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ORIGINAL ARTICLE

Modified cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy with or without rituximab in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL

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Abstract The feasibility and efficacy of cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M)/ifosfamide, etoposide, and cytarabine (IVAC) therapy in Japanese adult patients with Burkitt lymphoma (BL) and B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and BL (intermediate DLBCL/BL) have never been reported. The effects of adding rituximab to CODOX-M/IVAC have not been published either. Fifteen consecutive patients with a median age of 39 years were treated with modified CODOX-M/IVAC regimen (particularly, reducing the dose of methotrexate to 3 g/m^2) with or without rituximab at our institution. Although all patients developed grade 4 neutropenia and grade 3/4 thrombocytopenia/anemia, 93% had febrile neutropenia, 60% showed transaminase elevation, and 40% had mucositis/stomatitis (all grade 3), there were no treatment-related deaths. Two of nine patients treated with rituximab developed biphasic late-onset neutropenia. Thirteen patients (87%) showed complete responses. The remaining two patients had refractory disease; one had presented with peritoneal dissemination and complex chromosomal abnormalities, while the other had double *IGH–MYC* and *IGH–BCL2* translocations. The estimated 5-year overall and progression-free survival were 87% each, with a median follow-up of 74 months. In conclusion, our modified CODOX-M/IVAC regimen is well tolerated and highly effective in Japanese adult patients with BL and intermediate DLBCL/BL, warranting a larger study for confirmation.

Keywords CODOX-M/IVAC · Burkitt lymphoma · Burkitt-like lymphoma · Rituximab

1 Introduction

Burkitt lymphoma (BL) is a highly aggressive B cell lymphoma that most commonly occurs in children and young adults [1–3]. The incidence of BL is low, constituting 1–2% of all lymphomas in adults [1, 2, 4]. According to the third edition of the World Health Organization (WHO) classification [1], BL is histopathologically characterized by monomorphic medium-sized B cells with round nuclei and clumped chromatin, a 'starry sky' appearance with numerous macrophages. Furthermore, genetically translocations involving *MYC* are required for the diagnosis of BL. Typical immunophenotypic features of BL include positivity of tumor cells for CD10 and CD20, negativity for BCL2, and a proliferation fraction measured by Ki67 immunohistochemistry (MIB-1 index) of nearly 100%. In the fourth edition of the WHO classification, a combination of several diagnostic techniques, such as morphology, genetic analysis and immunophenotyping, is necessary for diagnosis of BL, and *MYC* translocation is not specific to

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BL [2]. Burkitt-like lymphoma (BLL) was proposed as an independent category of high-grade B cell lymphoma for cases in which the cell size and nuclear morphology are intermediate between BL and diffuse large B cell lymphoma (DLBCL) regardless of *MYC* translocation in the Revised European-American Lymphoma (REAL) classification [5]. On the other hand, in the third edition of the WHO classification [1], BLL patients with *MYC* translocation are diagnosed as having atypical BL, and others are considered to have DLBCL. In the fourth edition of the WHO classification, the term BLL has been dropped in favor of a provisional category named "B cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (intermediate DLBCL/BL)" [6].

BL patients treated with chemotherapeutic regimens such as CHOP [cyclophosphamide (CPA), doxorubicin (DOX), vincristine (VCR), and prednisone (PDN)] have demonstrated poor prognosis [7, 8]. Several groups have reported excellent therapeutic results in pediatric or adolescent patients with BL treated with short-term intensive multi-agent chemotherapy regimens including fractionated alkylating agents, high-dose methotrexate (MTX) and cytarabine (Ara-C), and adequate central nervous system (CNS) prophylaxis [9–12]. It has been recognized that radiotherapy plays no role in these modern treatments for BL, even for localized disease [13]. The role of consolidative high-dose chemotherapy followed by autologous stem cell transplantation in first remission is unclear [14]. The Southwest Oncology Group (SWOG) concluded that BLL represents a high-grade lymphoma much more similar to BL than DLBCL, and retention of the BLL category or inclusion of BLL as a variant of BL is biologically and clinically more appropriate than absorbing the category of BLL into DLBCL [15].

Since BL and intermediate DLBCL/BL are rare subtypes of lymphomas in adults, it is difficult to perform a prospective randomized trial to establish a standardized treatment. CPA, VCR, DOX, and high-dose MTX (CODOX-M)/ifosfamide (IFM), etoposide (VP-16), and high-dose Ara-C (IVAC) therapy are among the representative short-term intensive regimens for the patients with BL/BLL in Western countries initially described by Magrath [16] and successfully accomplished in the multicenter LY06 study [17]. Although this treatment was effective in young adults, it was too toxic to be given to elderly patients. Two phase II trials have utilized this regimen with minor modifications (in particular, reducing the dose of MTX from 6.7 to 3 g/m^2), and have demonstrated preserved efficacy with decreased severe toxicities even in relatively older patients [18, 19]. On the other hand, the feasibility and efficacy of CODOX-M/IVAC therapy for Japanese patients has never been reported.

