

Case report

DA-EPOCH-R therapy for high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements in a patient with renal dysfunction

Masaki Mitobe,¹⁾ Keisuke Kawamoto,¹⁾ Takaharu Suzuki,¹⁾ Tatsuya Suwabe,¹⁾
Yasuhiko Shibasaki,¹⁾ Masayoshi Masuko,¹⁾ Kanako Inoue,²⁾ Hiroaki Miyoshi,²⁾
Koichi Ohshima,²⁾ Hirohito Sone,¹⁾ Jun Takizawa¹⁾

High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, also known as double-hit lymphoma, has been reported as refractory to R-CHOP therapy and requires more intensive regimens. However, intensive and safe regimens for patients with renal dysfunction are unknown. Herein, we report the successful use of DA-EPOCH-R therapy for double-hit lymphoma in a 64-year-old man with renal dysfunction. The patient had lymphoma-induced bilateral ureteral obstruction. Although renal dysfunction remained after removing the obstruction using R-CHOP therapy, we completed six cycles of DA-EPOCH-R therapy without any major adverse events. DA-EPOCH-R therapy may be a safe regimen for renal dysfunction patients.

Keywords: DA-EPOCH-R therapy, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, double-hit lymphoma, renal dysfunction, renal impairment

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) with *MYC* and *BCL2* rearrangements is often reported to be refractory to R-CHOP therapy, with a poor prognosis.¹⁻⁴ The 2016 revision of the World Health Organization classification of lymphoid neoplasms newly characterized high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements,⁵ widely and commonly referred to as double-hit lymphoma (DHL) or triple-hit lymphoma (THL).

Although no standard initial treatment for DHL or THL has been established, it has been reported that if organ function is preserved, progression-free survival (PFS) is improved by selecting intensive regimens such as dose-adjusted (DA)-EPOCH-R therapy,⁶⁻⁸ R-HyperCVAD/MA therapy,⁹ or R-CODOX-M/IVAC therapy,¹⁰ rather than R-CHOP therapy.¹¹⁻¹³ However, there are few known intensive regimens that can be safely administered to patients with DHL/THL who have moderate to severe renal dysfunction.

We report a case of double-hit lymphoma with renal

dysfunction in a patient who underwent DA-EPOCH-R therapy according to the protocol, without initial dose reduction.

CASE REPORT


The patient was a 64-year-old Japanese man with no noteworthy medical or family history. He experienced malaise and abdominal distention three weeks before admission, and chest discomfort and orthopnea began five days before admission. The day before admission, he visited the emergency department, presenting with arm and leg edema and right pleural effusion seen on chest X-ray. Heart failure was suspected, and he was prescribed furosemide. The next day, he visited the internal department of the general hospital. Plain computed tomography (CT) revealed bilateral hydronephrosis and a retroperitoneal mass lesion. He was then transferred to the urology department of our hospital as an emergency case. Blood tests showed elevated soluble interleukin-2 receptor (sIL-2R) levels at 9334 IU/L, and he was referred to our department with suspicion of malignant

Received: September 6, 2020. Revised: December 19, 2020. Accepted: December 22, 2020. J-STAGE Advance Published: February 6, 2021
DOI:10.3960/jslrt.20043

¹⁾Department of Hematology, Endocrinology and Metabolism, Faculty of Medicine, Niigata University, Niigata, Japan, ²⁾Department of Pathology, School of Medicine, Kurume University, Kurume, Japan

Corresponding author: Keisuke Kawamoto, Department of Hematology, Endocrinology and Metabolism, Faculty of Medicine, 1-757, Asahimachidori, Chuo-Ku, Niigata 951-8570, Japan. E-mail: kawakeis@med.niigata-u.ac.jp, rasprotein@yahoo.co.jp

Copyright © 2021 The Japanese Society for Lymphoreticular Tissue Research

 This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

lymphoma.

On admission, he was fully conscious, his temperature was 35.7°C, pulse was 53 beats per minute, blood pressure was 177/87 mmHg, and SpO₂ was 98% on room air. He had no anemia in the foveal conjunctiva and no jaundice in the ocular conjunctiva. Respiratory and cardiac sounds were normal. The abdomen was flat and soft, and the liver and spleen were not palpable. Both lower limbs had pitting edema. Inguinal lymph nodes were 3-cm in size and elastic, hard, and smooth-textured on palpation bilaterally. No other superficial lymph nodes were palpated. There were no abnormal neurological findings. His Eastern Cooperative

Oncology Group Performance Status (ECOG PS) was 2. He had no systemic B symptoms (fever, night sweats, or weight loss).

Laboratory data on admission (Table 1) showed a markedly elevated creatinine (Cre) of 17.31 mg/dL, blood urea nitrogen (BUN) of 121 mg/dL, potassium (K) of 7.3 mEq/L, and inorganic phosphorus (IP) of 10.1 mg/dL. Lactate dehydrogenase (LDH) and sIL-2R were elevated to 666 IU/L and 9334 IU/mL, respectively. Plain CT (Figure 1) showed a 9 cm × 5 cm retroperitoneal mass causing bilateral hydronephrosis and partially kidney invasive lesion. It also showed pleural effusions and right cardiophrenic and bilateral

