Long-term Outcome of Hodgkin Disease Patients Following High-Dose Busulfan, Etoposide, Cyclophosphamide, and Autologous Stem Cell Transplantation

Navin Wadehra,1 Sherif Farag,2 Brian Bolwell,3 Patrick Elder,1 Sam Penza,1 Matt Kalaycio,3 Belinda Avalos,1 Brad Pohlman,3 Guido Marcucci,1 Ronald Sobecks,3 Thomas Lin,1 Steven Andrèsen,3 Edward Copelan1

1Division of Hematology and Oncology, The Ohio State University Hospitals, Columbus, Ohio; 2Department of Medicine, Division of Hematology and Oncology, Indiana University, Indianapolis, Indiana; 3Hematologic Oncology and Blood Disorders, The Cleveland Clinic, Cleveland, Ohio

Correspondence and reprint requests: Sherif Farag, MD, PhD, Department of Medicine, Division of Hematology and Oncology, Indiana University, 635 Barnhill Drive, Indianapolis, IN 46202 (e-mail: ssfarag@iupui.edu).

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ABSTRACT
Busulfan (Bu)-based preparative regimens have not been extensively investigated in Hodgkin disease (HD). The purposes of this study were to investigate the toxicity and efficacy of a novel preparative regimen of Bu 14 mg/kg, etoposide 50-60 mg/kg, and cyclophosphamide 120 mg/kg in patients with primary refractory and relapsed HD. One hundred twenty-seven patients with a median age of 33 years (range, 14-67 years) underwent transplantation. The regimen was well tolerated, with 5.5% treatment-related mortality at 100 days after transplantation. With a median follow up of 6.7 years, the 5-year progression-free survival was 48% and the 5-year overall survival was 51%. A Cox proportional hazards model identified refractory disease at time of transplantation as the only significant factor affecting relapse and overall survival, whereas disease bulk >10 cm affected overall survival. Five patients died between 5.3 and 9.3 years of late complications, including secondary myelodysplasia or acute myeloid leukemia, secondary solid malignancies, and pulmonary toxicity. This novel Bu regimen is comparable to other radiation-free preparative regimens in its effectiveness in the control of HD and with a low-risk of early treatment-related mortality.

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KEY WORDS
Hodgkin’s disease ● Busulfan ● Autotransplant

INTRODUCTION
Hodgkin disease (HD) is a chemosensitive disease, with 50%-60% of patients cured with conventional chemotherapy and radiation [1,2]. However, only a small proportion of patients who do not achieve complete remission or relapse after induction chemotherapy is cured with standard salvage chemotherapy [3]. For these patients, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) can improve outcome [4-9]. Although several preparative regimens with or without total body irradiation (TBI) have been investigated in HD, no superiority of a single regimen has been established [10,11]. In particular, only 1 study investigated the efficacy of high-dose busulfan (Bu)-based regimens specifically in patients with HD [12]. Bu-based preparative regimens have been extensively examined and shown to be effective in ASCT and allogeneic transplantation for a wide variety of other hematologic disorders including acute and chronic leukemias and non-Hodgkin lymphoma (NHL) [13-22].

We previously reported our experience with Bu-based preparative regimens in myeloid disorders and NHL [14,16,20]. The initial study with Bu 16 mg/kg and cyclophosphamide (Cy) 120 mg/kg (BuCy2) was originally evaluated but was associated with a high incidence of severe hepatic veno-occlusive disease and...
treatment-related mortality (TRM) [14]. The BuCy2 regimen was subsequently revised in NHL to lower the dose of Bu from 16 to 14 mg/kg to decrease severe veno-occlusive disease and TRM. In addition, etoposide was added to improve effectiveness without increasing toxicity substantially. Using this regimen in NHL, 382 patients were treated with Bu, Cy, and etoposide at doses comparable to those used in our HD patient population. It was found to be effective, with a 46.9% progression-free survival (PFS) and a 2.6% TRM [20]. The Fred Hutchinson Group examined a regimen of Bu 12 mg/kg, melphalan 100 mg/m² and thiotepa 500 mg/m² in 92 patients with HD. The TRM was 15% and 6-year overall survival (OS) was 55% [12]. The purpose of the present study was to investigate the long-term clinical results of the largest series of patients with primary refractory and relapsed HD treated with a radiation-free Bu regimen.

