI) received granulocyte colony-stimulating factor (3 patients at 8, 3 patients at 16, and 1 patient at 32 μg/kg daily) for 3 weeks after transplantation as part of a study designed to examine its effectiveness in accelerating engraftment. These patients were not included in the comparisons of engraftment. A total of 11 patients prepared with CY-TBI and 7 patients prepared with BU-CY received pentoxifylline in a randomized controlled trial of its effectiveness in preventing regimen-related toxicities in patients undergoing allogeneic marrow transplantation.

**Engraftment**

One patient (who received CY-TBI) died on day 18 from CMV-associated IP without achieving 0.1 × 10⁹ circulating granulocytes per liter. All other patients had granulocyte counts that dropped below 0.5 × 10⁹/L and subsequently achieved levels of circulating granulocytes greater than 1 × 10⁹/L. The mean number of days with granulocytes less than 0.5 × 10⁹/L was 16.2 for patients treated with CY-TBI and
There was no difference between the arms in the mean day of achieving 0.5 × 10^9 granulocytes per liter.

There was no difference between the regimens in the time taken to achieve sustained platelet levels of 20 × 10^9/L without transfusion (22.49 days for the CY-TBI arm and 21.0 days for the BU-CY arm).

**Transplant-Related Toxicity**

**Bilirubin.** The maximum serum bilirubin level during the first 14 posttransplant days was compared with the pre-treatment bilirubin level (bilirubin ratio). The bilirubin ratios were higher in the patients receiving CY-TBI (mean, 10.65) than in patients receiving BU-CY (mean, 9.67), but this difference was not significant (P = 0.87, Wilcoxon). There was no difference between the groups in the day on which the maximum bilirubin increase occurred. There was no significant difference between the groups in the maximum serum bilirubin levels during the first 28 days after transplant. For the 69 patients in the CY-TBI arm, the maximum bilirubin during the first 28 days was greater than 2.0 mg/dL in 48 (70%) and greater than 3.0 mg/dL in 43 (62%). The corresponding incidences for the 72 patients in the BU-CY arm were 51 (71%) and 39 (54%).

Weight gain. Weight gain during the transplant period is frequently associated with venoocclusive disease (VOD). The mean maximum weight gain as a percentage of pretreatment weight was 3.88% in the patients treated with CY-TBI and 4.07% in those who received BU-CY (P = 0.36, Fisher’s exact test). Maximum weight increases of 5% and 10% occurred in 31 (45%) and 5 (7%) patients, respectively, in the CY-TBI arm and in 38 (53%) and 8 (11%) patients, respectively, in the BU-CY arm.

Creatinine levels and ratios. The mean maximum serum creatinine level during the first 28 days after transplantation was 1.54 mg/dL for patients in the CY-TBI group (range, 0.8 to 4.8 ± 0.8) and 1.34 for patients in the BU-CY group (range, 0.7 to 3.9 ± 0.5; P = 0.07, t test). A total of 5 patients (4 treated with CY-TBI and 1 with BU-CY) had maximum serum creatinine levels greater than 3.0 mg/dL.

The maximum serum creatinine level during the first 28 posttransplant days was compared with the day-0 creatinine level (creatinine ratio). These ratios were significantly higher for patients receiving CY-TBI (mean, 2.03) than for those in the BU-CY group (mean, 1.55; P = 0.002, t test). The proportions of patients with creatinine ratios of 2 or more were 38% in the CY-TBI group and 12% in the BU-CY group (P = .0008, Fisher’s exact), and 10% of patients receiving CY-TBI had creatinine ratios of 3 or more compared with 5% in the BU-CY group (P = .36, Fisher’s exact test).

**Infection**

Days of fever. A total of 40 patients in the CY-TBI group and 35 patients in the BU-CY group had at least 1 day of fever during the first hospital admission (P = .24, Fisher’s exact). For those patients who developed fever, the mean number of days of fever was 7.00 for patients who received CY-TBI and 4.69 for patients receiving BU-CY (P = .03, Wilcoxon).
Positive blood cultures during the first 100 posttransplant days. A total of 25 patients conditioned with CY-TBI and 13 patients conditioned with BU-CY had at least 1 blood culture positive for bacteria or fungi (\(P = .015\) Fisher’s exact). In 15 CY-TBI patients and 8 BU-CY patients, the positive blood cultures were associated with fever and/or hypotensive shock (\(P = .11\), Fisher’s exact). A total of 5 of the 15 symptomatic episodes in CY-TBI patients and 2 of the 8 episodes in BU-CY patients occurred when granulocytes were less than 0.1 \(\times 10^9/\text{L}\).