Rituximab has activity in most B cell lymphomas. CHOP/CHOP-like regimens with rituximab for patients with DLBCL [20, 21] or advanced-stage follicular lymphoma (FL) [22] significantly improved their prognosis compared with patients treated with CHOP/CHOP-like regimens alone. On the other hand, several reports suggested that rituximab increases such risks as late-onset neutropenia [23] and opportunistic infections [24–27]. Although one study described rituximab as having possible beneficial effects on patients with BL/BLL in cases when it was added to the hyper-CVAD [28], the report was a single-arm phase II study and therefore the degree to which intensive short-term chemotherapy is enhanced by rituximab remains unclear. Furthermore, there is limited data available regarding rituximab in combination with CODOX-M/IVAC therapy [29–31].

In an effort to help clarify the feasibility and efficacy of modified CODOX-M/IVAC (mCODOX-M/IVAC) therapy with or without rituximab in a form covered by health insurance in Japan, we are reporting our results from a study of 15 consecutive patients with BL and intermediate DLBCL/BL.

2 Patients and methods

2.1 Patient selection

We retrospectively reviewed the medical records of 30 consecutive patients diagnosed with BL or intermediate DLBCL/BL at our institution between April 2000 and April 2009. Fifteen patients aged greater than 18 and less than 60 years who were initially treated at our institution and who had no history of FL were identified as subjects. Patients who received PDN alone or CHOP/CHOP-like therapy prior to mCODOX-M/IVAC with or without rituximab were allowed to enroll in this study if their initial diagnosis of BL or intermediate DLBCL/BL had not been obtained or their clinical condition was considered to be inadequate for receiving the mCODOX-M/IVAC. Written informed consent was obtained from each patient before the start of the treatment according to the Declaration of Helsinki.

2.2 Histopathological analysis

All pathological materials were obtained from biopsies. All specimens for routine examinations were reviewed by three experienced hematopathologists (A.M.M., H.T. and Y.M.) according to the criteria of the fourth edition of the WHO classification [2, 6].

2.3 Interphase fluorescence in situ hybridization (FISH) analysis

Sections 4-μm thick were cut from each paraffin block and used for FISH analyses. At first, we used the LSI MYC Dual Color, Break Apart Rearrangement probe (Vysis, Abbott Molecular, Abbott Park, IL, USA) to detect the *MYC* rearrangement in all 15 patients, and the specimens which showed the *MYC* rearrangement were further investigated with the LSI IGH/MYC, CEP 8 Tri-Color, Dual Translocation Probe (Vysis) to detect the *IGH–MYC* translocation. The *IGH–BCL2* fusion was detected with the LSI IGH/BCL2 Dual Color, Dual Fusion Translocation Probe (Vysis). FISH analysis was performed as described previously [32, 33]. In our patients, G-banding analysis was not performed routinely at diagnosis.

2.4 Treatment regimen

The treatment regimen is presented in Tables 1 and 2. Several modifications were made to the original Magrath's A (CODOX-M) and B (IVAC) regimens [16]. In Regimen A, VCR was capped at 2 mg, and the dose of intrathecal (i.t.) Ara-C (mixed with 20 mg PDN) was reduced from 70 to 50 mg to lessen the incidence of neurotoxicity. The dose of intravenous (i.v.) MTX was decreased from the original 6,720 to 3,000 mg/m^2/day so as to be covered by Japanese health insurance, and the initial dose of leucovorin rescue was reduced from the original 192 to 85.7 mg/m^2 in accordance with the dose of MTX given. In Regimen B, the dose of mesna was also reduced from 360 to 300 mg/m^2 to comply with Japanese health insurance restrictions. In both the regimens, i.t. MTX was increased from 12 to 15 mg as an appropriate dose for adults, mixed with 10 mg PDN. Further dose reductions for patients 50 years or older were as follows: 20% decreases in doses of CPA, VCR, DOX, and MTX in Regimen A, and the same percentage decreases of IFM, VP-16, and Ara-C in Regimen B.

The treatment regimen consisted of alternating cycles of Regimens A and B for a total of four cycles (A–B–A–B) without additional radiotherapy and maintenance therapy. Patients who had been using non-steroid anti-inflammatory

Table 1 Regimen A: R-CODOX-M

Drug	Dose	Method	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	~
CPA	800 mg/m^2/2 h	i.v.	↓																	
	200 mg/m^2/2 h	i.v.		↓	↓	↓	↓													
VCR	1.5 mg/m^2 (max: 2 mg)	i.v.	↓							↓							(↓)[a]			
DOX	40 mg/m^2/30 min	i.v.	↓																	
MTX[b]	536 mg/m^2/h for 1 h	i.v.										↓								
	107 mg/m^2/h for 23 h	i.v.										↓								
Leucovorin[c]	85.7 mg/m^2 + 12 mg/m^2	i.v. + p.o.											○	○	○	○	~			
AraC + PDN	40 mg + 20 mg	i.t.	↑		↑		(↑)[d]													
MTX + PDN	15 mg + 10 mg	i.t.															↑[e]		(↑)[d,e]	
G-CSF	See below[f]	s.c.													↓	↓	↓	↓	↓	~
Rituximab	375 mg/m^2	i.v.						↓												↓[g]

