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ELEVENTH ANNUAL MEETING

MCVAC CONDITIONING REGIMEN FOLLOWED BY AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH RELAPSED AND REFRACTORY HODGKIN LYMPHOMA: A SINGLE-INSTITUTION RETROSPECTIVE STUDY.

Ken Naganuma[1],Yasuyuki Takahashi[1], Anan Tomoe[1], Yasushi Kubota[1,2], Shuji Momose[3], Morihiro Higashi[3], Jun-ichi Tamaru[3], Masahiro Kizaki[1], Takayuki Tabayashi[1]

1. Department of Hematology, Saitama Medical University Saitama Medical Center, Saitama, Japan
2. 2. Department of Transfusion and Cell Therapy, Saitama Medical Center, Saitama Medical University, Japan
3. 3. Department of Pathology, Saitama Medical University Saitama Medical Center, Saitama, Japan

埼玉医科大学 Saitama Medical University

SMC Hematology

INTRODUCTION

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDC/ASCT) is a therapeutic option and can cure an additional portion of relapsed or primary refractory patients[1]. However, evidence on conditioning regimens used for HDC/ASCT is limited, with BEAM (Carmustine, etoposide, cytarabine, and melphalan) therapy being the generalized treatment in Europe and the United States[2]. In Europe and the United States, Carmustine is approved to treat people who have classical Hodgkin lymphoma (CHL); in Japan, it is an unapproved medication.

AIM

Ranimustine (MCNU), which is also a nitrosourea anticancer agent, is used as MEAM (MCNU, etoposide, cytarabine, and melphalan) based regimen [3,4]. However, there is limited knowledge of its strategy in Japan.

MCVAC (High-dose MCNU, cytarabine, etoposide and cyclophosphamide) regimen was reported as a conditioning regimen in relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL), as it possessed a high anticancer effect with acceptable toxicity for DLBCL [5]. Therefore, we report a retrospective analysis evaluating the efficacy and toxicity of HDC/ASCT and aim to assess whether MCVAC regimen might result in a safe and favorable outcome with relapsed or primary refractory CHL.

METHOD

We retrospectively analyzed 10 patients with relapsed or refractory Hodgkin lymphoma who underwent MCVAC conditioning regimen followed by ASCT between January 2009 and December 2021 in our institution. This study complied with the guidelines for human studies and was conducted ethically in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. This study was approved by the Institutional Ethics Committee of Saitama Medical University Saitama Medical Center.

The MCVAC conditioning regimen was intravenously administered at ranimustine 250 mg/m2 on day −9 and 200 mg/m2 on day −4, cytarabine 2.0 g/m2 twice daily on days −8 to −5, etoposide 200 mg/m2 twice daily on days −8 to −5, and cyclophosphamide 50 mg/kg on days −3 and −2 before ASCT.

The PFS time and rate were calculated and defined as the time from ASCT to progressive disease or death from any cause. The OS time and rate were calculated as the time between the day of ASCT and death or last follow-up. The Kaplan-Meier method was used to estimate the time of events. All statistical analyses were performed using the EZR version 1.55 software.

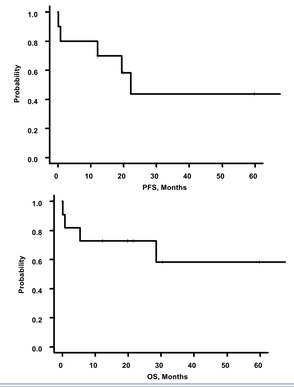
RESULTS

Patient's Characteristics

No.	Age, Sex	PS	Stage	Histological type	Initial treatment	Refractory <12m	Salvage regimen	CD34+cells ($\times 10^6$/kg)	Days until neutrophil engraftment	Days until platelet engraftment
#1	27, M	1	3B	NS	ABVD	YES	ESHAP	3.53	10	13
#2	23, F	1	4B	NS	ABVD	NO	ESHAP	5.83	9	14
#3	31, F	1	3A	NS	ABVD	YES	ESHAP	1.26	11	18
#4	64, M	1	3A	NC	ABVD	YES	ESHAP	6.84	18	-
#5	52, F	2	2B	NS	ABVD	YES	ESHAP DeVIC	4.00	11	19
#6	37, M	2	2A	NC	ABVD	YES	ESHAP	9.75	9	16
#7	37, M	1	4B	NC	ABVD	YES	ESHAP BV	7.27	8	10
#8	50, F	1	2A	NS	ABVD	YES	ESHAP	2.3	-	-
#9	29, M	1	4B	NS	ABVD	NO	ESHAP	7.42	11	15
#10	36, F	1	4B	NS	ABVD	YES	ESHAP	9.00	10	22

