CASE REPORT

Intravenous busulfan-based conditioning with autologous stem cell transplantation for refractory B-cell lymphoma with central nervous system involvement

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Abstract : The prognosis of relapsed or refractory lymphoma with central nervous system (CNS) involvement remains poor because of the lack of anticancer drugs with sufficient CNS penetration. [Case 1] A 65-year-old man was diagnosed with Stage IV mantle cell lymphoma. After two courses of chemotherapy and autologous hematopoietic stem cell (HSC) collection, urinary retention with fever developed. Cerebrospinal fluid analysis revealed leptomeningeal involvement, which was refractory to high-dose methotrexate therapy. Autologous peripheral blood stem cell transplantation (ASCT) was performed, followed by intravenous busulfan (ivBU), cyclophosphamide, and etoposide ; thereafter, no relapse has been detected for over six years. [Case 2] A 40-year-old woman with right lower hemiplegia was diagnosed with primary CNS lymphoma. Although four courses of high-dose methotrexate therapy were administered, the cerebral tumor increased in size. HSCs were collected after methotrexate therapy, and ASCT was performed in addition to conditioning using ivBU, cyclophosphamide, and etoposide, followed by whole-brain and local boost irradiation. She achieved complete remission, but relapsed two years after ASCT. High-dose ivBU-containing conditioning regimens with ASCT may be useful for refractory B-cell lymphoma with CNS involvement. J. Med. Invest. 68 : 196-201, February, 2021

Keywords **:** *busulfan, malignant lymphoma, central nervous system, autologous peripheral blood stem cell transplantation*

INTRODUCTION

Involvement of the central nervous system by malignant lymphoma is a serious event for lymphoma patients. High-dose methotrexate (MTX)-based combination chemotherapy is commonly performed for patients with primary or secondary CNS invasion of malignant lymphoma in Japan. However, as they have a poor prognosis, new therapeutic strategies are needed.

We report two MTX resistant B-cell lymphoma patients with central nervous system invasion in whom autologous peripheral blood stem cell transplantation (ASCT) followed by intravenous busulfan (ivBU)-based conditioning chemotherapy was effective.

CASE REPORT

[Case 1] A 65-year-old man with a past history of glaucoma perceived right inguinal lymphadenopathy in X-6. Needle biopsy demonstrated the proliferation of abnormal lymphocytes positive for CD5, CD20, and cyclin D1, and negative for CD3 and CD10, and he was diagnosed with mantle cell lymphoma in January X. 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) and bone marrow examination revealed the involvement of paraaortic, axillary, and right inguinal lymph nodes and bone marrow, and the disease was Stage IV based on the Ann-Arbor classification. He achieved a partial response after we administered two courses of rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate-cytarabine (R-hyper-CVAD/MTX-AraC), and collected his peripheral blood stem cells during the period of leucocyte recovery. High fever with bladder and rectal disturbance developed in June X. Cerebrospinal fluid (CSF) revealed lymphocytosis (163/μL) (cytology class IV) with increased protein (129 mg/dL). High signal in the spinal cord at the level of Th12 was noted on T2-weighted MRI, confirming leptomeningeal involvement of mantle cell lymphoma. Systemic MTX chemotherapy with an increased dose of 3.5 g/m^2 with repetitive intrathecal chemotherapy did not remove the lymphoma cells in the CSF. We administered ivBU (3.2 mg/kg/day ; days -7, -6, -5, and -4), cyclophosphamide (CY) (40 mg/kg/day ; days -3 and -2), and etoposide (VP-16) (200 mg/m^2 ; days -5 and -4) as conditioning chemotherapy after receiving written informed consent, followed by ASCT with CD34-positive cells at 6.79×10^6/kg for residual lymphoma in the CNS (Figure 1). He developed no serious adverse events except for neutropenia and thrombocytopenia, with grade 4 oral mucositis and grade 3 febrile neutropenia. He achieved engraftment on day 10 for neutrophils, day 21 for reticulocytes, and day 21 for platelets. No relapse has been detected for over 7 years.