Deaths from infection. In the BU-CY arm, 1 patient died of bacterial septicemia on day 49, and 6 died from fungal disease between days 150 and 355. In the CY-TBI arm, there were no deaths from bacterial or fungal infection in the first 100 days; 1 patient died from aspergillus infection on day 134, and 1 died from mucor infection on day 186.

CMV excretion and infection. CMV was isolated from blood, urine, or throat culture during the first 100 days after transplant from 18 (23%) of the patients prepared with CY-TBI, 2 of whom died (on days 73 and 94) from CMV IP. CMV was isolated during the first 100 days from 16 (22%) of the patients prepared with BU-CY, 1 of whom died on day 316 from complications of chronic GVHD. Of patients who excreted CMV, all patients except 2 in each group were serologically CMV-positive before transplant, and the exceptions had CMV-seropositive marrow donors.

Duration of Hospitalization

The mean duration of stay for the first hospitalization was 39.13 days (range, 24 to 63 \(\pm 6.85\)) for patients in the CY-TBI group and 38.52 days (range, 26 to 69 \(\pm 8.19\)) for patients treated with BU-CY (\(P = .13\), Wilcoxon). A total of 45 patients treated with CY-TBI had more than one hospital admission during the first 100 days, compared with 24 patients treated with BU-CY (\(P = .0002\), Fisher’s exact). The mean number of admissions per patient was 2.12 for patients receiving CY-TBI (range, 1 to 4 \(\pm 1.03\)) and 1.49 for patients receiving BU-CY (range, 1 to 4 \(\pm 0.81\); \(P = .0005\), Wilcoxon). The two most common reasons for hospital readmission were fever that required intravenous antibiotic administration and GVHD of the gut that necessitated total parenteral alimentation. In the CY-TBI arm, 15 patients required readmission because of fever, and 8 because of gut GVHD. In the BU-CY arm, 5 patients were readmitted because of fever, and 2 because of gut GVHD. The mean total number of hospital inpatient days was 49.99 (range, 27 to 91 \(\pm 15.08\)) for patients receiving CY-TBI and 43.55 (range, 26 to 127 \(\pm 14.51\)) for those receiving BU-CY (\(P = .015\), Wilcoxon).

Prophylaxis of Acute GVHD

One patient in each arm died within the first 28 days posttransplant (on days 18 and 25). A total of 53 CY-TBI patients and 60 BU-CY patients received at least 80% of each dose of MTX. There was no significant difference between the arms in the number of patients who received 80% or more of the prescribed dose of CSP during the first, second, and fourth weeks after transplant. During the third week, 44 patients in the CY-TBI arm and 59 patients in the BU-CY arm received 80% or more of the prescribed dose of CSP (\(P = .03\), Fisher).

Incidence of GVHD

The Kaplan-Meier incidence of acute GVHD grade 2 or more was 0.48 in the patients treated with CY-TBI and 0.35 in those treated with BU-CY (Fig 1, \(P = .049\)). The probability of developing grade 3 or 4 acute GVHD was 0.20 for patients treated with CY-TBI and 0.14 for patients who received BU-CY (\(P = .25\)). A total of 29 patients treated with CY-TBI and 30 patients treated with BU-CY developed clinical, extensive chronic GVHD.

Survival

Seven patients (4 who received CY-TBI and 3 who received BU-CY) died during the first 100 days after trans-
plantation. Of these deaths, 5 were caused by IP (3 associated with CMV and 2 idiopathic); 1 patient died of acute respiratory distress syndrome, and 1 died of septicemic shock.

The Kaplan-Meier probabilities of survival at 3 years were 0.80 for each group. The probabilities of event-free survival were not different between the arms (0.68 for patients who received CY-TBI and 0.71 for patients who received BU-CY; \( P = .43 \)). The 3-year probabilities of dying from causes other than relapse were 0.24 for patients who received the CY-TBI regimen and 0.18 for patients who received the BU-CY regimen. There were no significant differences between the groups with respect to these statistics (Fig 2).

The Kaplan-Meier probabilities of event-free survival at 3 years were 0.66 for patients treated with CY-TBI and 0.70 for patients who received BU-CY \(( P = .36; \text{Fig 3})\).

A total of 51 CY-TBI patients and 50 BU-CY patients were transplanted less than 1 year after diagnosis. The 4-year probabilities of survival were 0.86 in each of these groups. The 3-year Kaplan-Meier probabilities of developing persistent relapse were 0.13 for both CY-TBI patients and BU-CY patients \(( P = .43; \text{Fig 3})\).

Clinical relapse. Evaluation of the probability of clinical relapse was obstructed by a policy of therapeutic intervention with interferon (IFN) in patients who developed more than 50% Ph-positive metaphases among a minimum of 20 marrow metaphases on 2 samplings. A total of 3 patients in each group developed clinical relapse before this threshold was detected, and 1 patient in the BU-CY group developed clinical relapse while being treated with IFN.

