

Autologous Noncryopreserved Hematopoietic Stem Cell Transplant With CEAM as a Modified Conditioning Regimen in Patients With Hodgkin Lymphoma: A Single-center Experience With a New Protocol

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Abstract

Objectives: A BEAM regimen including carmustine (BiCNU: bis-chloroethyl nitrosourea), etoposide, cytarabine (cytosine arabinoside), and melphalan is a widely used conditioning regimen for autologous stem cell transplant in patients with Hodgkin lymphoma. We report the results of noncryopreserved autologous stem cell transplant of 45 patients with Hodgkin lymphoma given an alternative regimen, modified BEAM-like regimen (CEAM regimen: lomustine, etoposide, cytarabine, and melphalan), in which carmustine (BiCNU IV) was substituted by oral lomustine (CCNU: 2 chloroethyl cyclohexyl nitrosourea).

Patients and Methods: Forty-five eligible patients with relapsed/refractory Hodgkin lymphoma were consecutively enrolled and underwent conditioning regimen with BEAM-like regimen protocol as follows: Lomustine 200 mg/m² on day -3; etoposide 1000 mg/m² on day -3 and -2; cytarabine 1000 mg/m² on days -3, -2; and Melphalan 140 mg/m² on day -1.

Results: All 45 patients showed engraftment of infused stem cell, and there was no graft failure in the study group. The median mononuclear cell dose

was 3.4×10^8 . The median time to absolute neutrophil count $> 0.5 \times 10^9/L$ was 11 days, and the median time to platelet count $> 20 \times 10^9$ was 14 days. Grade 2 and grade 3 mucositis was seen in 64.5% of our patients. Transplant-related mortality at 100 days occurred in 1 patient (2.2%). With a median follow-up of 27 months, median disease-free survival was 20 months, mean overall survival was 27 months, and median overall survival has not yet been reached.

Conclusions: These data demonstrate the safety and feasibility of BEAM-like regimen as a new and modified regimen; longer follow-up is required to evaluate fully efficacy and long-term safety of our method.

Key words: Stem cell, Transplant, Lymphoma, Hodgkin disease, Autologous

Introduction

Hematopoietic stem cell transplant has become an established procedure for many congenital and acquired disorders of the hematopoietic system.^{1, 2} Although multiagent chemotherapy alone or in combination with radiation therapy cures more than 80% of patients with Hodgkin lymphoma,³ other approaches are needed for those with recurrent disease. For patients with persistent disease, or for those who relapse after chemotherapy and/or radiotherapy, high-dose chemotherapy followed by autologous stem cell transplant (ASCT) is associated with superior event-free survival compared with salvage chemotherapy alone.^{4, 5}

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The BEAM regimen, which includes carmustine (BiCNU), etoposide, cytarabine (Ara-C), and melphalan, is a widely used conditioning regimen for ASCT in patients with Hodgkin lymphoma because of its acceptable toxicity and high effectiveness.⁶ Adverse events associated with BEAM are related in part to BiCNU and include severe mucositis, chemotherapy-induced nausea, vomiting, diarrhea, hepatotoxicity, and nephrotoxicity.⁶⁻⁹

Hematopoietic stem cell transplant was established at our center in 1993 for adult and pediatric patients.¹⁰⁻¹² Since 2003, we have been using peripheral blood as the source of stem cells for almost all malignant diseases including Hodgkin lymphoma. In this study, we report the results of ASCT in 45 patients with Hodgkin lymphoma after using a modified BEAM-like conditioning regimen (CEAM) in which lomustine (CCNU) was substituted for BiCNU. Our primary objective was to assess the safety of the CEAM regimen in terms of acute toxicity and its efficacy and feasibility.

Materials and Methods

Forty-five eligible patients with relapsed/refractory Hodgkin lymphoma were enrolled in the study. Patients were treated with intensive chemotherapy followed by reinfusion of noncryopreserved autologous stem cells. All patients signed a written, informed consent form before treatment. Eligible patients were required to have histologically proven relapsed/refractory disease after receiving ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) as first-line chemotherapy. Other eligibility criteria included a Karnofsky performance score > 60, and normal pulmonary, cardiac, hepatic, and renal function. All protocols were approved by the local ethics committee of the institution before the study began, and they conformed to the ethical guidelines of the 1975 Helsinki Declaration.

The ESHAP regimen was the primary salvage chemotherapy (intravenous etoposide 40 mg/m² over 1 to 3 hours daily for 4 days, intravenous methylprednisolone 500 mg daily for 4 days, cisplatin 25 mg/m²/d as a continuous infusion over 24 hours daily for 4 days, and intravenous Ara-C 2 g/m² over 2 to 3 days after completion of cisplatin on day 5). All patients received 3 to 6 (median, n=4) courses of ESHAP after relapse.