METHODS

Between February 1990 and December 1998, 127 consecutive eligible patients with HD underwent high-dose therapy with Bu, Cy, and etoposide (BuCyVP) followed by ASCT at The Ohio State Medical Center and the Cleveland Clinic Foundation. The protocol was approved by the institutional review boards at both institutions and patients provided written informed consent. The techniques for marrow aspiration and peripheral blood stem cell harvest after the administration of human granulocyte colony-stimulating factor with chemotherapy, cryopreservation, thawing, and infusion have been described previously [23-25].

HD was classified according to the Rye histopathologic classification [26]. All patients were required to have adequate cardiac, renal, and hepatic functions.

Preparative Regimen

The regimen was administered as previously described [20]. Briefly, Bu was administered at a dose of 1 mg/kg orally every 6 hours for 14 doses beginning 8 days before stem cell infusion. Etoposide 50-60 mg/kg was initiated 2 hours after the last dose of Bu as a 36-hour continuous intravenous infusion. Then Cy 60 mg/kg was administered intravenously on 2 consecutive days. Bone marrow and peripheral blood stem cells were infused 2 days after the completion of Cy. Phenytoin was given prophylactically for the prevention of seizures before and during Bu administration. Bu levels were not measured. Granulocyte colony-stimulating factor 5 μg/kg was administered daily after transplantation until the neutrophil count reached 0.5 × 10⁹/L. Prophylactic systemic antibiotics were administered when the absolute neutrophil count was <0.5 × 10⁹/L and were discontinued after neutrophil engraftment when counts recovered to an absolute neutrophil count >0.5 × 10⁹/L.

Statistical Analysis

A partial remission required at least a 50% decrease in the tumor size measured by the sum of the products of the perpendicular diameter of all areas of known disease. No response was defined as less than a 50% decrease in tumor size. A complete remission was defined as no evidence of residual lymph node enlargement by computed tomographic scan. Progressive disease was defined as an increase in size of any area of known disease or the appearance of new disease. Relapse was defined as a recurrence >6 months after the completion of initial chemotherapy. A sensitive relapse was defined as at least a partial response to salvage therapy immediately before transplantation. Patients were considered to have refractory disease if they progressed through their initial chemotherapy regimen or if their disease showed less than a partial response to salvage chemotherapy before transplantation.

Overall survival (OS) was measured from the time of transplantation until death regardless of cause, with censoring for patients alive. The cumulative incidence of relapse or progression was calculated from the time of transplantation until relapse or death, except that death in remission was regarded as a competing risk. Univariate analyses of survival and event-free survival used the Kaplan-Meier product limit method with log-rank tests of survival curves [27]. To study the independent effect of the preparative regimen and control for other baseline clinical factors such as number of previous treatments, age, presence of bulky disease (>10 cm) at the time of diagnosis, B symptoms at the time of diagnosis, and lactate dehydrogenase at the time of transplantation, and bone marrow involvement at the time of transplant, a Cox proportional hazards model was constructed for OS [28]. For all analysis, a 2-sided P value <.05 was considered statistically significant.

RESULTS

Patient Characteristics

The baseline patient characteristics are presented in Table 1. There were 91 men and 36 women in this study. The median age was 33 years (range, 14-67 years). Seventy one percent of patients had responsive disease, and 13% had bulky disease (>10 cm). Ninety patients were in complete or partial remission and 37 were refractory to their last therapy at the time of transplantation. Most patients (76%) had <3 prior chemotherapy regimens.
Overall Survival/Progression-free Survival

With a median follow-up of 6.7 years (range, 3.5-10.2 years), the 5-year PFS was 48% (95% confidence interval, 38%-58%; Figure 1) and the 5-year OS was 51% (95% confidence interval, 42%-60%; Figure 2). The median OS was 5.7 years and the median PFS was 3.9 years. Of 20 patients alive and in remission beyond 5 years, only 2 patients died of late relapse at 5.1 and 6.8 years.

