Bone Marrow Transplantation for Leukemia Following a New Busulfan and Cyclophosphamide Regimen

By Peter J. Tutschka, Edward A. Copelan, and John P. Klein

Busulfan 16 mg/kg and cyclophosphamide 120 mg/kg were used as conditioning prior to allogeneic marrow transplantation in 50 adult patients with acute nonlymphocytic leukemia (ANLL), acute lymphocytic leukemia (ALL), and chronic myelogenous leukemia (CML). A standard risk group of 20 patients included those with acute leukemia in remission and CML in chronic phase. A high-risk group of 30 patients included individuals with refractory acute leukemia, acute leukemia in relapse, acute leukemia following preleukemia, and CML in accelerated and blastic phase. Complete remission and sustained complete engraftment were achieved in all evaluable patients. The duration of aplasia was remarkably short (median of 8 days), resulting in a low infection rate during the period of neutropenia, a reduced need for blood product support, and a short length of hospital stay. Three-year actuarial relapse-free survival in both standard-risk (88.9% ± 10.6%) and high-risk (50.5% ± 9.6%) groups compares favorably with that reported with total body irradiation (TBI) containing regimens.

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MATERIALS AND METHODS

All patients were entered on a study protocol that had been reviewed and approved by The Ohio State University Institutional Review Board.

Patient accrual. Fifty adult patients were consecutively entered into the study. Eligibility for the study required a diagnosis of ALL, ANLL, or CML, regardless of the remission status. All patients were ambulatory, had an HLA-identical sibling donor, and were aged >15 and ≤50 years. No other medical parameters were used as exclusion criteria. All diagnoses of leukemia were confirmed by examination of the bone marrow aspirate and biopsy. On admission, all patients had a bone marrow aspirate and bone marrow biopsy as well as a diagnostic lumbar puncture to assess the status of the leukemia. Presence of leukemic cells in the spinal fluid was not an exclusion criterion. All data are analyzed as of February 14, 1987. The patients were transplanted between February 13, 1984 and August 14, 1986; therefore, the observation period for these patients has been a minimum of 6 months and a maximum of 3 years.

Study groups. The study involved two groups of patients. A standard-risk group consisted of patients with acute leukemia in the first or second remission, or CML in the chronic phase. Twenty patients, 11 with ANLL in remission, 2 with ALL in remission, and 7 with CML in chronic phase were in this group. The high-risk group consisted of 30 patients with refractory acute leukemia, acute leukemia in relapse, or CML in accelerated or blastic phase. Refractory acute leukemia was defined as leukemia that failed to remit after two courses of conventional chemotherapy. Patients were considered to be in the accelerated phase of CML if they had ≥10% blasts in blood or marrow together with major perturbations of the leucocyte or platelet count unresponsive to chemotherapy with busulfan or hydroxyurea. They were considered to be in the blastic phase if they had ≥30% blasts in the blood or bone marrow. Among the patients in the high-risk group were two previously untreated patients in whom leukemia developed after a preleukemic syndrome (UPN 4 and UPN 17). Twelve patients had ANLL, 4 had ALL, and 14 patients had CML in accelerated (n = 9), or blastic phase (n = 5).

Patient criteria. The median age of the recipients was 28 years (range 15 to 50 years). The median age of patients in the standard-risk group was 32 years (range 19 to 50 years), and the median age of...
the high-risk group 27 years (range 15 to 48 years). Thirty-four patients were male and 16 patients were female. Thirty-four patients were sex matched with their recipients (20 male to male, 9 female to female transplants), and 16 patients were sex mismatched (6 male to female and 10 female to male transplants). All patients were identical for A, B, C, D/Dr locus with their allogeneic sibling donors. The technical aspects of the procedure have been described elsewhere. All donors tolerated the marrow aspiration well and were discharged between 1 and 2 days after the marrow harvest. No significant complications of the marrow harvest procedure occurred.