[Case 2] A 40-year-old woman developed incomplete right leg muscle weakness with numbness in July Y-1. Brain CT revealed a tumor of 2 cm in diameter at the left cingulate convolution with surrounding widespread edema (Figure 2). Stereotactic biopsy of the brain tumor in September Y-1 demonstrated diffuse proliferation of atypical large lymphocytes positive for bcl-2, MUM-1, and CD20, and negative for CD3, CD5, and CD10 on immunostaining. We diagnosed her with diffuse large B-cell lymphoma

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and performed intravenous high-dose MTX and Ara-C combination chemotherapy with rituximab, and intrathecal chemotherapy using MTX and Ara-C with dexamethasone. She achieved a partial response after three courses of chemotherapy, but the disease progressed with right leg paralysis. Autologous stem cell collection was performed after receiving written informed consent after the fifth course of R-MTX/Ara-C therapy, and high-dose chemotherapy followed by ASCT with CD34-positive cells at 4.93×10^6/kg was administered. The conditioning regimen was ivBU (3.2 mg/kg/day ; days -7, -6, -5, and -4), CY (60 mg/day ; days -3 and -2), and VP-16 (400 mg/m^2 ; day -4) (Figure 3). She developed no serious adverse events except for neutropenia and thrombocytopenia with grade 4 oral mucositis and grade 3 febrile neutropenia. She achieved engraftment on day 10 for neutrophils and day 20 for platelets. After engraftment, we performed whole-brain radiotherapy (36 Gy/18 fractions) followed by local boost irradiation (10 Gy/5 fractions). Two years and two months after ASCT, she developed a cerebeller lesion, which was suspected to be relapsed lymphoma, and died.