R-CODOX-M rituximab, cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate; *CPA* cyclophosphamide; *i.v.* intravenous; *VCR* vincristine; *DOX* doxorubicin; *MTX* methotrexate; *p.o.* by mouth; *Ara-C* cytarabine; *PDN* prednisone; *i.t.* intrathecal; *G-CSF* granulocyte colony stimulating factor; *s.c.* subcutaneous

[a] The day 15 dose of VCR is not given in the first Regimen A, and given only if no severe neuropathy of grade 2 or more is observed during in the second Regimen A

[b] Commence MTX (total 3,000 mg/m^2) regardless of blood counts

[c] Commence leucovorin 36 h after the start of MTX infusion; 85.7 mg/m^2 i.v. at 36 h and 12 mg/m^2 every 6 h thereafter until the serum MTX level is less than 0.05 μM. Leucovorin 12 mg/m^2 is given orally first if patients were without nausea; otherwise i.v. administration is allowed

[d] Patients with proven central nervous system disease at diagnosis receive additional doses of i.t. therapy during the first Regimen A: i.t. Ara-C on day 5 and i.t. MTX on day 17

[e] The day 15 (and day 17, if any) dose of i.t MTX is given only if there are no non-hematological toxicities of grade 2 or more and serum MTX level is less than 0.05 μM

[f] G-CSF (75 μg of filgrastim or 100 μg of lenograstim) is administered s.c. from day 13 until the absolute granulocyte count is over 1,000/μL with platelet recovery

[g] Rituximab is administered within 2 days of a patient fulfilling the criteria for commencing subsequent cycles of therapy. The next cycle should be started within 2 days from the day of rituximab administration

Table 2 Regimen B: R-IVAC

Drug	Dose	Method	1	2	3	4	5	6	7	8	9	10	11	12	13	~
IFM	1500 mg/m^2/2 h	i.v.	↓	↓	↓	↓	↓									
Mesna[a]	300 mg/m^2/30 min TID	i.v.	○	○	○	○	○									
VP-16	60 mg/m^2/2 h	i.v.	↓	↓	↓	↓	↓									
Ara-C[b]	2000 mg/m^2/2 h	i.v.	↓↓	↓↓												
AraC + PDN	40 mg + 20 mg	i.t.							(↑)[c]		(↑)[c]					
MTX + PDN	15 mg + 10 mg	i.t.					↑									
G-CSF	See below[d]	s.c.							↓	↓	↓	↓	↓	↓	↓	~
Rituximab	375 mg/m^2	i.v.						↓								↓[e]

R-IVAC rituximab; ifosfamide, etoposide, and high-dose cytarabine; *IFM* ifosfamide; *i.v.* intravenous; *TID* three times a day; *VP-16* etoposide; *Ara-C* cytarabine; *PDN* prednisone; *i.t.* intrathecal; *MTX* methotrexate; *G-CSF* granulocyte colony stimulating factor; *s.c.* subcutaneous

[a] Mesna is administered i.v. simultaneously with IFM, and at 4 and 8 h afterwards for 30 min

[b] Ara-C is administered i.v. every 12 h on days 1 and 2 for 2 h, with steroid eye drops of 5 times a day, on days 1–3

[c] Patients with proven central nervous system disease at diagnosis receive additional doses of i.t. therapy during the first Regimen B: i.t. Ara-C on days 7 and 9

[d] G-CSF (75 μg of filgrastim or 100 μg of lenograstim) is administered s.c. from day 7 until the absolute granulocyte count is over 1,000/μL with platelet recovery

[e] Rituximab is administered within 2 days of a patient fulfilling the criteria for commencing the subsequent cycle of therapy. The next cycle should be started within 2 days from the day of rituximab administration

drugs mainly because of pain, or who had massive pleural or pericardial effusion or ascites at diagnosis were treated in the reverse order (B–A–B–A) to avoid the toxicities caused by high-dose MTX. Regimen A (Table 1) consisted of 800 mg/m^2 CPA i.v. on day 1 and 200 mg/m^2 i.v. on days 2–5 for 2 h; 1.5 mg/m^2 VCR i.v., with a maximum dose of 2 mg on days 1 and 8 in the first cycle and on days 1, 8, and 15 in the second cycle, with day 15 administration withheld if a peripheral neuropathy of grade 2 or greater was present; and 40 mg/m^2 DOX i.v. on day 1 for 30 min. A total of 3,000 mg/m^2 MTX i.v. was administered, with 536 mg/m^2 during the first 1 h followed by 107 mg/m^2 each hour for 23 h on day 10 regardless of complete blood cell count. Forty milligram Ara-C with 20 mg PDN i.t. was given on days 1 and 3, and 15 mg MTX with 10 mg PDN i.t. on day 15 as CNS prophylaxis unless non-hematological toxicity of grade 2 or greater was present.

Regimen B (Table 2) consisted of 1,500 mg/m^2 IFM i.v. on days 1–5 for 2 h; 60 mg/m^2 VP-16 i.v. on days 1–5 for 2 h; 2,000 mg/m^2 Ara-C i.v. every 12 h for 2 h on days 1 and 2, comprising four doses in total, with steroid eye drops (5 times a day, on days 1–3); and 15 mg MTX with 10 mg PDN i.t. on day 5.