A total of 4 patients were less than 17 years old at the time of transplant. Both of the 2 patients treated with CY-TBI, aged 13 and 6 years, are alive and disease-free. Of the 2 who were treated with the BU-CY regimen, both aged 7 years, 1 never cleared the marrow of Ph-positive metaphases and died in continuing relapse on day 606, and the other had negative marrow cytogenetics on days 21 and 78 but presented with clinical relapse on day 278.

A total of 3 patients (in the BU-CY group) died on days 606 and 698 and at 3.5 years as a consequence of relapse. A total of 6 CY-TBI-treated patients and 3 BU-CY-treated patients died from causes associated with GVHD.

### Relapse

Table 3 summarizes the patterns of relapse.

**Cytogenetic relapse.** A total of 15 patients treated with CY-TBI and 10 patients who received BU-CY had Ph chromosomes present in at least 1 marrow sample after transplant. A total of 6 of these relapses in CY-TBI patients and 2 in BU-CY patients occurred before day 80. Among the CY-TBI patients, 5 occurrences (first detected on days 53, 62, 83, 236, and 361) were transient with positive metaphases spontaneously becoming undetectable, and 6 of the 10 persistent relapses were first detected before day 100. Among the BU-CY patients, 3 occurrences (first detected on days 69, 84, and 643) were transient, and 1 of the 7 persistent relapses was first detected before day 100 (Table 3). All patients who had transient cytogenetic relapses remain alive and disease-free.

The 3-year Kaplan-Meier probabilities of developing persistent relapse were 0.13 for both CY-TBI patients and BU-CY patients \(( P = .43; \text{Fig 3})\).

**Clinical relapse.** Evaluation of the probability of clinical relapse was obstructed by a policy of therapeutic intervention with interferon (IFN) in patients who developed more than 50% Ph-positive metaphases among a minimum of 20 marrow metaphases on 2 samplings. A total of 3 patients in each group developed clinical relapse before this threshold was detected, and 1 patient in the BU-CY group developed clinical relapse while being treated with IFN.

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### Table 2. Causes of Death

<table>
<thead>
<tr>
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<th>CY-TBI</th>
<th>BU-CY</th>
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<tbody>
<tr>
<td>Total deaths</td>
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<td>15</td>
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<td>Associated with GVHD</td>
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<td>Chronic GVHD</td>
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<td>1</td>
</tr>
<tr>
<td>IP-CMV</td>
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<td>1</td>
</tr>
<tr>
<td>IP-idiopathic</td>
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<td>1</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fungal infection</td>
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<td>3</td>
</tr>
<tr>
<td>Liver failure</td>
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<td>0</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
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<td>0</td>
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<tr>
<td>Respiratory failure</td>
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<td>0</td>
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<tr>
<td>Leukemia</td>
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<tr>
<td>Without GVHD</td>
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<tr>
<td>ARDS</td>
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<tr>
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<td>Pulmonary fibrosis</td>
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<tr>
<td>Fungal infection</td>
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</tr>
<tr>
<td>Leukemia</td>
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<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: ARDS, adult respiratory distress syndrome.

### Table 3. Relapse Characteristics

<table>
<thead>
<tr>
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<th>CY-TBI</th>
<th>BU-CY</th>
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</thead>
<tbody>
<tr>
<td>Total cytogenetic</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Transient cytogenetic</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IFN before clinical relapse</td>
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<td>3</td>
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<tr>
<td>Clinical relapse before IFN</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Total clinical relapse</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
patients were treated with IFN for posttransplant relapse, and 1 of these patients has died.

Current Status of Survivors

In the CY-TBI group, 44 of the 55 survivors have Karnofsky performance scores (KPS) of 90 or more, compared with 53 of the 58 survivors in the BU-CY group (P = .11, Fisher).

In the CY-TBI group, 4 survivors have KPS between 80 and 90 associated with IFN therapy for relapse in 1 patient and with recurrent infections and mild chronic GVHD in 3 patients. A total of 6 CY-TBI patients have KPS between 70 and 80 associated with steroid therapy of chronic GVHD in 3 patients, with IFN therapy of relapse in 2, and with bronchiolitis obliterans requiring supplemental oxygen therapy in 1. One CY-TBI patient has a KPS of 20 associated with intractable severe chronic GVHD.

In the BU-CY group, 1 patient has a KPS of 80 associated with IFN therapy of relapse, 3 have KPS of 70 associated with chronic GVHD, and 1 has a KPS of 60 associated with a severe autoimmune hemolytic anemia and thrombocytopenia.