Preparative regimen. All patients were given methotrexate intrathecally (10 mg/m² of body surface but not more than 12 mg total) 10 days prior to marrow transplantation. Three patients who had central nervous system (CNS) leukemia at the beginning of the transplant procedure were given four intrathecal treatments of methotrexate. Patients received busulfan orally at a dose of 1 mg/kg of ideal body weight four times daily for 4 consecutive days for a total dose of 16 mg/kg. Cyclophosphamide at a daily dose of 60 mg/kg of ideal body weight was administered intravenously (IV) over a 1-hour period for 2 consecutive days. Bone marrow was infused 2 days after the final dose of Cy.

Supportive therapy. On the day of hospitalization, all patients were placed in ultraclean rooms equipped with HEPA-filtered laminar air flow. Patients were treated in strict isolation. "Sterile diet" with very low bacterial content was begun on day 4 requiring antiemetic therapy. None of the patients developed severe oral mucositis, but most patients complained of mild sore throat between 7 and 11 days after transplantation for acute leukemia if they showed a completely normal bone marrow and peripheral blood status together with the absence of lymphohematopoietic cells of recipient origin by cytogenetic analysis.

Patients were considered to be in complete remission after transplantation for CML if they showed a completely normal bone marrow and peripheral blood status together with the absence of lymphohematopoietic cells of recipient origin by cytogenetic analysis. Patients who showed the presence of the Philadelphia chromosome prior to transplantation required the complete and persistent disappearance of this chromosomal abnormality after transplantation to qualify for complete remission status.

GVHD. All patients received a combination of cyclosporine and methylprednisolone to prevent GVHD. Cyclosporine started 1 day prior to transplantation and was given as a continuous infusion of 5 mg/kg daily for 4 days. After that time, the dose of cyclosporine was reduced to 3 mg/kg given IV over 6 hours daily until day 14. From day 14 through day 35, the dose of cyclosporine was increased to 3.75 mg/kg given IV. Thereafter, cyclosporine was slowly tapered until day 180, after which time it was discontinued. At discharge, patients were given oral cyclosporine at a dose four times higher than the IV dose. Methylprednisolone was started on day 7 at a dose of 0.5 mg/kg/day. On day 14, the dose was increased to 1 mg/kg/day, and was given until day 28. Then, until day 72, the methylprednisolone was slowly tapered. All patients received prophylaxis for CNS leukemia. Between day 70 and day 90 after bone marrow transplant, four intrathecal doses of 10 mg/m² each of methotrexate were administered over 2 to 4 weeks.

Acute GVHD was assessed according to the grading system described in the literature. Chronic GVHD was assessed using descriptive criteria reported previously. Patients were assumed to have chronic GVHD if they had the typical features of the disease and/or were given adrenal steroids after day 100. Patients with chronic GVHD were divided into three groups according to severity, grade 1 disease showing mild symptoms that resolve within 2 months, grade 2 showing mild symptoms that require 2 to 6 months for resolution without sequelae, and grade 3 disease showing marked symptoms that require >6 months of therapy.

Other common complications. Intestinal pneumonia was diagnosed when bilateral interstitial/alveolar infiltrates on chest x-ray were associated with hypoxemia (PO₂ on room air of ≤65 mm Hg). Hemorrhagic gastroenteritis was diagnosed when diarrhea of greater than 1,000 mL/day was present that was either bloody or maroon and persisted for >3 days.

Statistical analysis. Estimates of survival probabilities and the probability of being in remission were computed by using the product-limit estimates of Kaplan and Meier. In estimating the probability of being in remission, we treated those patients who died free of leukemic disease as censored observations. A Cox's proportional-hazards analysis was performed in each of the clinical variables displayed in Tables 1 and 2. Significance was judged using the maximum likelihood chi-squared statistic.

RESULTS

Early toxicity of the preparative regimen. The preparative regimen was generally very well tolerated. Mild nausea and vomiting were noted during busulfan administration in nine patients; the remaining patients all tolerated busulfan well. On the days during which Cyclophosphamide was administered, most patients experienced nausea and vomiting requiring antiemetic therapy. None of the patients developed severe oral mucositis, but most patients complained of mild sore throat between 7 and 11 days after transplantation.
transplant. Of the 50 patients, 32 had no evidence of hemorrhagic cystitis. Eight showed minimal microscopic hematuria, 5 patients showed macroscopic hematuria, and 5 patients showed severe hemorrhagic cystitis. Clinical symptoms of venoocclusive disease occurred in one patient (UPN 37), but resolved without any sequelae.