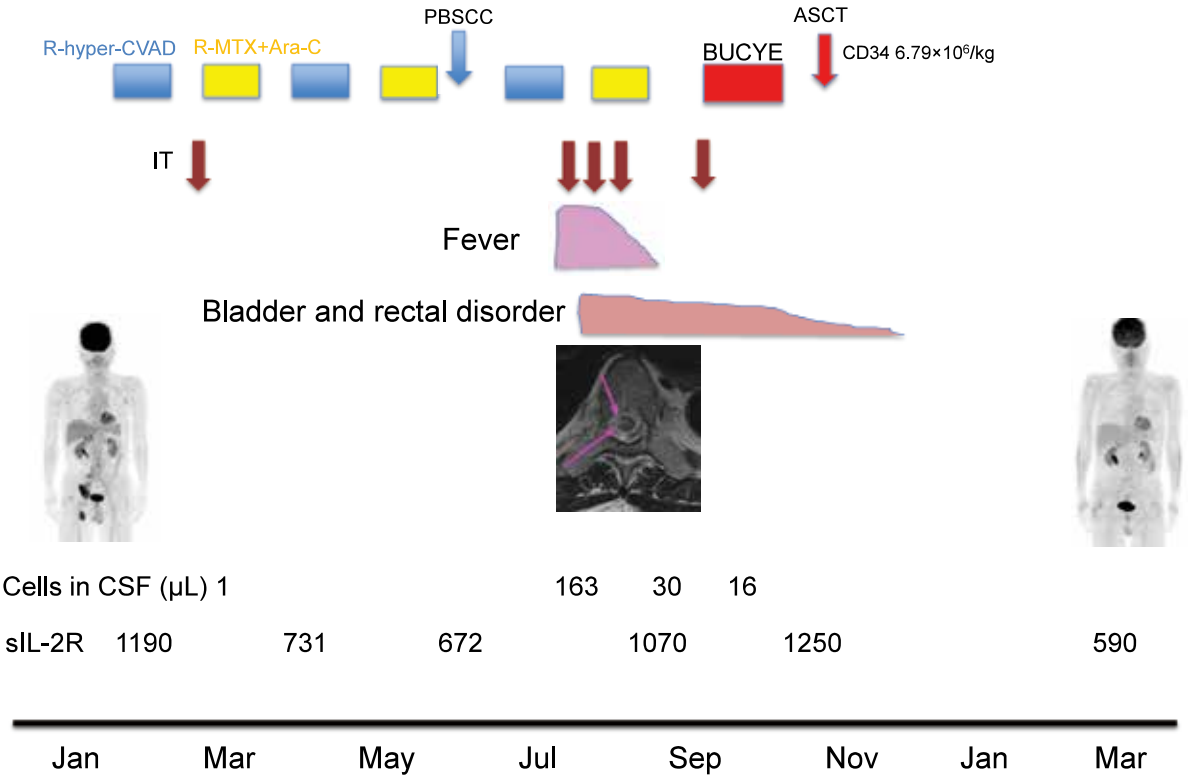

Figure 1. Clinical course of case 1
A 65-year-old man with Stage IV mantle cell lymphoma patient was treated using R-hyperCVAD/MTX+Ara-C chemotherapy. After the third course of R-hyper-CVAD, fever with bladder and rectal disorder developed. Increased lymphocytosis with cytology class IV and abnormal Th12 signal on T2-weighted MRI revealed leptomeningeal involvement of malignant lymphoma. He was resistant to MTX ; therefore, we administered ivBU, cyclophosphamide, and etoposide (BUCYE) conditioning chemotherapy followed by ASCT. He maintained a complete response for over six years.

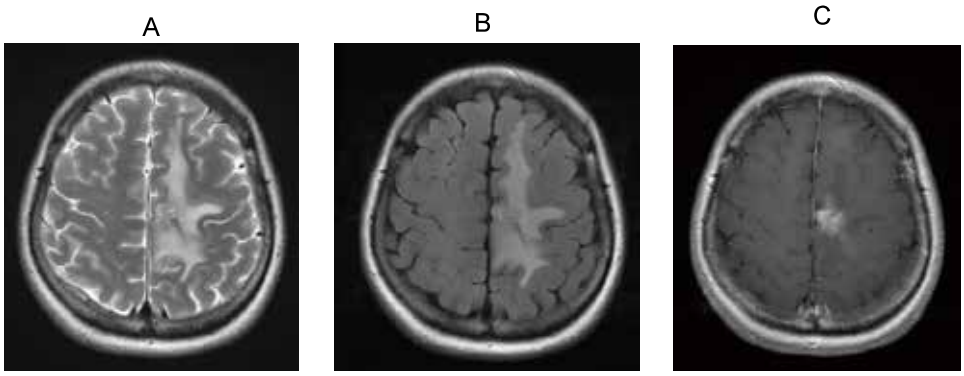

Figure 2. Brain MRI at initial presentation showed a left cingulate tumor surrounded by widespread edema on T2-weighted imaging (A), diffusion-weighted imaging (B), and gadolinium-enhanced T1-weighted imaging (C).