To maintain dose intensity, subsequent cycles were initiated when the unsupported white blood cell count was ≥2,000/μL, neutrophil count was ≥1,000/μL, platelet count was ≥10 × 10^4/μL, and all the non-hematological toxicities were recovered to below grade 2. Further dose modifications were never performed based on the degree or duration of myelosuppression in the first cycle.

For patients treated after November 2003, an additional eight doses of rituximab were included as part of the mCODOX-M/IVAC therapy. Rituximab was administered at 375 mg/m^2 i.v. on day 6 of both Regimens A and B as well as on the day when a patient fulfilled the criteria for commencing subsequent cycles of therapy.

2.5 Supportive care

Oral allopurinol and intensive intravenous hydration (at least 3,000 mL/day) mixed with sodium bicarbonate were given to alkalinize the urine (≥pH 7.5) to avoid tumor lysis syndrome. To prevent hemorrhagic cystitis potentially caused by CPA or IFM, vigorous hydration with alkalinization and twice-daily urinalysis including assessment of pH and occult blood were performed during CPA or IFM administration. In Regimen A, 85.7 mg/m^2 i.v. leucovorin was begun 36 h after the start of i.v. MTX, then administered at 12 mg/m^2 every 6 h thereafter until the serum MTX level was less than 0.05 μM. Leucovorin 12 mg/m^2 was given orally first if patients were free of nausea, otherwise i.v. administration was allowed if necessary. In Regimen B, administration of 300 mg/m^2 mesna was started simultaneously with IFM as well as at 4 and 8 h afterwards for 30 min. Granulocyte colony stimulating factor (G-CSF) was administered subcutaneously (s.c.) from day 13 in Regimen A and day 7 in Regimen B until the neutrophil count was over 1,000/μL. All patients were provided with trimethoprim–sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) from

the start of chemotherapy to 6 months after treatment completion.

2.6 Clinical staging, response and toxicity criteria

Clinical stage was determined according to the Ann Arbor staging system [34]. Bulky disease was defined as lymphoma greater than 10 cm in the maximal diameter. For assessment of response, we used the International Workshop Response Criteria [35] or its revised version [36] only for patients who underwent fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT), since both FDG-PET/CT and the revised criteria [36] were available. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [37].

2.7 Statistical analysis

For the full-set analysis (15 patients), overall survival (OS) was calculated from the date chemotherapy was initiated to the date of death from any cause. Progression-free survival (PFS) was calculated from the date chemotherapy was begun to the date of disease progression, relapse, or death from any cause. Patients in continued complete response (CR) were censored on the last date of follow-up. All survival curves were estimated by the Kaplan–Meier analysis method.

3 Results

3.1 Patient characteristics

Details concerning the 15 patients are shown in Table 3. All patients were HIV-negative. The median age was 39 years (range 19–59). Five patients were older than 50 years. Four patients (27%) had clinical stage I disease, three (20%) had stage II, and eight (53%) had stage IV. Ten (67%) showed elevated serum lactate dehydrogenase levels, three (20%) had bulky diseases, and six (40%) were high-intermediate- or high-risk patients based on the International Prognostic Index [38]. Four had bone marrow involvement, patients numbers 8 and 9 had less than 10% lymphoma cells, and patients numbers 13 and 15 had greater than 90% in their bone marrow. None of the enrolled patients had B symptoms or CNS disease at diagnosis. Lymphomas of all 15 patients except one (patient 15) showed the typical BL immunophenotype including positivity of tumor cells for CD10 and CD20, negativity for BCL2, and a MIB-1 index of nearly 100%. Lymphoma cells of only four (patients 2, 6, 7, and 12) in all 15 patients showed positivity for EBER-1 in situ hybridization. FISH analysis of all 15 patients revealed that nine (60%) had *MYC* rearrangement (*MYC* break apart), and all of nine had *IGH–MYC* (Table 3). One of them who had *MYC* rearrangement had *IGH–BCL2* (patient 15) (Table 3). In other words, the *MYC* rearrangement was not detected in the remaining six patients. According to the fourth edition of the WHO classification, four patients were diagnosed as having BL and 11 patients as having intermediate DLBCL/BL (Table 3).

3.2 Clinical course

Eight patients (53%) received chemotherapy (four received one cycle of CHOP, and one each received one cycle of CPA and DOX, PDN and CPA, PDN alone, and two cycles of CHOP) prior to mCODOX-M/IVAC because of poor physical condition (patient 14) or initial diagnostic uncertainty. Patient number 14 with BL, who presented with gastric perforation with peritoneal dissemination at diagnosis, received CPA and DOX after abdominal surgery. Three days after initiation of chemotherapy, he developed acute renal failure due to tumor lysis syndrome and consequently temporary dialysis was required. Nine patients (60%) including three out of four patients (75%) with BL and six out of 11 patients (55%) with intermediate DLBCL/BL received rituximab in addition to mCODOX-M/IVAC. Twelve patients (80%) completed the protocol-defined four cycles of alternating mCODOX-M/IVAC; three patients (20%) aged over 50 years received three cycles (reasons for cessation were as follows: patient 2 rejected the treatment after improvement of grade 3 bacterial pneumonia, patient 3 declined therapy despite non-hematologic toxicities lower than grade 3, and patient 15 experienced disease progression). One (patient 11) was treated with the B–A–B–A schedule so as to avoid the toxicities caused by high-dose MTX because of the presence of massive ascites at diagnosis. The median interval between cycles 1 and 2 was 27 days (range 19–54), that between cycles 2 and 3 was 20 days (range 15–28), and between cycles 3 and 4 was 30 days (range 18–37). The median overall treatment period in the 12 patients who completed four cycles was 99 days (range 81–127).