Filgrastim (granulocyte-colony stimulating factor,

G-CSF, Neupogen, Roche Oncology, Roche Holdings Inc. Genentech, Inc., South San Francisco, CA, USA) 300 µg was administered subcutaneously twice daily until completion of peripheral blood stem cell collection. The minimum apheresis target was 2.5×10^8 mononuclear cells (MNCs) per kg or 2.5×10^6 CD34⁺ cell per kg. All patients received the CEAM conditioning regimen as follows: CCNU 200 mg/m² orally on day -3; intravenous etoposide 1000 mg/m² on days -3 and -2; intravenous Ara-C 1000 mg/m² on days -3, -2; and intravenous melphalan 140 mg/m² on day -1.

After a day of rest, unmanipulated noncryopreserved autologous peripheral stem cells were infused on day 0. All apheresis products were kept in a conventional blood bank refrigerator at 4°C for 3 days before infusion. Stem cells were re-infused without purging after CEAM conditioning. After autotransplant, all patients received G-CSF 5 µg/kg/d until the absolute neutrophil count (ANC) was $> 0.5 \times 10^9$ /L for 2 consecutive days.

All patients were treated in a HEPA-filtered room and kept in isolation until engraftment. Prophylactic antibiotics along with acyclovir and fluconazole were administered during neutropenic episodes. Blood products were given if hemoglobin levels were < 100 g/L and platelet counts were < 30×10^9 /L. Overall survival (OS) was calculated from day 0 until death or the date of last contact. Disease-free survival (DFS) was calculated from the day of transplant to the date of relapse, death in remission, or last follow-up in complete remission (CR). Transplant-related mortality was defined as any death related to a fatal complication in the absence of underlying disease within 100 days from transplant. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria version 3.

Results

A total of 45 patients underwent high-dose therapy and ASCT at our center during a 6-year period from October 2003 until November 2009. There were 29 men (64.5%) and 16 women (35.5%). The mean age was 30 years (median 26 y; range, 16 to 50 y). Disease status before transplant is shown in Table 1.

All patients showed engraftment of infused stem cells, and there was no graft failure in the study group. The mean number of MNCs collected was 3.8×10^8 /kg. The median MNC dosage was 3.4×10^8

Table 1. Disease status before transplant.

Stage disease at first presentation	Number (%)
I	1 (2.2)
II	25 (55.5)
III	14 (31.1)
IV	5 (11.1)
No. of previous courses of chemotherapy	
1	0
2	33 (73.3)
3 or more	12 (26.6)
Disease status at ASCT	
Second and third CR	36 (80)
Refractory	9 (20)

Abbreviations: ASCT, autologous stem cell transplant; CR, complete remission

(range, 1.9×10^8 to 9×10^8 /kg). The median time to an ANC $> 0.5 \times 10^9$ /L was 11 days (range, 8 to 18 d), and the median time to a platelet count $> 20 \times 10^9$ was 14 days (range, 11 to 29 d). Posttransplant patients received G-CSF for a median of 12 days (range, 8 to 23 d).

Overall, CEAM conditioning was well tolerated. Nonhematologic toxicity consisted primarily of mucositis, nausea and/or vomiting, and diarrhea. Mucositis (grades 2/3) was seen in 64.5% of patients (median duration, 7 d; range, 4 to 14 d), while chemotherapy-induced nausea and vomiting (grades 2/3) were seen in 22 patients (49%). There were no cases of grade 4 mucositis. Sixteen of 45 patients (35.5%) experienced diarrhea (grades 2/3), but there were no grade 4 cases (Table 2). Liver and renal toxicity was generally mild and transient. There were no cases of veno-occlusive liver disease. Administration of the CEAM regimen was not associated with any acute pulmonary adverse events.

Table 2. Engraftment results and regimen-related toxicity data.

	Median (range)
Number of MNC cells infused $\times 10^8$ /kg	3.4 (1.9 to 9)
Neutrophil recovery $> 500 \times 10^9$ /L	11 days (8 to 18)
Platelet recovery $> 20 \times 10^9$ /L	14 days (11 to 29)
Transfusion support	Number of patients (%)
Packed cell transfusion	30 (66.6)
Platelet transfusion	45 (100)
Febrile neutropenia	22 (49)
Sepsis (TRM)	1 (2.2)
Mucositis	
Grades 0-1	16 (35.5)
Grades 2-3	29 (64.5)
Grade 4	0
Nausea/vomiting	
Grades 0-1	23 (51)
Grades 2-3	22 (49)
Grade 4	0
Diarrhea	
Grades 0-1	30 (66.6)
Grades 2-3	15 (33.3)
Grade 4	0

Abbreviations: MNC, mononuclear cells; TRM, transplant-related mortality

Transplant-related mortality at 100 days was 2.2% (1 patient) owing to sepsis after full hematologic recovery had been achieved.