Prognostic Factors

A Cox proportional hazards model identified refractory disease at time of transplantation (hazard ratio, 2.0; 95% confidence interval, 1.5%-2.6%; \( P = .007 \)) as the only significant factor affecting relapse, whereas disease bulk >10 cm (hazard ratio, 2.9; 95% confidence interval, 2.2%-3.5%; \( P = .002 \)) and refractory disease (hazard ratio, 1.9; 95% confidence interval, 1.4%-2.4%; \( P = .014 \)) at time of transplantation were significant factors affecting OS (Figure 3). There

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
</tr>
<tr>
<td>Range</td>
<td>14-67</td>
</tr>
<tr>
<td>Male/Female</td>
<td>91/36</td>
</tr>
<tr>
<td><strong>Remission status at diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Responsive (CR/PR)</td>
<td>90 (71%)</td>
</tr>
<tr>
<td>Refractory</td>
<td>37 (29%)</td>
</tr>
<tr>
<td><strong>Number of prior regimens</strong></td>
<td></td>
</tr>
<tr>
<td>1-2 Regimens</td>
<td>96 (76%)</td>
</tr>
<tr>
<td>≥3 Regimens</td>
<td>31 (24%)</td>
</tr>
<tr>
<td><strong>Stem cell source</strong></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>PBSC</td>
<td>86 (68%)</td>
</tr>
<tr>
<td><strong>Largest disease bulk</strong></td>
<td></td>
</tr>
<tr>
<td>≤10cm</td>
<td>111 (87%)</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>16 (13%)</td>
</tr>
<tr>
<td><strong>LDH at time of transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>48 (38%)</td>
</tr>
<tr>
<td>Elevated</td>
<td>79 (62%)</td>
</tr>
<tr>
<td><strong>Prior radiation therapy</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>60 (47%)</td>
</tr>
<tr>
<td>Prior RT</td>
<td>67 (53%)</td>
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LDH, Lactate dehydrogenase; PBSC, peripheral blood stem cells.

Figure 1. PFS of all patients (n = 127) with HD who received Bu/Cy/VP16 preparative regimen.

Figure 2. OS of all patients (n = 127) with HD who received Bu/Cy/VP16 preparative regimens.

Figure 3. Cox multivariate regression analyses showing (A) a significant difference in remission status on OS and (B) a statistically significant difference in the presence of bulky disease on OS. CR indicates complete remission; PR, partial remission.
was no statistically significant influence of age, bone marrow involvement, lactate dehydrogenase, or number of chemotherapy regimens used before transplantation (Table 2).

**Regimen-related Toxicity**

The regimen was well tolerated, with 5.5% TRM at 100 days after transplantation. Three patients died within the first 30 days. There were a total of 7 patients who had a TRM by day 100. Hepatic toxicity was the most common life-threatening toxicity and was the cause of death in 4 patients. All 3 patients who died from interstitial pneumonitis had received radiation during their treatment.

The long-term toxicity of this regimen was analyzed. Three patients developed myelodysplasia (MDS) or acute myeloid leukemia (AML) at 1.9, 4.1, and 5.7 years after transplantation. All 3 patients eventually died of AML. One patient developed transitional cell bladder carcinoma 4 months after transplantation. Overall the 8-year actuarial risk of secondary malignancy was 9% (Figure 4). One patient died of long-term pulmonary complications from the transplantation.

**DISCUSSION**

Several preparative regimens in HD with or without TBI have been investigated, with no clear superiority in part because many of the studies have been small [10,11,29]. A higher incidence of secondary malignancies has been observed after TBI-containing regimens (up to 20%) compared with high-dose chemotherapy regimens [30,31]. As a consequence, several radiation-free conditioning regimens have been investigated, including, high-dose Cy, carmustine, etoposide (CBV); carmustine, etoposide, cytarabine and melphalan (BEAM); and BCNU, etoposide, cytarabine and Cy (BEAC) [31-35]. Although Bu preparative regimens are commonly used, there are few published data evaluating the efficacy and tolerability of Bu-based regimens.

