A Prospective Randomized Comparison of Total Body Irradiation-Etoposide Versus Busulfan-Cyclophosphamide as Preparatory Regimens for Bone Marrow Transplantation in Patients With Leukemia Who Were Not in First Remission: A Southwest Oncology Group Study

By Karl G. Blume, Kenneth J. Kopecky, Jean P. Henslee-Downey, Stephen J. Forman, Patrick J. Stiff, C. Frederick LeMaistre, and Frederick R. Appelbaum

Two novel preparatory regimens for conditioning of patients with leukemia for allogeneic bone marrow transplantation (BMT) from histocompatible sibling donors have been tested in a phase III trial under the auspices of the Southwest Oncology Group (SWOG 8612). These two regimens consisted either of fractionated total body irradiation and etoposide (FTBI/VP-16) or high-dose busulfan with cyclophosphamide (BU/CY). Only patients who had failed prior conventional management at least once were study eligible, i.e., no patients with acute leukemia in first remission (CR) or in first chronic phase (CP) of chronic myelogenous leukemia (CML) participated. Patients were stratified according to the following risk criteria: “good-risk” patients were those who were in second CR of their acute leukemia or in accelerated phase (AP) of CML; “poor-risk” patients had further advanced stages of leukemia. During a 52-month period, 131 patients were registered of whom 122 (93%) were study eligible. Sixty-one eligible patients were randomized to the FTBI/VP-16 arm and 61 to the BU/CY regimen. Of these 122 patients, 114 (93%) proceeded to BMT according to protocol. Posttransplant immunosuppression was performed at Johns Hopkins University where higher doses of CY had been used. Both regimens were well tolerated with no regimen-related deaths encountered during the 6-week period after BMT. This study also confirmed the efficacy of the CSA/PSE combination in the prevention of GVHD with 23 of 113 (20%) of BMT recipients developing moderate to severe acute GVHD. The leading cause for treatment failure was leukemic relapse (45 of the 114 BMT recipients suffered a recurrence of their leukemia), whereas 38 patients died without evidence of relapse. Thirty-one patients are alive and in continued CR after marrow transplantation; four are alive in relapse. It is concluded that the two preparative regimens do not differ significantly with respect to toxicity, incidence of acute GVHD, overall survival, or DFS.

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RECURRENCE of the underlying hematologic malignancy represents a major cause for treatment failure after myeloablative/immunosuppressive therapy and allogeneic bone marrow transplantation (BMT). The regimen used in most BMT centers worldwide to prepare patients with leukemia for BMT consists of fractionated total body irradiation (FTBI) and high-dose cyclophosphamide (CY). With this regimen, the relapse rate for patients transplanted in first complete remission (CR1) of acute myeloblastic leukemia (AML) and acute lymphoblastic leukemia (ALL) or during the chronic phase (CP) of chronic myelogenous leukemia (CML) is approximately 10% to 25%. This rate increases to about 25% to 50% if patients are in their second complete remission (CR2) of AML and ALL or if CML has proceeded to the accelerated phase (AP). Finally, posttransplant relapse rates range from 50% to 80% in patients with even further advanced stages of acute leukemia, i.e., in third complete remission (CR3), after remission induction failure (IF), or in florid relapse (REL), or in those patients whose CML has entered the blastic phase (BP).

During the past 20 years, several BMT teams have attempted to intensify or modify the “standard” FTBI/CY regimen with the goal of achieving improved long-term disease-free survival (DFS) and higher cure rates. Two pilot trials have been performed with particularly promising results. A team of investigators at the City of Hope National Medical Center had explored a regimen consisting of FTBI and etoposide (VP-16) in a phase I/II trial. The FTBI technique followed the method that had been developed at the Memorial Sloan Kettering Cancer Center. The other regimen containing a combination of high-dose busulfan (BU) and CY was tested by a team of investigators at Ohio State University. This preparative regimen was based on an earlier study performed at Johns Hopkins University where higher doses of CY had been used.

In December 1986, the Southwest Oncology Group (SWOG) activated a phase III trial to test the efficacy of these regimens.
two novel regimens with respect to toxicities and DFS in a prospective controlled fashion. Only patients with leukemia whose disease had advanced beyond the stages of CR1 of AML and ALL or those whose CML was no longer in first CP were eligible for this trial (SWOG 8612).

PATIENTS AND METHODS

It was a requirement for enrollment that patients sign a consent form describing the details of this trial as required by the institutional review boards of the participating centers.

Between March 1987 and June 1991, nine SWOG-accredited BMT centers enrolled 131 patients with leukemia, of whom 122 (93%) were eligible for registration. Nine patients were found to be ineligible for this study: three because of treatment with myelosuppressive chemotherapy less than 28 days before registration, and one each because of active central nervous system leukemia, invasive fungal infection, bilirubin exceeding 2 mg%, poor cardiac status (MUGA <45%), prior radiation therapy, and absence of a presudy lumbar puncture (in a patient with ALL).