Antileukemic effect. With the exception of one patient who died on day 2 (UPN 38), all patients experienced a complete remission. This includes all patients with refractory disease and those in blast crisis of CML.

None of the patients transplanted in the standard-risk group to date have shown evidence of relapse. Among the 30 patients in the high-risk group, five patients all transplanted for acute leukemia experienced a complete clinical remission (UPN 2, 7, 21, 22, and 52). Of the 14 patients transplanted for CML in accelerated or blastic phase, only one patient has shown evidence of relapse by cytogenetic analysis (UPN 21). This patient, who developed recurrence of the Philadelphia chromosome in the marrow, was retransplanted using the same conditioning regimen. She is alive, disease-free 777+ days after the first transplant and 185+ days after the second transplant. The remaining 13 patients transplanted for CML in the accelerated or blastic phase to date remain in complete remission with a normal bone marrow and peripheral blood status, absence of the Philadelphia chromosome, and presence of lymphohematopoietic cells of exclusively donor type. A Kaplan-Meier product limit estimate for the probability of being in remission is shown in Fig 1.

Engraftment and marrow function. One patient who died on day 2 from cardiac failure (UPN 38) could not be evaluated for engraftment. One other patient (UPN 71) showed a recovery marrow on day 14, but never reached a WBC level >1.0 x 10^9/L. The remaining 48 patients all showed complete and sustained engraftment. The patients maintained a WBC level >1.0 x 10^9/L for a median of 15 days (range 11 through 36). The median time to reach a self-sustaining platelet count of 40 x 10^9/L was 19 days (range 11 through 38). Bone marrow biopsies obtained on day 14 after transplant showed the presence of all hemapoietic cell lines, including megakaryocytes in all patients except the one patient who could not be evaluated for engraftment (UPN 38).

The degree of chimerism was assessed primarily by cytogenetic analysis. Cytogenetic analysis of the bone marrow was performed with each bone marrow aspirate. Cytogenetic analysis of the peripheral blood was performed every 2 weeks during the first 3 months and thereafter at each visit of the patient to the transplant center.

At day 14 after transplant, all patients had a marrow aspirate performed. Twenty-three patients showed technically sufficient cytogenetic preparations (14 sex markers and 9 autosomal markers) with a mean of 12.6 metaphases examined per patient. All cells identified cytogenetically at day 14 were of donor origin.

At least one second bone marrow examination was carried out, the latest performed at a mean of 123 days after transplantation. Twenty-six patients showed technically sufficient cytogenetic preparations with a mean of 18.4 metaphases examined per patient. Of these 26 patients, 24 had exclusively donor cells in their marrow. One patient (UPN 66) showed two of ten metaphases to be of recipient type at 71 days after transplant. He remains in complete remission on day 243+ after transplantation. One other patient (UPN 13) showed 1 of 17 cells to be of recipient type on day 446 after transplant. This patient, transplanted for CML in blast crisis, remains alive in complete remission on day 919+ after transplantation.

The cytogenetic analysis of the peripheral blood cells can be summarized as follows. Two hundred twenty-six samples were taken from 34 patients or an average of 6.64 samples per patient. The median number of samples per patient was 6.5 (range 1 to 15). Four thousand six hundred eleven cells were examined, an average of 20.40 per sample or 135.61 per patient. The number of cells per patient examined ranged from 13 (1 determination) to 390 (15 determinations). The

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Table 1. Cytogenetic Analysis of Cells in Peripheral Blood