3.3 Toxicities

The worst toxicity grades experienced during mCODOX-M/IVAC therapy are shown in Table 4. All 15 patients developed grade 4 leukopenia and neutropenia, and grade 3 or 4 thrombocytopenia and anemia. All patients required a median transfusion of 40 units of platelets (range 10–140) and a median of 16 units of red blood cells (range 6–68) during the entire treatment period. There were no patients who developed grade 2 or greater peripheral neuropathy. Grade 3 non-hematologic toxicities were as follows: 14 patients with

Table 3 Patient characteristics

Pt No.	Sex	Age (years)	CS[a]	Involved sites	PS	LDH elevation	Bulky disease (site)[b]	IPI	Diagnosis[c]	Immunostaining				FISH		Prior therapy[d]	R	Response[e]	Outcome	Follow-up duration (months)
										CD20	CD10	BCL2	MIB-1 (%)	*IgH–MYC*	*IgH–BCL2*					
1	M	21	IA	Cervical LN	1	+	−	L	Int	+	+	−	≥95	−	−	−	−	CR	Alive	89
2	F	55	IA	Tonsil	0	−	−	L	Int	+	+	−	100	+	−	−	+	CR	Alive	76
3	M	53	IA	Stomach	0	−	−	L	Int	+	+	−	100	+	−	2 cycles of CHOP	+	CR	Alive	66
4	M	19	IA	Cervical LN	0	−	−	L	Int	+	+	−	≥95	−	−	−	+	CR	Alive	20
5	M	31	IIA	Stomach and regional LN	0	−	−	L	Int	+	+	−	100	+	−	1 cycle of CHOP	+	CR	Alive	73
6	M	59	IIA	Cervical LN and tonsil	0	+	−	L	Int	+	+	−	100	+	−	−	−	CR	Alive	101
7	F	40	IIA	Stomach and regional LN	1	+	−	L	BL	+	+	−	100	−	−	1 cycle of CHOP	+	CR	Alive	25
8	F	52	IVA	Retroperitoneal LN and BM	1	+	+ (Retroperitoneal LN)	LI	Int	+	+	−	100	−	−	1 cycle of CHOP	+	CR	Alive	32
9	M	22	IVA	Cervical LN, axillary LN and BM	1	−	−	LI	Int	+	+	−	≥95	−	−	−	−	CR	Alive	122
10	M	25	IVA	Rectum, bone, liver and multiple LNs	1	+	+ (Rectum)	HI	Int	+	+	−	≥95	+	−	−	−	CR	Alive	126
11	M	41	IVA	Ileum, retroperitoneal LN and ascites	2	+	−	H	Int	+	+	−	100	+	−	1 cycle of CHOP	+	CR	Alive	82
12	F	23	IVA	Ovary and stomach	0	+	+ (Ovary)	HI	BL	+	+	−	100	−	−	−	−	CR	Alive	101
13	M	34	IVA	BM and multiple LNs	2	+	−	H	BL	+	+	−	100	+	−	PDN alone	+	CR	Alive	54
14	M	39	IVA	Stomach, pancreas, peritoneum and ascites	3	+	−	H	BL	+	+	−	100	+	−	CPA plus DOX	+	PD	DOD	16
15	F	59	IVA	BM, kidney, bone, nasal cavity, duodenum, thyroid and multiple LNs	2	+	−	H	Int	+	+	+	100	+	+	CPA plus PDN	−	PD	DOD	7

Pt No. patient number; *CS* clinical stage; *PS* performance status; *LDH* lactate dehydrogenase; *IPI* International Prognostic Index; *FISH* fluorescence in situ hybridization; *R* rituximab; *M* male; *LN* lymph node; *L* low risk; *Int* B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma; *CR* complete response; *F* female; *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone; *BL* Burkitt lymphoma; *BM* bone marrow; *LI* low–intermediate risk; *HI* high–intermediate risk; *H* high risk; *PDN* prednisone; *CPA* cyclophosphamide; *DOX* doxorubicin; *PD* progressive disease; *DOD* dead of disease

[a] CS was determined according to the Ann Arbor staging system [34]

[b] The bulky disease was defined as lymphoma greater than 10 cm in the maximal diameter

[c] Histopathological diagnosis according to the fourth edition of the World Health Organization classification

[d] Eight patients received chemotherapy prior to modified CODOX-M/IVAC ± rituximab because of poor physical condition (patient 14) or initial diagnostic uncertainty

[e] Responses were assessed according to the International Workshop Response Criteria [35] or its revised version [36]