Patients were stratified for age (0 to 20 years v 21 to 50 years), type of leukemia (AML v ALL v CML) and disease status (CR2 or AP [so-called "good-risk" group] v CR3, IF, in relapse or BP [so-called "poor-risk" group]) to ensure an approximate balance of treatment assignment with respect to these factors.\textsuperscript{18} Sixty-one eligible patients were randomized to be treated with the FTBI/VP-16 regimen and 61 patients were randomized to the BU/CY treatment arm. There were eight major protocol violations: seven patients did not receive protocol BMTs and one patient underwent splenectomy 3 days after registration. Seven of the eight were in the "poor-risk" group and one in the "good-risk" group. All eight were excluded from analyses of posttransplant outcomes such as graft-versus-host disease (GVHD) and DFS, but not from the analysis of survival. A summary of the 122 eligible patients' characteristics is presented in Table 1.

Patients were randomized to receive one of two preparatory regimens. The FTBI/VP-16 regimen consisted of total body irradiation with 1,320 cGy (11 fractions of 120 cGy delivered between days −7 and −4) and VP-16 (60 mg/kg) on day −3.\textsuperscript{14} The BU/CY regimen consisted of BU (16 mg/kg) administered orally in 16 doses over 4 days, days −7 to −4) and CY (120 mg/kg in two equal doses administered intravenously on 2 successive days, days −3 and −2).\textsuperscript{16} All patients received marrow grafts from their histocompatible siblings. The marrow grafts were obtained following a commonly used method and were administered on the day of BMT, day 0.\textsuperscript{16} Both groups of BMT recipients were treated with a uniform regimen to prevent GVHD.\textsuperscript{16} This protocol contained the two drugs cyclosporine (CSA) and prednisone (PSE), a combination that had originally been studied at the City of Hope National Medical Center and at Johns Hopkins University.\textsuperscript{20,21} The dose schedule for CSA/PSE used in this study followed the regimen as described by the investigators at Ohio State University.\textsuperscript{16} The drugs VP-16, BU, CSA, and PSE were administered using the patients' actual body weights, whereas CY was adjusted to the ideal body weights. The design of SWOG trial 8612 is illustrated in Fig 1.

Overall survival based on the 122 eligible patients was counted from the day of entry into the study until death from any cause. DFS based on the 114 eligible patients receiving transplants was counted from the day of BMT until relapse or death from any cause. Time to relapse was counted from the day of BMT until relapse and censored for patients who died without relapse. Distributions of survival and DFS were estimated by the method of Kaplan and Meier.\textsuperscript{22} Comparisons of overall survival, DFS, or relapse between the treatment groups were based on proportional hazards regression models, which allow adjustment for stratification factors.\textsuperscript{23} Relative risks (RRs) estimated from these models express the rate of death (for survival), death or relapse (for DFS), or relapse among BU/CY patients as a multiple of the corresponding rate among FTBI/VP-16 patients. RRs greater or less than 1.0 indicate greater or less risk, respectively, among BU/CY patients. Statistical significance was expressed in terms of two-sided P values.

This study was expected to accrue 120 patients over 3 years. With 2 additional years of follow-up, this would provide statistical power...

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**Table 1. Pretransplant Characteristics, Classified by Disease Status and Treatment Arm for the 122 Protocol Eligible Patients**

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>FTBI/VP-16 (n = 21)</th>
<th>BU/CY (n = 27)</th>
<th>FTBI/VP-16 (n = 40)</th>
<th>BU/CY (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) Median</td>
<td>29</td>
<td>39</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Minimum</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Maximum</td>
<td>48</td>
<td>47</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>0-20 yr</td>
<td>5 (24)</td>
<td>3 (11)</td>
<td>15 (38)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>21-50 yr</td>
<td>16 (76)</td>
<td>24 (89)</td>
<td>25 (63)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>Sex</td>
<td>Males: 13 (62)</td>
<td>23 (85)</td>
<td>27 (68)</td>
<td>21 (62)</td>
</tr>
<tr>
<td></td>
<td>Females: 8 (38)</td>
<td>4 (15)</td>
<td>13 (33)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Race</td>
<td>White: 19 (90)</td>
<td>23 (85)</td>
<td>33 (83)</td>
<td>29 (85)</td>
</tr>
<tr>
<td></td>
<td>Black: 2 (10)</td>
<td>1 (4)</td>
<td>2 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>Other: 0 (0)</td>
<td>3 (11)</td>
<td>5 (13)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>ALL: 8 (38)</td>
<td>6 (22)</td>
<td>17 (43)</td>
<td>17 (60)</td>
</tr>
<tr>
<td></td>
<td>AML: 5 (24)</td>
<td>6 (22)</td>
<td>17 (43)</td>
<td>12 (35)</td>
</tr>
<tr>
<td></td>
<td>CML: 8 (38)</td>
<td>15 (56)</td>
<td>6 (15)</td>
<td>5 (15)</td>
</tr>
</tbody>
</table>