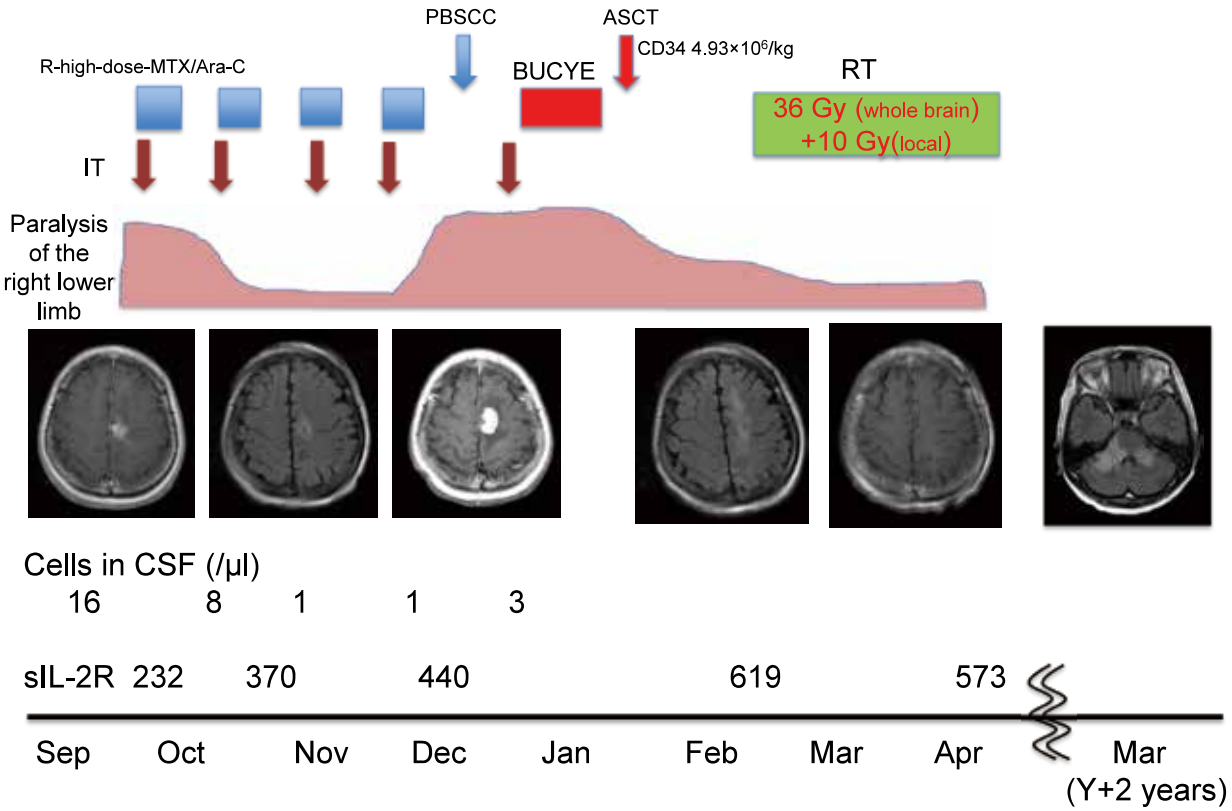

Figure 3. Clinical course of case 2
A 40-year-old woman with primary CNS lymphoma was treated using R-MTX + Ara-C chemotherapy. After three courses, she developed epilepsy with paralysis of the right lower limb. We administered ivBU, cyclophosphamide, and etoposide conditioning chemotherapy followed by ASCT. After engraftment, we performed whole-brain and local brain irradiation as consolidation therapy. She survived for two years and two months after ASCT.

DISCUSSION

We report two patients with relapsed or refractory B-cell lymphoma with CNS involvement in whom a conditioning regimen using ivBU, cyclophosphamide, and etoposide (BUCYE) followed by ASCT was effective. This study was approved by the internal review board of Tokushima University (permission number 3041).

Systemic chemotherapy using high-dose MTX, intrathecal chemotherapy, and whole-brain and/or local irradiation has been performed for malignant lymphoma with CNS involvement. However, its prognosis has not improved. In a historical lymphoma case series that included patients with secondary CNS involvement, the reported median survival was four months (1, 2). In primary CNS lymphoma, a primary refractory disease whereby there is an insufficient response to initial methotrexate therapy, similar to our case 2, has a particularly poor prognosis, with a median survival of less than 2 months without additional treatment (3). Almost all anticancer drugs do not satisfactorily penetrate the blood brain barrier, and few drugs, such as MTX and Ara-C, which can relatively easily penetrate the CNS, have been approved for treating lymphoma in Japan. As a result, it is difficult to achieve good outcomes by ranimustine, VP-16, Ara-C, and melphalan, which is a commonly administered conditioning regimen (termed MEAM regimen) for relapsed lymphoma patients in Japan, because it does not penetrate the CNS. Thus, conditioning regimens using anticancer drugs that preferentially enter the CNS for ASCT have been employed abroad. Thiotepa is an alkylating drug that has good CNS penetration, and has been reported to rapidly equilibrate in the lumbar and ventricular CSF in rhesus monkeys (4). Although thiotepa was available until 2009 in Japan, it was repurposed in 2019 for conditioning chemotherapy for ASCT with malignant lymphoma or pediatric solid cancer patients. Therefore, few alternative drugs for conditioning regimens of ASCT are available for adult malignant lymphoma patients with CNS involvement who are refractory/resistant to MTX and/or Ara-C.

BU is another alkylator and its penetration of the CNS is nearly equal to that of blood plasma (5). It is frequently used in conditioning regimens for allogeneic hematopoietic cell transplantation (6). There are several reports about ivBU-based conditioning regimens followed by ASCT for refractory or resistant malignant lymphoma with CNS involvement (Table 1). We found nineteen reports in which both thiotepa and ivBU were administered for primary or secondary CNS involvement by lymphoma as conditioning chemotherapy followed by ASCT (7-24), and BUCYE was administered in one report (25). The overall survival was relatively satisfactory in most reports. In addition, treatment-related mortality was not high in most reports, although the treatment-related mortality was 14.2% in one report, which was thought to be due to sepsis during neutropenia (7). We performed ASCT with a BUCYE conditioning regimen for two malignant lymphoma patients with CNS involvement who were resistant to MTX. Although we reduced the dose of VP-16 in case 1, there were no adverse events except for neutropenia, grade 4 thrombocytopenia, and mucosal damage. There are few

Table 1. Reported case of autologous stem cell transplantation for relapsed/refractory malignant lymphoma with central nervous system involvement.
TRM: treatment-related mortality, ND : not described, OS : overall survival, BU: busulfan, CY : cyclophosphamide, CNS : central nervous system, PCNSL : primary central nervous system lymphoma, NHL : non-Hodgkin's lymphoma.