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of Samples</th>
<th>No. of Patients</th>
<th>Median Day</th>
<th>No. of Donor Cells</th>
<th>Total Cells</th>
<th>Donor Cells (%)</th>
<th>SE</th>
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<tr>
<td>0-20</td>
<td>26</td>
<td>22</td>
<td>17</td>
<td>438</td>
<td>513</td>
<td>85.4</td>
<td>1.56</td>
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<td>21-40</td>
<td>32</td>
<td>24</td>
<td>29</td>
<td>403</td>
<td>514</td>
<td>78.4</td>
<td>1.81</td>
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<td>41-70</td>
<td>35</td>
<td>23</td>
<td>60</td>
<td>537</td>
<td>634</td>
<td>84.7</td>
<td>1.43</td>
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<td>36</td>
<td>25</td>
<td>84</td>
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<td>777</td>
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<td>1.02</td>
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<td>101-160</td>
<td>25</td>
<td>21</td>
<td>130</td>
<td>620</td>
<td>665</td>
<td>93.2</td>
<td>0.97</td>
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<tr>
<td>161-220</td>
<td>18</td>
<td>15</td>
<td>184</td>
<td>395</td>
<td>404</td>
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<td>0.73</td>
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<tr>
<td>221-365</td>
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<td>18</td>
<td>284</td>
<td>608</td>
<td>613</td>
<td>99.2</td>
<td>0.36</td>
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<td>25</td>
<td>9</td>
<td>593</td>
<td>491</td>
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Table 2. Clinical Parameters Associated With Survival (Cox-Hazards)

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<thead>
<tr>
<th>Parameter</th>
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<th>SE</th>
<th>P Value</th>
<th>SE</th>
<th>Relative Risk</th>
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<tbody>
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<td>Refractoriness</td>
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<td>0.69</td>
<td>0.0034</td>
<td>5.98</td>
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<tr>
<td>Interstitial pneumonia</td>
<td>1.28</td>
<td>0.319</td>
<td>0.0001</td>
<td>3.60</td>
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<tr>
<td>Acute GVHD (≤grade 2)</td>
<td>2.61</td>
<td>0.872</td>
<td>0.0028</td>
<td>13.59</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>2.584</td>
<td>0.68</td>
<td>0.0001</td>
<td>13.316</td>
<td></td>
</tr>
</tbody>
</table>
median number of cells per patient examined was 115.5. The median number of cells per sample was 20 (range 1 to 50). The mode was 32. The median day of these examinations was 87.5 (range 12 to 767). The interquartile range was 117.5.

During the first 20 days, 85.4% of the cells were classified as donor. With time, the number of donor cells increased steadily until by day 365 after transplant only donor cells could be identified in the peripheral blood. A breakdown of the quantitative analysis over time is given in Table 1.

Support during the first 30 days after transplantation. Due to the brief period of aplasia, relatively few blood products were required to maintain a hemoglobin of ≥10 g/dL and a platelet count of ≥20 x 10⁹/L. Patients transplanted in the high-risk group were given a median of 5 U RBCs (range 0 through 42) and five transfusions of single donor platelets (range 0 through 137). The patients transplanted in the standard-risk group received a median of 3 U RBCs (range 0 through 10) and a median of four transfusions of platelets (range 0 through 20). Eleven high-risk and eight standard-risk patients (38%) did not develop a temperature >100.5°F in the first 30 days and required no therapeutic antibiotics. Only one patient was given amphotericin-B for a fungal infection (UPN 71). One patient was documented to have bacteremia with Pseudomonas aeruginosa (UPN 43), probably derived from a cutaneous Pseudomonas abscess that antedated the transplant procedure. This patient responded promptly to appropriate antibiotic therapy. Two patients developed stomatitis with herpes simplex virus, which responded to Acyclovir. Three patients developed Candida esophagitis documented by endoscopy. All three responded promptly to oral nonabsorbable antifungal agents. Patients were discharged from the hospital when their granulocyte count was >0.5 x 10⁹/L on three successive days and platelet and RBC counts were self-sustaining. Furthermore, they were required to be afebrile, off therapeutic antibiotics, and no longer receiving parenteral nutrition. The median day of discharge of all patients was 22 days (range 18 to 71), of the patients in the standard-risk group it was 21 days (range 18 to 33), and of the patients in the high-risk group it was 26 days (range 19 to 71).