At a median follow-up of 27 months (range, 8 to 60 mo), the median DFS was 20 months (range, 4 to 60 mo), the mean OS was 27 months (range, 8 to 60 mo), and the median overall survival was not yet been reached. After a follow-up of more than 2 years, the 2-year DFS in 30 evaluable patients was 77% (23/30), and the 2-year OS was 84% (25 of 30).

Discussion

Use of ASCT is now considered the standard of care for Hodgkin lymphoma in relapse. High-dose chemotherapy and ASCT for patients with persistent disease or those who relapse after chemotherapy/radiotherapy are associated with superior event-free survival compared with salvage chemotherapy alone.^{4,5}

Since both early- and long-term mortality after ASCT are related to the conditioning regimen, recent studies have focused on increasing tolerability and reducing toxicity. Chemotherapy protocol of BEAM is the most widely used conditioning regimen for ASCT in patients with Hodgkin lymphoma owing to its acceptable toxicity and high antitumor activity.^{6-9,13}

Autologous stem cell transplant using high-dose chemotherapy requires storage of stem cells before subsequent reinfusion. Storage of frozen stem cells in liquid nitrogen is now the procedure of choice. Before stem cell freezing, dimethyl sulfoxide is added as a cryoprotectant to prevent the formation of harmful ice crystals within the cells. A good alternative to cryopreservation is use of a shortened storage time at 4°C. This method saves both time and money, and may be suitable in countries with limited access to high-level technical laboratory support. In our study, we used noncryopreserved unmanipulated hematopoietic peripheral stem cells that had been maintained in a conventional blood bank refrigerator at 4°C for 3 days before infusion.

In a nonrandomized retrospective analysis, Preti and associates compared the engraftment kinetics of 54 patients who received cryopreserved marrow cells with 45 patients who received refrigerated cells. The refrigerated cells were stored for a median of 4 days (range, 3 to 9 d). No difference between the 2 groups was found with regard to engraftment kinetics.¹⁴

All patients in our study showed hematopoietic engraftment after receiving the CEAM conditioning regimen, with neutrophil and platelet recovery times comparable to those reported for most carmustine-based regimens.^{6-9, 13, 15, 16} The need for transfusion support, the rate and severity of neutropenia, and the incidence of neutropenic fever in our study group did not differ from those reported for BEAM and other BEAM-like regimens.^{6-9, 15, 16} Transplant-related mortality in our study was only 2.2%, which compares favorably with other studies that used carmustine-based regimens (0% to 11%).^{6-9, 13, 15-17} Our study also showed that the CEAM regimen has a favorable toxicity profile compared with BEAM. In several large studies in which patients received BEAM conditioning, the incidence of chemotherapy-induced nausea and vomiting and diarrhea (grades 3/4) ranged between 15% and 25%.^{6-9, 13, 16}

High-dose chemotherapy followed by ASCT is now an established treatment modality for Hodgkin and non-Hodgkin lymphoma, and is associated with long-term survival in 30% to 50% of patients who do not respond to initial multiagent chemotherapy.^{15, 18-20} Clinical outcomes and survival after ASCT depend on disease chemosensitivity at transplant, the efficacy of the conditioning regimen at eradicating the residual tumor cell clone after salvage chemotherapy, and transplant-related mortality and morbidity.^{9, 18, 15, 20, 21} At a median follow-up of 27 months (range, 8 to 60 mo), the median DFS in our group was 20 months (range, 4 to 60 mo). With a follow-up of more than 2 years, the DFS was 77% (23/30 patients), and the 2-year OS was 84% (25/30 patients). In a large cohort study from 2009, Majhail and associates reported that patients with Hodgkin lymphoma who survived for at least 2 years in remission after undergoing autologous hematopoietic stem cell transplants had favorable outcomes, with overall 10-year posttransplant survival rates of 72% to 82%.²²

In spite of our relatively short follow-up, we have shown that noncryopreserved ASCT after CEAM conditioning induces long-term disease control in high-risk and poor-prognosis Hodgkin disease patients after relapse. Although toxicity, engraftment times, and survival are comparable to the BEAM regimen, longer follow-up is needed to evaluate the clinical efficacy and long-term safety of this approach. More importantly, modification of the apheresis collection procedure based on local

conditions can save time and resources and may lead to increased availability of ASCT for more patients.

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