Percentages are in parentheses.
Table 2. Leading Causes for Failure/Death Classified by Disease Status and Treatment Arm for the 114 Patients Who Underwent BMT According to Protocol

<table>
<thead>
<tr>
<th>Cause</th>
<th>&quot;Good Risk&quot; (n = 20)</th>
<th>&quot;Good Risk&quot; (n = 27)</th>
<th>&quot;Poor Risk&quot; (n = 32)</th>
<th>&quot;Poor Risk&quot; (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>-</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>CMV pneumonia</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other pneumonia</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Other infections</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Veno-occlusive disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Other drug toxicities</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Relapse</td>
<td>3</td>
<td>7</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Alive in relapse</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Alive in continued CR</td>
<td>9</td>
<td>3</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviation: CMV, cytomegalovirus.

RESULTS

Of the 122 eligible patients, 114 (93%) received BMT according to protocol. All but one of the patients receiving transplants survived at least 28 days after BMT and showed signs of marrow engraftment; the other patient died 5 days after BMT with persisting AML.

Eighty-seven of the 122 eligible patients have died. The remaining 35 patients were known to be alive between 10 and 58 months (median, 31 months) after registration on the study. Of the 114 eligible patients receiving transplants included in the analyses of posttransplant events, 31 are alive and in continued complete remission, whereas 83 have relapsed or died of leukemia or other causes (ie, are counted as "events" in the analysis of DFS). Of these 83 patients, 4 were last known to be alive in relapse, 41 had died with or after relapse, and 38 had died without evidence of relapse. The causes for treatment failure (relapse) or death are summarized in Table 2. The estimated distributions of overall survival and DFS are shown by disease status and treatment arms in Figs 2, 3, and 4.

![Fig 2. Estimated distribution of DFS by treatment arm of 114 patients receiving transplants with follow-up.](image)

![Fig 3. Estimated distribution of overall survival by disease status and treatment arm of 122 eligible patients with follow-up.](image)

![Fig 4. Estimated distribution of DFS by disease status and treatment arm of 114 patients receiving transplants with follow-up.](image)
Disease status ("good risk" v "poor risk") impacted significantly on survival (P = 0.0018), DFS (P = 0.0014), and relapse (P = 0.0002), whereas age group (0 to 20 v 21 to 50) did not (P = .77 for survival, .71 for DFS, and .22 for relapse). After adjusting for disease status, the two treatment groups did not differ significantly with respect to survival (P = .89), DFS (P = .69), or relapse (P = .95). After adjusting for both disease status and age, essentially identical results were obtained.

The treatment comparisons concerning all patients are summarized in terms of relative risks in Table 3. The estimated RR of death (for BU/CY patients relative to FTBI/VP-16 patients) is 0.97, with a 95% confidence interval of 0.64 to 1.48. This indicates that there was slightly but not significantly less mortality among the BU/CY patients. Similarly, from the analysis of the DFS, the rate of relapse or death without relapse was slightly higher in the BU/CY group (RR, 1.09; 95% CI, 0.71 to 1.69). The rate of relapse was slightly higher in the BU/CY group (RR, 1.02; 95% CI, 0.56 to 1.86).

Figure 3 and Table 3 suggest that FTBI/VP-16 may have been more beneficial than BU/CY in the "good-risk" patients. The estimated probability of DFS at 3 years was 55% (standard error, .04 of 55 patients (18%) on the FTBI/VP-16 arm as compared with 13 of 58 patients (22%) who had been treated with BU/CY (P = .64). Based on patients who survived at least 100 days after BMT, chronic GVHD occurred in 13 of 48 (27%) of patients on the FTBI/VP-16 treatment arm as compared with 14 of 45 (31%) patients prepared with the BU/CY regimen.

At the time of the most recent evaluation, the median performance status of the surviving patients was 90% on the Karnofsky scale for both treatment arms, ranging from 60% to 100% for the FTBI/VP-16 patients and from 50% to 100% for patients prepared with the BU/CY regimen.

DISCUSSION

Over a period of 52 months, 122 eligible patients were enrolled in this multi-institutional trial and 114 patients received the prescribed treatment, ie, one of two preparatory regimens, followed by allogeneic marrow grafting from histocompatible siblings. The compliance rate of 93% is relatively high and compares favorably with that of other cooperative group studies in cancer chemotherapy. The follow-up of transplanted patients has been rigorous and the median observation time of the patients remaining alive now exceeds 30 months.