GVHD. Acute GVHD was present in 15 patients. Of these fifteen patients, eleven showed grade 1 disease, one showed grade 2 disease, two showed grade 3 disease, and one showed grade 4 disease. All three patients with severe GVHD (grades 3 and 4) died in part from the GVHD. Chronic GVHD of grade 1 occurred in 5 patients, chronic GVHD of grade 2 occurred in 15 patients, and chronic GVHD of grade 3 occurred in 5 patients. Chronic GVHD resolved with no sequelae in all but two patients. Chronic GVHD was associated with death in 2 patients with grade 3 disease. Chronic GVHD has been completely absent to date in 16 of the 35 surviving patients. Of the 45 patients surviving 100 days, 19 or 42% have shown clinically significant chronic GVHD of grade 2 or greater at any time during their transplant.

Interstitial pneumonia and hemorrhagic gastroenteritis. Interstitial pneumonia occurred in six patients, four of whom died with the disease. In 2 patients cytomegalovirus could be identified by bronchoalveolar lavage, 2 patients had idiopathic interstitial pneumonia, and 1 patient each had pneumonia associated with Legionella and Pneumocystis carinii. Two patients developed hemorrhagic gastroenteritis. In one of the two patients, hemorrhagic gastroenteritis was associated with severe GVHD, of which the patient died. The other patient recovered.

Late infections. Late infections (past day 50) occurred in 13 patients. Two patients developed systemic fungal infections (Candida albicans, UPN 24; Aspergillus fumigatus, UPN 19), and 12 patients developed bacterial infections, all with gram-positive organisms. Of these 12 bacterial infections, 8 were caused by Streptococcus pneumoniae, and 4 by Staphylococcus epidermidis. All bacterial infections presented with fever and minimal associated clinical symptoms and had documented bacteremia. Most bacterial infections (11 of 12) occurred after day 120 and have not been seen after IV immunoglobulin therapy was extended to 1 year posttransplant.

Survival. Of the 50 patients transplanted, 35 remain alive in unmaintained clinical remission. The actuarial 3-year survival rate of this patient population is 65%. The survival curves for all patients transplanted are shown in Figs 2 and 3. All patients in the standard-risk group transplanted for either ANLL or CML are disease-free survivors, and only 1 of the 20 patients transplanted in the standard-risk group (for ALL, UPN 19) has died. This death was associated with chronic GVHD and systemic Aspergillus infection, the patient being in complete remission at the time of death.

Of the 30 patients transplanted in the high-risk group, 16 are alive at present in unmaintained clinical remission. Nine of the 14 patients transplanted for CML in accelerated or blastic phase are alive, and 7 of the 16 patients transplanted for advanced acute leukemia are alive in unmaintained complete remission. The survival curves for these patient groups are shown in Figs 4 and 5.

Parameters affecting survival. Parameters that might
affect survival were entered into a Cox regression proportional hazards model for death as outcome variable. The parameters included: diagnosis; disease status; risk group; age and sex of the recipient; time of return of blood counts; day of discharge; number of late infections; and the complications of hemorrhagic cystitis, hemorrhagic gastroenteritis, interstitial pneumonia, acute GVHD, and chronic GVHD. Refractory disease, interstitial pneumonia, hemorrhagic cystitis, and acute GVHD of grade 2 or greater were all significantly associated with death. These data are shown in Table 2.

**DISCUSSION**

Busulfan and Cy are an attractive combination for pretransplant conditioning. Preclinical studies in a rat model have demonstrated the importance of myelosuppression in combination with immunosuppression for preparing marrow graft recipients. In this model, the addition of busulfan, a nonimmunosuppressive but highly myelotoxic agent, to Cy, a moderately myelotoxic but highly immunosuppressive agent, permitted the reduction of Cy without compromising engraftment. Previous clinical trials using a combination of busulfan and high-dose Cy demonstrated excellent antileukemic efficacy, but serious toxicity similar to TBI-containing regimens. The present study attempted to show that the reduction of Cy would not compromise antileukemic effectiveness of the combination, but would markedly reduce the complication rate. The reduction of Cy to 120 mg/kg, the commonly used dose in TBI-containing regimens, permitted furthermore the direct comparison of busulfan to TBI in the hope of achieving overall a lower complication rate.