Table 4 Worst toxicity (grade 3 or 4) experienced during the entire treatment protocol ($N = 15$)

Adverse event	Regimen A				Regimen B				Total			
	Grade 3		Grade 4		Grade 3		Grade 4		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Leukopenia	2	13	13	87	0	0	15	100	0	0	15	100
Neutropenia	4	27	11	73	0	0	15	100	0	0	15	100
Anemia	12	80	2	13	11	73	2	13	13	87	2	13
Thrombocytopenia	3	20	8	53	1	7	14	93	1	7	14	93
Febrile neutropenia	12	80	0	0	12	80	0	0	14	93	0	0
Infection with grade 3 or 4 neutropenia	1	7	0	0	5	33	0	0	6[a]	40	0	0
AST elevation	9	60	0	0	0	0	0	0	9	60	0	0
ALT elevation	9	60	0	0	0	0	0	0	9	60	0	0
Mucositis/stomatitis	6	40	0	0	0	0	0	0	6	40	0	0
Creatinine elevation	1	7	0	0	0	0	0	0	1	7	0	0

Regimen A CODOX-M (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate) ± rituximab; *Regimen B* IVAC (ifosfamide, etoposide, and high-dose cytarabine) ± rituximab; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase

[a] Documented infectious complications including 4 sepsis and 2 bacterial pneumonia

febrile neutropenia (93%), nine with alanine aminotransferase/aspartate aminotransferase elevation (60%), six with mucositis/stomatitis (40%), and one with serum creatinine elevation (7%). One patient (patient 5) developed grade 3 serum creatinine elevation after administration of high-dose MTX during the first cycle. After improvement of renal function by supportive treatment without dialysis, cycle 2 (Regimen B) was started on day 55 of Regimen A and this patient completed the treatment without a dose reduction of any of the agents included in the mCODOX-M/IVAC-without-MTX protocol. Documented infections occurred in 6 of 15 patients (40%), specifically four with sepsis and two with bacterial pneumonia. Although toxicities in patients treated with rituximab were similar to those who did not receive the drug, two patients (patients 11 and 13) treated with rituximab developed self-limiting neutropenia after completion of treatment. Interestingly, biphasic late-onset neutropenia in both patients was observed on days 52 and 199 (patient 11), and on days 81 and 256 (patient 13) of the last cycle of chemotherapy in each patient, respectively. Neither patient experienced infectious complications.

3.4 Response and survival

The median follow-up duration was 74 months (range 16–126). Thirteen of 15 patients (87%) obtained CRs, and the remaining two (patients 14 and 15) had refractory disease. The CR rates of BL and intermediate DLBCL/BL were 75 and 91%, respectively. Although patient number 14 with BL completed four cycles without disease progression during the treatment, his lymphoma progressed 2 months after treatment completion, and died of disease progression 16 months after diagnosis. Patient number 15 with intermediate DLBCL/BL had double *IGH–MYC* and *IGH–BCL2* translocations, and died 7 months after diagnosis. There were no therapy-related deaths. All of the 13 complete responders including three with BL and ten with intermediate DLBCL/BL have maintained CRs. The estimated 5-year OS and PFS for all 15 patients were 87% each (Fig. 1). The estimated 5-year OS of BL and intermediate DLBCL/BL were 75 and 91%, respectively.

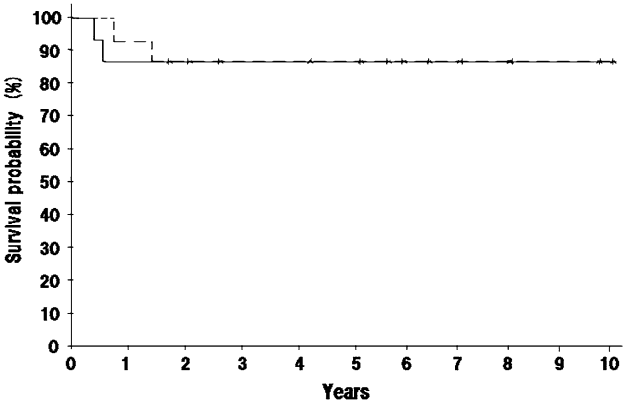

Fig. 1 Overall survival (OS) and progression-free survival (PFS) for all 15 patients with Burkitt lymphoma or B cell lymphoma, unclassifiable, with features intermediate between diffuse large B cell lymphoma and Burkitt lymphoma treated with modified CODOX-M/IVAC therapy with or without rituximab with a median follow-up duration of 74 months. Kaplan–Meier analyses estimated that 5-year OS (*dashed line*) and PFS (*solid line*) were 87% each

