Leukemia Research 35 (2011) 183–187

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

BEAM or BuCyE high-dose chemotherapy followed by autologous stem cell transplantation in non-Hodgkin's lymphoma patients: A single center comparative analysis of efficacy and toxicity

Jeong Eun Kim[a], Dae Ho Lee[a], Changhoon Yoo[b], Shin Kim[a], Sang-We Kim[a], Jung-Shin Lee[a], Chan Jeong Park[c], Jooryung Huh[d], Cheolwon Suh[a,*]

[a] Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 86 Asan byeongwon-gil, Songpa-gu, 138-736 Seoul, Republic of Korea
[b] Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[c] Diagnostic Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[d] Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 14 April 2010
Received in revised form 10 July 2010
Accepted 12 July 2010
Available online 3 August 2010

Keywords:
BuCyE
ASCT
Non-Hodgkin's lymphoma
High-dose chemotherapy
BEAM

ABSTRACT

We compared the efficacy and toxicity of BEAM (BCNU, etoposide, cytarabine and melphalan) and BuCyE (busulfan, cyclophosphamide and etoposide), given prior to autologous stem cell transplantation (ASCT), in 65 patients with non-Hodgkin's lymphoma. Of these 65 patients, 43 received BEAM and 22 received BuCyE. Their age, gender distribution, International Prognostic Index, status of disease at ASCT and median number of infused $CD34^+$ cells/kg were similar. Neutrophil and platelet engraftment were significantly faster in the BuCyE group. Rates of mucositis, nausea/vomiting, diarrhea, bleeding and infections were similar in the two groups. Median overall survival and event-free survival did not differ significantly between the two groups. These findings indicate that BuCyE is an effective conditioning regimen, showing similar survival outcomes and toxicity profiles as BEAM. Furthermore, hematologic recovery is significantly faster in patients given the BuCyE conditioning regimen.

1. Introduction

High-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) is the current standard of care after failure of primary therapy for patients with aggressive non-Hodgkin's lymphoma (NHL). ASCT has been used to improve the long-term outcome of NHL patients with chemosensitive relapse and as a consolidation treatment to improve the survival of young patients with high-risk NHL [1–4]. Patient status at transplant and sensitivity to conventional chemotherapy are prognostic factors for survival. The impact of conditioning regimens on ASCT is uncertain, although previous studies have examined the efficacy and safety of various conditioning regimens [5–7].

Among the most commonly used HDC regimens are carmustine (BCNU) and total body irradiation (TBI). Due to limited information on the toxicity and efficacy of different preparative regimens, their relative effectiveness has not been clearly determined. Busulfan-based preparative regimens are often used prior to allogeneic stem cell transplantation [8], but they have also been used prior to ASCT in patients with lymphoma [7,9,10]. For example, patients with aggressive NHL treated with the BuCyE (busulfan, cyclophosphamide and etoposide) regimen followed by ASCT have shown good long-term survival and acceptable toxicity [7,10–12].

Although toxicities associated with the BEAM (BCNU, etoposide, cytarabine and melphalan) [3,13,14] and BuCyE [7,10–12] regimens are well defined, there is limited information on their comparative toxicities and efficacies. We therefore compared the toxicity and efficacy of the BEAM and BuCyE regimens in patients with NHL.

2. Patients and methods

2.1. Patients

Between February 2002 and April 2008, 65 NHL patients underwent HDC with BEAM ($N = 43$) or BuCyE ($N = 22$), followed by ASCT, at the Asan Medical Center. BEAM was used from February 2002 to October 2005, and BuCyE was used from November 2005 to April 2008. Patients considered at high-intermediate to high-risk at diagnosis or with relapsed or refractory pathologically confirmed NHL were eligible for ASCT. Other inclusion criteria were age less than 65 years, adequate cardiac, pulmonary, hepatic, renal and

* Corresponding author. Tel.: +82 2 3010 3209; fax: +82 2 3010 6961.
E-mail address: csuh@amc.seoul.kr (C. Suh).

0145-2126/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2010.07.016

hematopoietic function, and Eastern Cooperative Oncology Group (ECOG) performance status of no more than two at the time of ASCT.

2.2. Mobilization and collection of peripheral blood stem cells

Sixty-two patients received disease-specific chemotherapy plus granulocyte-colony stimulation factor (G-CSF; 10 μg/kg/day; Lenograstim, Neutrogin, Choongwae, Seoul, Korea) as mobilization therapy and 3 patients received cyclophosphamide (4 g/m^2) plus G-CSF as mobilization therapy. Hematopoietic stem cells (targeted number, >3 × 10^6 CD34$^+$ cells/kg) were collected from all patients using a large-volume leukapheresis apparatus via a central venous catheter as described previously in Refs. [11,15–20].

2.3. Transplant procedure and supportive care

Patients administered the BEAM regimen received BCNU 300 mg/m^2 on day −6 (6 days before stem cell infusion), etoposide 200 mg/m^2 per day (total dose 800 mg/m^2) and cytarabine 400 mg/m^2 per day (total dose 1600 mg/m^2) on days −5 to −2, and melphalan 140 mg/m^2 on day −1. Patients administered the BuCyE regimen received intravenous busulfan 0.8 mg/kg every 6 h from days −7 to −5, cyclophosphamide 50 mg/kg on days −3 and −2, and etoposide 400 mg/m^2 on days −5 and −4. Hematopoietic stem cells were infused on day 0. Chemotherapy doses were based on actual body weight.