The data presented in this report bear out these predictions. The preparative therapy was well tolerated, and apart from moderate yet transient nausea and vomiting associated with Cy, no immediate toxicity occurred. Apart from one patient who died too early for evaluation, all patients, including those with refractory leukemia or in blastic phase of CML, achieved complete remissions and complete sustained engraftment. As predicted from the animal model, marrow recovery occurred rapidly. Fully functioning hematopoietic grafts were usually achieved within the first 2 weeks after transplantation. It is tempting to speculate that the busulfan, by virtue of its “space making” properties, was responsible for this short aplasia. It is equally possible, on the one hand, that the avoidance of TBI was less damaging to the microenvironment, permitting earlier engraftment. On the other hand, substituting cyclosporine and methylprednisolone for methotrexate in the prevention of GVHD might have reduced the induced aplasia after transplantation. This short period of aplasia resulted in a markedly reduced need for blood product support and, most important, in a surprisingly low incidence of infectious complications. There was a virtual absence of bacteremia (one patient) and only one patient required amphotericin-B administration. Other common complications, such as acute GVHD were also infrequent. The low incidence of severe acute GVHD may have resulted from prophylaxis with a new combination regimen of cyclosporine/methylprednisolone. The low incidence of early infectious complications resulting from short aplasia, lesser amounts of tissue toxicity, and ultraclean environmental conditions may have led to a reduced incidence of
GVHD, a postulate supported by a number of preclinical and clinical observations.11,18

It is unclear to what extent the reduced incidence of interstitial pneumonia can be credited to the preparative regimen. Because radiotherapy and acute GVHD contribute to the development of interstitial pneumonia,19 the low incidence in our study is probably not just a spurious observation. Furthermore, the patients received IV immunoglobulin preparations and blood products derived from cytomegalovirus-antibody-negative donors, both procedures reportedly associated with a lower incidence of viral interstitial pneumonia.20,22

Late complications seen after allogeneic bone marrow transplantation were not altered in frequency when compared with TBI-containing regimens. Some patients developed gram-positive bacteremias after 100 days, none of which led to the death of the patients. These often quite insidious infections have not been observed since the administration of IV immunoglobulin was extended to 1 year posttransplant.

Similarly, chronic GVHD occurred frequently. Fortunately, this complication has been very mild and in most patients chronic GVHD has resolved completely without sequelae.

The antileukemic efficacy of this regimen is apparent. Although the disease-free survival in regular-risk patients so far is outstanding, clearly additional follow-up time is required to ascertain that these patients are indeed cured. The excellent results achieved in advanced disease demonstrate a potent antileukemic effect, however. The results in accelerated and blastic phase of CML compare favorably to published results in recent studies that use TBI and Cy.3

The patients studied here were at high risk for several reasons. They were older than patients in most comparable studies, some of our patients being 50 years old. Older age clearly increases the transplant risk.23,24 Many had advanced disease, including high-risk factors such as pretransplant hepatic dysfunction, cytogenetic abnormalities, CNS disease, and cutaneous involvement, all parameters associated with poor prognosis.

The results of this study are encouraging. This regimen may be more effective and less toxic than TBI-containing regimens for patients generally considered to be good transplant candidates, eg, those with acute leukemia in remission and CML in chronic phase. In addition, this regimen offers promise in circumstances such as CML in accelerated or blastic phase and in refractory acute leukemia in which transplantation results have been so poor that valid questions as to the appropriateness of allogeneic marrow transplantation have been raised. Furthermore, the low toxicity of this regimen might permit the use of additional antileukemic agents in patients with advanced disease.

This report suggests that this new regimen provides an alternative to traditional conditioning regimens that include TBI. It offers substantial promise in decreasing the morbidity and improving the outcome of patients undergoing allogeneic marrow transplantation.

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