4 Discussion

Although CODOX-M/IVAC therapy is considered to be one of the standard regimens for young patients with BL as

well as intermediate DLBCL/BL in Western countries, there are no data regarding this treatment for Japanese adult patients. In addition, worldwide there have been only three reports in abstract form regarding the combination of rituximab with CODOX-M/IVAC [29–31]. To our knowledge, our data are the first to report the use of CODOX-M/IVAC with or without rituximab for BL and intermediate DLBCL/BL patients, modified so as to be covered by the Japanese health insurance system, incorporating consecutive patients initially treated at a single institution with strict supportive care management and pathologic review. There were no therapy-related deaths. Our results showed that grade 4 neutropenia and mucositis/stomatitis during Regimen A were reduced compared with the frequency of these adverse events during the original Magrath's regimen [16] (Table 5). Furthermore, grade 2 or greater peripheral neuropathy was never observed in this study, whereas the original Magrath's regimen with concurrent granulocyte–macrophage colony stimulating factor administration was associated with unusual neurotoxicity with profound and painful disabling neuropathy [16, 39]. One patient (patient 5) developed grade 3 serum creatinine elevation after administration of high-dose MTX and renal biopsy revealed acute tubular necrosis. With regard to infections, Magrath et al. [16] showed that febrile neutropenia, documented infection, and sepsis occurred in 32, 57, and 21% of adult patients, respectively. LaCasce et al. [18], who used a modified Magrath regimen, reported that febrile neutropenia occurred in 17 and 43% of patients during Regimens A and B, respectively. In our study, febrile neutropenia and documented infection were observed in 93 and 40% over the course of the entire treatment, respectively (Table 4). Although we did not achieve a lower incidence of infection than the previous reports mentioned above [16, 18], all observed toxicities were transient and could be managed by administration of both antibiotics and G-CSF. Two modified CODOX-M/IVAC regimens [18, 19] showed preserved efficacy in older patients while reducing the severe toxicities of the original Magrath's regimen [16]. We also showed superior data regarding the prognosis of patients with a relatively long-term follow-up duration (Table 5). In our study, all the intermediate DLBCL/BL patients except one with double *IGH–MYC* and *IGH–BCL2* translocations are still alive without disease. As for BL patients, only one patient died of disease progression. Three out of four patients with BL and six out of 11 patients with intermediate DLBCL/BL received additional rituximab. We could not see a significant difference in the CR rate and survival between patients with BL and intermediate DLBCL/BL, although the proportion of the patients who received rituximab was different between BL and intermediate DLBCL/BL. Patient number 14 with BL, who presented with gastric perforation with peritoneal dissemination at diagnosis, demonstrated disease progression in a pelvic lymph node other than the primary site after completion of four cycles with rituximab. After his disease progressed, bone marrow examination revealed involvement of BL with complex chromosomal abnormalities, such as 52, XY, +X, +add(1)(p13), +6, +7, t(8;14)(q24;q32), +11, +13, as analyzed by the G-banding method. The poor response to mCODOX-M/IVAC with rituximab might be attributable to the presence of complex chromosomal abnormalities.

The role of rituximab in the treatment of BL and intermediate DLBCL/BL remains elusive. A single-arm phase II trial that evaluated hyper-CVAD with rituximab in patients with BL/BLL showed that the 2-year OS was approximately 89%. Although the authors concluded that multivariate analysis including historical control (hyper-CVAD alone) identified additional rituximab as favorable factor [28], we wonder whether this statement would be true for the CODOX-M/IVAC. First, because the 3-year PFS (52%) of the patients treated with hyper-CVAD alone was lower than that of patients treated with CODOX-M/IVAC (60–92%) [16–18], there is a possibility that rituximab exerted an additional effect in favor of hyper-CVAD. Second, the median follow-up period of the R-hyper-CVAD (22 months) group was too short to draw definite conclusions. Finally, a recent report in abstract form revealed that the additional of four doses of rituximab to CODOX-M/IVAC did not significantly improve the outcome over CODOX-M/IVAC alone [31]. We administered rituximab on day 6 of both Regimens A and B when a number of the effector cells, such as macrophages, natural killer cells, and neutrophils, were still kept more than that at the time of bone marrow suppression by chemotherapy, and just before the next cycle after the bone marrow had recovered, to retain the efficacy of the antibody-dependent cell-mediated cytotoxicity and the possible synergistic effect between rituximab and chemotherapeutic drugs. However, the optimal schedule of combined rituximab and mCODOX-M/IVAC remains unknown and further investigations are needed. In our study, complete response and survival rates were extremely high regardless of the presence or absence of rituximab. Several reports have suggested that rituximab increase risks such as late-onset neutropenia [23], reactivation of hepatitis B virus [24], and opportunistic infections, e.g., progressive multifocal leukoencephalopathy [25, 26], PCP, and fungal infection [27]. Preliminary reports suggested that the addition of rituximab to CODOX-M/IVAC might increase the risk of infections [29] and delayed neutropenia [30]. In our experience, PCP was not observed in any patients during the follow-up period, because all patients were provided with trimethoprim–sulfamethoxazole as prophylaxis against PCP from the start of chemotherapy until 6 months

Table 5 Previous reports of CODOX-M/IVAC in patients with Burkitt or Burkitt-like lymphoma