Number of patients	Disease	Conditioning regimen	TRM	CR rate	OS	Reference
7	Primary PCNSL	Thiotepa/BU/CY	14.2%	100%	Median 24 months	7
16	Primary PCNSL	Thiotepa/BU	0%	68.8%	2-year OS 48%	8
43	Refractory NHL	Thiotepa/BU/CY	0%	ND	Median 18.3 months	9
11	Primary PCNSL	BUCYE	0%	90.9%	2-year OS 88.9%	25
21	Primary PCNSL	Thiotepa/BU/CY	14.2%	ND	5-year OS 44%	10
32	Refractory NHL	Thiotepa/BU/CY	3%	ND	1-year OS 93%	11
79	R/R PCNSL	Thiotepa/BU/CY	7.6%	83.5%	5-year OS 51%	12
16	Refractory PCNSL	Thiotepa/BU	12.5%	75%	1-year OS 62.5%	13
18	R/R PCNSL	Thiotepa/BU	0%	83.3%	ND	14
15	R/R primary or secondary CNS lymphoma	Thiotepa/BU/CY	0%	86.7%	3-year OS 93%	15
29	R/R Primary or secondary CNS lymphoma	Thiotepa/BU/CY	0%	100%	2-year OS 93%	16
12	R/R secondary CNS lymphoma	Thiotepa/BU	0%	ND	1-year OS 75%	17
26	Primary PCNSL	Thiotepa/BU/CY	7.7%	81%	2-year OS 81%	18
23	Primary or relapsed CNS lymphoma	Thiotepa/BU	8.7%	87%	2-year OS 76.1%	19
20	Primary NHL	Thiotepa/BU/CY	0%	ND	4-year OS 82%	20
15	R/R Secondary CNS lymphoma	BU/CY	0%	ND	1-year OS 25%	21
43	Primary and R/R PCNSL	Thiotepa/BU/CY	7%	ND	1-year OS 87%	22
46	Primary PCNSL	Thiotepa/BU/CY	0%	ND	2-year OS 95%	23
34	R/R secondary lymphoma	Semustine, hydroxyurea,BU/CY	2.9%	64.7%	2-year OS 81%	24

reports on ASCT for malignant lymphoma in Japan, but ivBU is widely administered for allogeneic stem cell transplantation in ivBU-based conditioning regimens. Therefore, ivBU-based conditioning regimens for ASCT are tolerable for lymphoma patients. As a point of benefit of ivBU-based conditioning chemotherapy, primary refractory for MTX in primary CNS lymphoma has a particularly poor prognosis with a median survival of less than 2 months, and salvage whole brain radiation also has a poor prognosis with median survival from initiation of whole brain radiotherapy reported to be 10.9 months (3, 26). Because case 2 survived 26 months after ASCT, ivBU-based chemotherapy may have contributed to extending her survival.

The sensitivity of lymphoma to BU is of concern. BU is used only for conditioning, and not as induction chemotherapy for malignant lymphoma. Therefore, we cannot confirm the sensitivity of BU before ASCT in clinical settings. However, many studies reported good survival of malignant lymphoma by ivBU-based conditioning followed by autologous or allogeneic transplantation (6, 25, 27). In addition, the IC50 of BU for Raji cell lines were 0.9-1.2 μM, which are similar to that of melphalan *in vitro* (28). In clinical practice, we administer ivBU once per day and not fractionated to increase its concentration in the CSF as much as possible. It was previously reported that once-daily intravenous administration achieved a four-fold higher Cmax than four-times-daily administration, although the AUC and t1/2 were similar (29). However, it is unknown whether once-daily administration of ivBU is more effective for malignant lymphoma with CNS involvement than four-times-daily administration. Thus, more clinical cases are warranted.

In conclusion, a high-dose ivBU-based conditioning regimen with ASCT may be useful for refractory lymphoma with CNS involvement.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest associated with this manuscript.

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