Recipient age was not found to be a significant factor for successful treatment outcome. The group of patients aged 0 to 20 years had a similar DFS rate as compared with that of those patients in the age group of 21 to 50 years. Other in-
vestigators had made the same observation in single institution trials, eg, in patients undergoing allogeneic marrow transplantation for AML during first remission. However, there were relatively few young patients in the current trial and an effect of age on outcome could have been missed.

DFS of the 114 patients receiving transplants with “good-risk” and “poor-risk” strata combined is approximately 20% for both treatment arms (Fig 2). It is a disadvantage of any analysis without consideration of disease status that it does not apply to a “real” patient. “Real” patients will either be in the “good-risk” group, in which case their treatment outcome will be better than that shown in Fig 2, or in the “poor-risk” group, in which their prognosis will be worse than illustrated in Fig 2. In addition, the results presented in Fig 2 are dependent on the ratio of “good-risk” to “poor-risk” patients on study. Had there been relatively more “good-risk” patients enrolled, the overall results would have been better, and had there been relatively more “poor-risk” patients in this trial, the result would have been worse. There were relatively more “good-risk” patients on the BU/CY arm (46%) as compared with the FTBI/VP-16 regimen (36%).

Under controlled conditions, the “good-risk” group treated with FTBI/VP-16 (median age, 29 years) had a rather favorable outcome of 55% ± 11% DFS at 3 years. These candidates had failed prior conventional therapy at least once, ie, they were patients in second complete remission of acute leukemia or AP of CML. Two other groups of investigators have reported similarly encouraging treatment results with this preparatory regimen.

The group of “good-risk” patients prepared with the BU/CY regimen had an estimated DFS of 34% ± 10% at 3 years. The median age of BU/CY patients was 10 years higher (median age, 39 years) than that of otherwise comparable candidates who received the FTBI/VP-16 regimen and, when adjusted for age, no statistically significant difference in outcome was found with the two treatments. Previous reports from Ohio State University had indicated that the BU/CY regimen was also effective in older patients and those with CML in AP or BP.

This study, with a planned 120 patients, was designed to detect reliably only fairly large treatment differences (89% power to detect an RR of 2.3). As it turned out, however, the data reported here provide somewhat more statistical power than was originally projected, because the number of relapses and death in the analysis of DFS (83) is higher than had been predicted. Using the formula of Schoenfeld, 83 events provide statistical power of about 88% to detect an RR of 2.0. Nevertheless, this study does not rule out the possibility that one of the two preparative regimens will produce better outcomes among patients at large.

In SWOG study 8612, the oral administration of BU was not adjusted to individual pharmacokinetic data derived from the initial drug dose, a matter that has become of increased interest for clinical trials using this agent. Both regimens have been well tolerated with no regimen-related deaths observed during the first 6 weeks after BMT. The acceptable toxicity of the two regimens has prompted other groups of investigators to add other agents to the BU/CY and to the FTBI/VP-16 regimen. Whether these modifications will result in an improvement of the treatment outcome remains to be tested in future comparative trials.

SWOG trial 8612 also confirmed that the immunosuppressive posttransplant combination of CSA/PSE was a useful approach to prevent acute GVHD. Under the controlled conditions of this trial, the incidence of grade II to IV acute GVHD was 18% and 22% for the two groups, confirming prior single institution observations.

The results of this study underscore again the enormous importance of pretransplant criteria for “good risk” versus “poor risk,” ie, the negative impact of advanced leukemia on the treatment outcome. Leukemic relapse remains a major cause for treatment failure after marrow transplantation. After all, it was the intent of the two novel regimens to decrease the relapse rate and to thus achieve a higher cure rate. As indicated above, the incidence of relapse was particularly high in “poor-risk” candidates.

In the meantime, collaborating institutions have tested the two new regimens (BU/CY and FTBI/VP-16) in patients who were in first remission of the acute leukemias and in first chronic phase of CML. These results have again been encouraging, with disease-free long-term survival in the order of 63% to 71% for the two regimens. Investigators in France have prospectively compared the BU/CY regimen with the standard combination FTBI/CY for treatment of AML and have found a significant advantage for those patients treated with the FTBI/CY regimen. Investigators in Seattle have completed a similar study for treatment of CML and have, to date, found equivalent outcomes. Another study currently being performed at the City of Hope National Medical Center and Stanford University is comparing the FTBI/VP-16 combination to FTBI/CY in a phase III trial. It will take the better part of the remaining years of this decade to define the ultimate role of novel pretransplant combinations.

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A prospective randomized comparison of total body irradiation-etoposide versus busulfan-cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a Southwest Oncology Group study

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