Author	*n*	Median age (years)	Median interval between cycles, days (range)			Toxicity of grade 3/4 (%)						CR (%)	2-year PFS (%)	2-year OS (%)	Median follow-up duration (months)
			Cycles 1–2	Cycles 2–3	Cycles 3–4	Neutropenia		Thrombocytopenia		Mucositis/stomatitis					
						Regimen A	Regimen B	Regimen A	Regimen B	Regimen A	Regimen B				
Magrath et al. [16]	20[a]	25	23[b]	18[b]	27[b]	2/98	0/100	9/40	4/96	29/20	3/0	95	92	NA	32
Mead et al. [17]	40[c]	38	25 (16–40)	20 (14–41)	27 (18–41)	3/95[d]		3/97[d]		38/15[d]		74	60	70	32
LaCasce et al. [18]	14	47	NA	NA	NA	74[e]	100[e]	36[e]	100[e]	7[e]		86	64	71	29
Mead et al. [19]	77[f]	39	27 (17–67)	21 (11–37)	29 (20–55)	1/99[d]		1/96[d]		38/11[d]		NA	49	52	29
Present study	15	39	27 (19–54)	20 (15–28)	30 (18–37)	27/73	0/100	20/53	7/93	40/0	0/0	87	87[g]	87[g]	74

CODOX-M cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate; *IVAC* ifosfamide, etoposide, and high-dose cytarabine; *Regimen A* CODOX-M ± rituximab; *Regimen B* IVAC ± rituximab; *CR* complete response; *PFS* progression-free survival; *OS* overall survival; *NA* not available

[a] Patients 18 years or older

[b] Range of interval between cycles was not described

[c] High-risk patients

[d] Toxicity profile of each regimen was not available

[e] Incidence of toxicity of grade 3 or more

[f] High-risk patients including 42 with Burkitt lymphoma and 35 with diffuse large B cell lymphoma

[g] 5-year PFS and OS

after treatment completion. Although varicella zoster virus (VZV) infection was not observed regardless of the lack of prophylaxis in this study, we cannot conclude that prophylaxis against VZV infection is not necessary because the number of analyzed patients was limited.

In the fourth edition of the WHO classification, a provisional category named intermediate DLBCL/BL was newly described [6]. These aggressive lymphomas have morphological and genetic features of both DLBCL and BL were previously classified as BLL [5] or atypical BL [1], and as a class may include some transformed FL. Because these lymphomas are heterogeneous in terms of their clinical behavior and genetic features, the optimal therapeutic choice in these cases remains controversial. Nomura et al. [40] retrospectively analyzed the clinical outcomes of patients with BLL and concluded that aggressive short-term chemotherapy improves survival in these patients, regardless of the tumor's genetic or immunophenotypic features. Furthermore, because our study and previous reports [16, 18] included patients with not only BL but also BLL, CODOX-M/IVAC is considered to be one of the appropriate aggressive short-term regimens for patients with BL/BLL. In the fourth edition of the WHO classification, there is a description that lymphomas with an immunoglobulin gene–*MYC* rearrangement as the sole chromosomal abnormality likely represent BL even if they are morphologically atypical. Conversely, although *MYC* rearrangement is common in intermediate DLBCL/BLs, many of these cases have non-immunoglobulin gene–*MYC* translocations and other complex karyotypic abnormalities [6]. In our results, although seven of 11 patients who were morphologically diagnosed as having intermediate DLBCL/BL had *IGH–MYC* translocation by FISH analysis, their lymphomas could not be diagnosed as BL. Because comprehensive cytogenetic analysis such as G-banding method to detect other chromosomal abnormalities than translocation involving the *MYC* locus on chromosome 8q24 to the *IGH* locus on chromosome 14q32 was not performed, their lymphomas did not fulfill the criteria of BL completely. Furthermore, there is a description in the fourth edition of the WHO classification that intermediate DLBCL/BL is a heterogeneous category that is not considered a distinct disease entity [6]. Consequently, we think that it is difficult to distinguish BL from intermediate DLBCL/BL perfectly, especially in case of lymphoma with *IG–MYC* translocation, and we believe that patients diagnosed as having intermediate DLBCL/BLs in our study population have lymphomas much more similar to BL than DLBCL.

In our analysis, a patient with intermediate DLBCL/BL with double *IGH–MYC* and *IGH–BCL2* translocations was refractory to mCODOX-M/IVAC and had an exceedingly poor prognosis, with a short survival of only 7 months from the time of diagnosis. Mead et al. [19] reported that all four patients with double *IGH–MYC* and *IGH–BCL2* translocations were dead less than 5 months from the start of CODOX-M/IVAC. The extremely poor prognosis of patients with these lymphomas was confirmed in a recent report [41]. Fifty-nine percent of them died within 6 months after diagnosis, and the authors indicated that even intensified chemotherapy could not overcome the aggressive tumor biology in these cases [41]. These results suggest that the patients with double *IGH–MYC* and *IGH–BCL2* translocations are candidates for alternative therapeutic approaches other than an intensified chemotherapy such as CODOX-M/IVAC.

In conclusion, although the total number of patients was relatively small, our results indicate that our modified regimen was highly effective and well tolerated in Japanese adult patients with BL or intermediate DLBCL/BL, suggesting that this regimen can be regarded as an acceptable standard regimen for these patients. Although the role of adding rituximab to mCODOX-M/IVAC should be further investigated in a large, prospective cohort study, we suggest caution regarding the possible increase in the risk of late-onset neutropenia.

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Conflict of interest None declared.

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