DISCUSSION

Blaise et al reported a randomized study comparing CY-TBI and BU-CY for the transplant conditioning of 101 patients with acute myeloid leukemia in first remission. There was some variability in the CY-TBI regimen, but 43 patients received fractionated CY-TBI to a median dose of 12 Gy. All patients received posttransplant immunosuppression with MTX and CSP. Survival and disease-free survival were significantly better in the CY-TBI group, and both transplant mortality and relapse were significantly worse in the BU-CY group. The patients treated with CY-TBI had an unusually good outcome, with a 78% survival and 76% disease-free survival.

The current study clearly shows that, for patients with CML in CP, the BU-CY regimen was not inferior to the CY-TBI regimen for any of the end points examined, whereas many of the measures of transplant-related toxicity significantly favor the BU-CY group. There was no difference between the groups in the speed of engraftment, although severe granulocytopenia was significantly more common and its duration significantly longer in the patients treated with CY-TBI.

Serum bilirubin elevation and weight gain have been identified as useful measures of VOD. There was no significant difference in the maximum weight gain or bilirubin elevation during the first 28 days after transplantation. Serum bilirubin elevations during the first 14 days after transplant more specifically indicate VOD than does the 28-day statistic, and this too was not significantly different between the 2 groups. There was a significantly higher proportion of patients in the CY-TBI group who had a doubling of the serum creatinine level during the first 28 days after transplantation that may have impaired the delivery of CSP for GVHD prophylaxis in these patients. This may have been, at least in part, responsible for a significantly higher incidence of acute GVHD in patients treated with CY-TBI.

In a major study of VOD by McDonald et al, the incidence of severe VOD in 45 patients transplanted for CML in CP with TBI-containing regimens was 4%. Biggs et al have reported the results of allogeneic marrow transplantation after treatment with BU-CY in 115 patients with CML (62 in CP). Patients in CP transplanted within 1 year of diagnosis had a 4-year survival of 70%, and the investigators concluded that the survival statistics and transplant-related mortality were similar to those observed in patients conditioned with regimens containing CY-TBI. The incidence of VOD in patients transplanted in CP was 6.6%. Essell et al reported that, in patients receiving MTX plus CSP for GVHD prophylaxis, hepatotoxicity (particularly VOD) was significantly higher for patients conditioned with BU-CY than for those conditioned with CY-TBI. The study did not allocate treatment by randomization, and it involved patients with several different types and stages of leukemia. In the studies reporting the use of BU-CY in patients with CML in CP, there is no consistent evidence of an increase in hepatotoxicity compared with that observed after CY-TBI, whereas there is consistent evidence of an increase in VOD in patients with other hematopoietic malignancies receiving BU-CY. One of the reasons for this difference may be the much greater exposure to pretransplant chemotherapy experienced by patients with acute leukemia.

There was significantly more fever in the CY-TBI patients, and the number of patients with blood cultures positive for bacteria or fungi was significantly higher in this group. This may reflect the increased incidence of acute GVHD and its treatment with steroids or the more prolonged severe granulocytopenia, or it may indicate a different pattern of tissue damage than that caused by BU-CY. However, the incidence of late fungal infection was higher in the BU-CY group, and we do not know what is responsible for this. There was no difference between the groups in the incidence of CMV excretion. Patients treated with CY-TBI had significantly more hospitalizations and longer total hospital stays than those treated with BU-CY.

A much longer follow-up will be required to determine whether the known late effects of CY-TBI (which have been reported to include the development of cataracts and second malignancies) also occur in patients treated with BU-CY.

In conclusion, the BU-CY regimen used in this study was better tolerated than the CY-TBI regimen and was associated with equivalent outcome. For the 101 patients transplanted within 1 year of diagnosis, the 4-year probability of survival with either regimen was .86. The number of patients required for randomized studies aimed at improving this survival would be very large, and it is difficult to devise a practicable study of regimens aimed at improving survival. The BU-CY regimen described in this report offers opportunities for studying protocols that might reduce the toxicity, cost, and inconvenience of marrow transplantation in this setting. Caution should be used in generalizing from the particulars of this study. The regimens used may have differing comparative toxicities in patients with other diseases and with a different history of pretransplant therapy.

The problem of posttransplant relapse remains both com-
plex and challenging. In this study, the 3-year probability of persistent cytogenetic relapse with either regimen was .13, which is not significantly different from that found in our last study of CML in CP where the probability of persistent cytogenetic relapse in 57 patients treated with the same CY-TBI regimen was .17. The testing of conditioning regimens for improved antileukemic effect will be very difficult. It may be more rewarding to study the effect of the treatment of, or prophylaxis against, clinical relapse in patients identified after transplantation as being at high risk for this event. For this purpose, we need a better understanding of the nature and definition of posttransplant relapse.

REFERENCES


PHASE 3 STUDY OF TBI VERSUS BU-CY FOR CML TRANSPLANTS


Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide

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