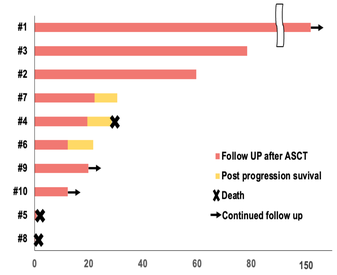
The patient characteristics are shown. A total of 10 patients (median [range] age, 36.5 [23–64] years), including five (50%) men and five (50%) women. The Eastern Cooperative Oncology Group performance status at recurrence was 0–1 and 2 in 8 patients (80%) and 2 patients (20%), respectively. The most common pathological subtypes were nodular sclerosis (7 patients, 70%), and mixed cellularity (3 patients, 27%). All patients had received ABVD as frontline therapy. At diagnosis, 7 patients (70%) had stage III or IV disease, 6 patients (60%) had B symptoms. Eight patients developed a disease that progressed within 12 months after induction. All patients received the ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin) regimen during the salvage regimen. One patient received DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) regimen, and one patient received BV regimen during the salvage regimen. The median dose of total and CD34 positive cells was 6.33 × 10^6/kg (range, 1.26-9.75).

Kaplan-Meier analysis



The results of therapeutic efficacy are shown in a swimmer plot. The median follow-up duration time of the patients received MCVAC conditioning regimen before ASCT was 25.0 months. **The median PFS and OS associated with the application of the MCVAC regimen and ASCT were 22.1 (range, 0.1-155) months and "not reached" (range, 0.1-155), respectively. The 36 months PFS and OS rate was 43.8 % (95% CI, 11.9%-72.6%) and 64.0% (95% CI, 22.6%-87.5%).**

Swimmer's plot



Adverse events

Toxicity	All grade	Grade ≥ 3
Febrile neutropenia	10	10
Anorexia	6	4
Diarrhea	5	0
Hepatic	2	0
Nausea	1	1
Stomatitis	1	1
Vomitting	1	1
Cardiac	1	1
Plumonary	1	1
Erythema	1	0

Three patients died, and one of three was directly attributable to the effects of PD. Patient 4 received two courses of brentuximab vedotin monotherapy and five courses of C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) regimen after relapse of HDC/ASCT but died of worsening of the primary disease. Patient 6 received three course of brentuximab vedotin monotherapy and three course of three courses of GCD (Gemcitabine, Carboplatin, and Dexamethasone) regimen after relapse of HDC/ASCT. Patient 7 received five courses of C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisolone) regimen and sequentially underwent an allogeneic stem cell transplant after relapse of HDC/ASCT. AEs are summarized in Table. All patients experienced AEs that were related to chemotherapy, and two of the patients experienced severe AEs (SAEs). All patients who received ASCT had febrile neutropenia. Non-hematological adverse events of grade >3 were anorexia, nausea, vomiting, pulmonary infection, and pericardial tamponade. Early death within 30 days was seen in 2 patients. Patient 8 presented developed pericardial tamponade from day 3 post-ASCT without neutrophil engraftment. Urgent pericardiocentesis was performed but died on the day 4 post-ASCT. Patient 5 presented pulmonary infection after neutrophil engraftment and died on the day 25 post-ASCT.

CONCLUSIONS

Craig et al did the randomized phase 3 trial (AETHERA trial) with unfavorable risk relapsed or primary refractory CHL who had HDC/ASCT to receive 16 cycles of brentuximab vedotin or placebo after transplantation, the median PFS and OS in the placebo group were 24.1 months and "not reached", respectively [6]. Carmustine is an unapproved medication. Ranimustine (MCNU), approved in Japan for the treatment of malignant lymphoma, is used as MEAM (MCNU, etoposide, cytarabine, and melphalan) based regimen [3,4], there is no date and this is the first report of an autologous transplant for Hodgkin's lymphoma alone from Japan. This observation suggests that therapy with MCVAC conditioning regimen followed by ASCT for relapsed or refractory CHL might provide at least similar PFS and OS benefits to what has already been seen in the international clinical setting in high-risk relapsed or refractory CHL.

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CONTACT INFORMATION

First author: Ken Naganumai MD
Department of Hematology, Saitama Medical University Saitama Medical Center, Saitama, Japan
1981, Kamoda, Kawagoe City, 350-8500, Japan
Phone number: +81 49-228-6941
Fax number: +81 49-228-6941
E-mail:k_naganu@saitama-med.ac.jp