We analyzed our experience with the novel regimen of Bu 14 mg/kg, Cy 120 mg/kg, and etoposide 50-60 mg/kg in patients with HD. This regimen yielded favorable results in patients with NHL [20]. The present patient population was heavily pretreated, with most having received radiation and 24% receiving ≥3 prior chemotherapy regimens. Despite this, there was a low rate of relapse and 5-year PFS and OS were a 48 ± 5% and 51 ± 5%, respectively. Similar results have been reported after therapy with other non-Bu, radiation-free regimens, although only a small number of patients with HD was treated [31,34,35]. In addition, our results compare favorably to other Bu preparative regimen studies that had a subset of patients with HD [12,21,36]. A German group treated 10 patients with HD with Bu (16 mg/kg), Cy (120 mg/kg), and VP16 (30-45 mg/kg) followed by ASCT and reported an 80% 3-year OS and a 67% event-free survival [21]. In addition, the Hutchinson Cancer Research Center treated 50 patients with HD with Bu 12 mg/kg, melphalan 100 mg/m², and thiotepa 500 mg/m² followed by ASCT and found 55% and 51% 5-year OS and event-free survival, respectively [12,37]. However, this regimen was associated with a relatively high TRM of 15% [12].

The present study also validates that the addition of etoposide to Bu and Cy is well tolerated [17,18,38]. Previous groups have used higher doses of Bu by reducing the dose of VP16 [17-19, 21]. Specifically, the TRM of 5.5% is comparable to other reported observations in this patient population [4,7,8,39-41]. Hepatic toxicity remained the most common life-threatening toxicity, causing the death of 4 patients. Parenteral Bu or blood level monitoring could further reduce the regimen’s hepatic toxicity, possibly by limiting hepatic exposure to Bu by providing superior dosing accuracy [42]. In addition, 3 patients who received prior radiation therapy died from interstitial pneumonitis [43]. Further, improved supportive care since the time of the study could potentially reduce toxicities, including the use of palifermin (recombinant human keratinocyte growth factor), which has been shown to reduce grade 3 or 4 oral mucositis [44].

![Figure 4. Overall 8-year actuarial risk for a secondary malignancy was 9%.

Table 2. Multivariate Analysis of Relapse Rate and Overall Survival (OS)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relapse Rate</th>
<th>OS</th>
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<tbody>
<tr>
<td>Bulky disease</td>
<td>NS</td>
<td>P  = 0.002</td>
</tr>
<tr>
<td>Refractory disease</td>
<td>P  = 0.007</td>
<td>P  = 0.014</td>
</tr>
<tr>
<td>Age</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Number of prior regimens</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stem cell source</td>
<td>NS</td>
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</table>

NS, nonsignificant.
In this study active disease at the time of transplantation and bulky disease had a significant adverse influence on OS and PFS after transplantation. Several groups have similarly found that disease status at the time of transplantation is an important prognostic factor [11,31,34,39,45,46]. Bulky disease at the time of transplantation was also an adverse factor predicting higher risk of relapse, which has been seen in previous studies [39,47].

Due to the long follow-up, the rate of late complications and secondary malignancies could be characterized. Three patients (2.3%) developed MDS/AML and 1 patient acquired a solid cancer with an 8-year follow-up [20,48]. The outcome for treatment-related MDS/AML is poor, with an median survival of 6 months and a 5-year survival of 0%-8% even after allogeneic bone marrow transplantation [49,50]. Our previous experience has shown that the incidence of MDS/AML is relatively low with Bu preparative regimens. In our study of 342 patients with NHL, only 4 patients (1.2%) developed AML or MDS 1-5 years after transplantation [20]. The relative contribution of preparative regimens containing TBI versus previous alkylating/topoisomerase II chemotherapy is still not fully known [31]. The European Bone Marrow Transplantation Group and Autologous Bone Marrow Transplant Registry have shown a low rate of MDS after transplantation with TBI regimens [7,8]. Several studies have concluded that the intensity of prior chemotherapy may be the genesis of MDS/A ML after transplantation [51]. However, single-institution studies have shown an increased rate of MDS/AML with radiation-containing regimens [52-55]. In particular, treatment-associated MDS and AML is seen as a relatively frequent complication (up to 20%) and lethal late complication, especially in TBI-containing regimens [55-57].

In summary, the novel regimen of Bu 14 mg/kg, etoposide 50-60 mg/kg, and Cy 120 mg/kg is a well-tolerated and active preparative regimen for autologous transplantation in patients with HD. It is associated with a low incidence of early and late TRM and a low incidence of secondary malignancy and MDS. Based on this large set of patients with long-term follow-up, it appears that the novel Bu-based preparative regimen, which also includes high-dose Cy and etoposide, is an effective and well-tolerated regimen in HD. Although promising, the definition of the optimal regimen in patients with HD will require prospective evaluation with other commonly used regimens.

REFERENCES