Patients in the BuCyE group were given phenytoin 1 g on the day prior to the first dose of busulfan, followed by phenytoin 300 mg per day for 4 days, for seizure prophylaxis; serum concentrations of phenytoin were not monitored. Uroepithelial prophylaxis for patients administered cyclophosphamide consisted of hyperhydration and mesna. All patients received subcutaneous G-CSF 5 μg/kg from day 1 of ASCT until neutrophil counts were >1000/mm^3 for 3 consecutive days. Patients were cared for in a single room, with reverse isolation strictly maintained to prevent infectious complications. All patients were administered prophylactic oral antimicrobial therapy consisting of ciprofloxacin, fluconazole and acyclovir. Administration of antimicrobial and antifungal agents to patients with febrile episodes, as well as treatment with antiemetics and blood components, were according to active protocols at our institution.

2.4. Definitions and response evaluation

Responses to initial induction chemotherapy, salvage chemotherapy and HDC were evaluated according to International Workshop Criteria [21]. Patients were considered to have chemosensitive disease if there was a reduction in measurable disease that met at least partial response (PR) criteria following salvage chemotherapy and before transplantation. Patients were considered to have chemoresistant disease if the reduction in measurable disease did not meet PR criteria.

Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count ≥0.5 × 10^9/L, while platelet engraftment was defined as the day that platelet count was ≥20 × 10^9/L with no requirement for platelet transfusion. Responses were evaluated 1 month after ASCT, every 3 months for the first 2 years, every 6 months for the next 3 years, and then yearly or whenever clinically indicated. Toxicities were evaluated and graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 grading system.

2.5. Statistical analysis

Between-group comparisons were assessed using the chi-square test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Event-free survival (EFS) was defined as the time from ASCT to the time of disease progression, relapse or death, or when patient was last known to be in remission. Overall survival (OS) was defined as the time from ASCT until death or the date the patient was last known to be alive. The survival curves of EFS and OS were plotted using the Kaplan–Meier method and compared using the log-rank test. Treatment-related mortality (TRM) was defined as any death related to a fatal complication that occurred in the absence of underlying disease within 30 days of transplantation. Two-tailed *p*-values less than 0.05 were regarded as significant.

Table 1
Patient characteristics (*N* = 65).

	BEAM (*N* = 43)	BuCyE (*N* = 22)	*p* value
Age (years)			
Median (range)	46 (15–65)	48.5 (28–65)	0.429
Gender			
Male	31 (72.1%)	15 (68.2%)	0.743
Female	12 (27.9%)	7 (31.8%)	
Histology subtype			
Diffuse large B-cell lymphoma	22 (51.2%)	4 (18.2%)	0.011
Other B-cell lymphoma	4 (9.3%)	10 (45.5%)	
Peripheral T-cell lymphoma	6 (13.9%)	3 (13.6%)	
Extranodal NK/T-cell lymphoma	3 (7.0%)	2 (9.1%)	
Other T-cell lymphoma	8 (18.6%)	3 (13.6%)	
Performance status at ASCT			
0–1	43 (100.0%)	22 (100.0%)	
IPI at ASCT			
Low	31 (72.1%)	19 (86.4%)	0.552
Low-intermediate	7 (16.3%)	3 (13.6%)	
High-intermediate	4 (9.3%)	0 (0.0%)	
High	1 (2.3%)	0 (0.0%)	
Status of disease at ASCT			
First CR	8 (18.6%)	7 (31.8%)	0.185
≥Second CR	7 (16.3%)	4 (18.2%)	
Initial PR	4 (9.3%)	5 (22.7%)	
Sensitive relapse	20 (46.5%)	4 (18.2%)	
Resistant relapse	4 (9.3%)	2 (9.1%)	

IPI: International Prognostic Index; CR: complete response; ASCT: autologous stem cell transplantation.

3. Results

3.1. Patient characteristics

The characteristics of the two groups of patients prior to ASCT are summarized in Table 1. Median age was 46 years (range: 15–65 years) in the BEAM group and 48.5 years (range: 28–65 years) in the BuCyE group ($p = 0.429$). Baseline characteristics, including gender distribution, International Prognostic Index (IPI) and status of disease at time of ASCT, were also similar in the two groups. A higher percentage of patients in the BEAM group had diffuse large B-cell lymphoma, whereas a higher percentage in the BuCyE group had other types of B-cell lymphoma including marginal zone B-cell lymphoma, mantle cell lymphoma and Burkitt's lymphoma. The proportion of patients with T-cell lymphoma was similar in the two groups, with peripheral T-cell lymphoma and extranodal NK/T-cell lymphoma being the most common types of T-cell lymphoma in both groups. Other patients had precursor T-cell lymphoma, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma and other types of T-cell lymphoma.

3.2. Hematopoietic engraftment

Engraftment results are summarized in Table 2. The median number of infused CD34$^+$ cells was similar in the BEAM and BuCyE