Table 1. Laboratory data on admission

RBC	424×10 ⁴ /μL	TP	6.5 g/dL	Ca	9.2 mg/dL
Hb	12.8 g/dL	Alb	3.5 g/dL	IP	10.1 mg/dL
Hct	37.0 %	AST	14 IU/L	CRP	3.17 mg/dL
MCV	87.3 fl	ALT	14 IU/L	sIL-2R	9334 IU/mL
MCH	30.2 pg	LDH	666 IU/L	Ferritin	417 ng/mL
MCHC	34.6 %	ALP	187 IU/L	IgG	467 mg/dL
WBC	9980 /μL	γ-GTP	19 IU/L	IgA	45 mg/dL
Neu	83.5 %	T-Bil	0.4 mg/dL	IgM	207 mg/dL
Lym	9.9 %	BUN	121 mg/dL	APTT	27.4 sec
Eos	5.3 %	Cre	17.37 mg/dL	(control)	26.7 sec
Bas	1.1 %	Na	130 mEq/L	PT%	98 %
Mon	0.2 %	K	7.3 mEq/L	PT-INR	1.01
Plt	45.7×10 ⁴ /μL	Cl	94 mEq/L		

RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, WBC: white blood cell, Neu: neutrophil, Lym: lymphocyte, Eos: eosinophil, Bas: basophil, Mon: monocyte, Plt: platelet, TP: total protein, Alb: albumin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, IP: inorganic phosphate, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, APTT: activated partial thromboplastin time, PT: prothrombin time, PT-INR: prothrombin time-international normalized ratio

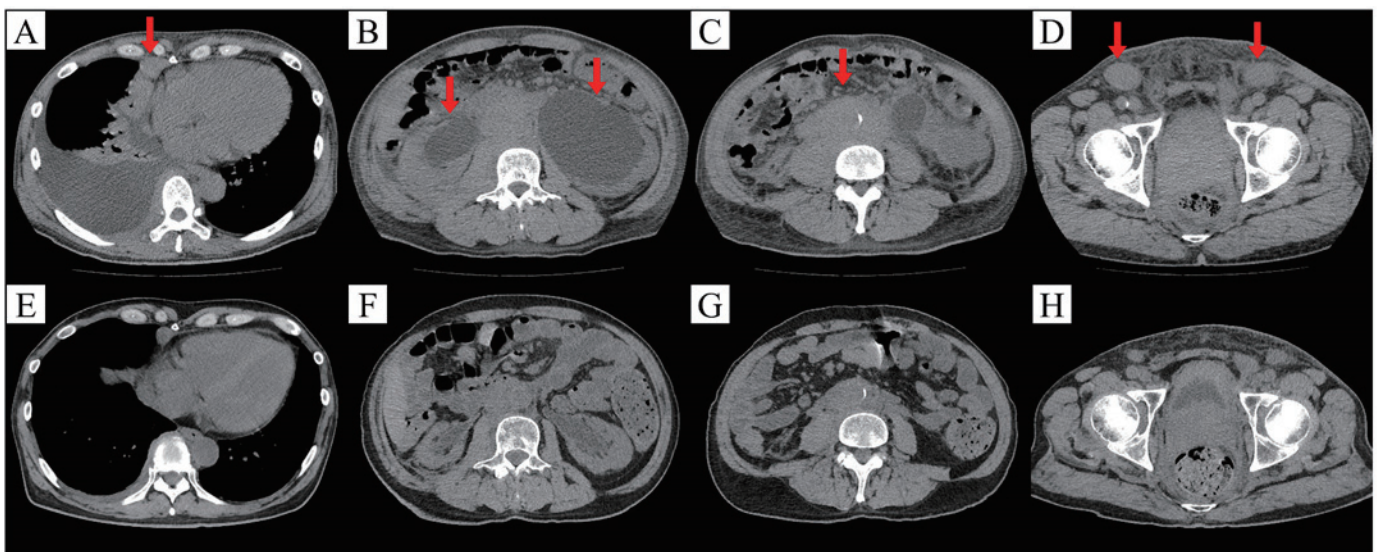


Fig. 1. Systemic computed tomographic (CT) scan on admission (*A, B, C, D*) and after 6 cycles of DA-EPOCH-R therapy (*E, F, G, H*). Systemic CT scan on admission shows a right cardiophrenic lymphadenopathy (arrow), pleural effusions (*A*), bilateral hydronephrosis (arrow) and renal infiltration (*B*), a 9 cm × 5 cm retroperitoneal mass (arrow) (*C*), and bilateral inguinal lymphadenopathies (arrow) (*D*). Each lesion shrank after 6 cycles of DA-EPOCH-R (*E, F, G, H*).

inguinal lymphadenopathies. Bone marrow examination revealed no apparent tumor cell infiltration, and Giemsa banding showed a normal 46,XY karyotype. Cytopathologic examination of pleural fluid showed invasion of large abnormal lymphocytes.

On the second day in hospital, inguinal lymph node biopsy was performed (Figure 2). Hematoxylin and eosin (H&E) staining showed a diffuse pattern of involvement with medium to large abnormal lymphocytes, and loss of the

normal structure of lymphoid follicles. Immunostaining showed that the tumor was negative for CD3 and Bcl-6, and positive for CD10, CD20, CD79a, Ki67, c-Myc, and Bcl-2. The positive rate of Ki67, c-Myc and Bcl-2 was over 90% for each. Fluorescence in situ hybridization (FISH) showed split signals at 8q24 (*MYC*) and 18q21 (*BCL2*) (Figure 3). Based on these findings, we diagnosed high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements. Ann Arbor stage was IV A and International Prognostic

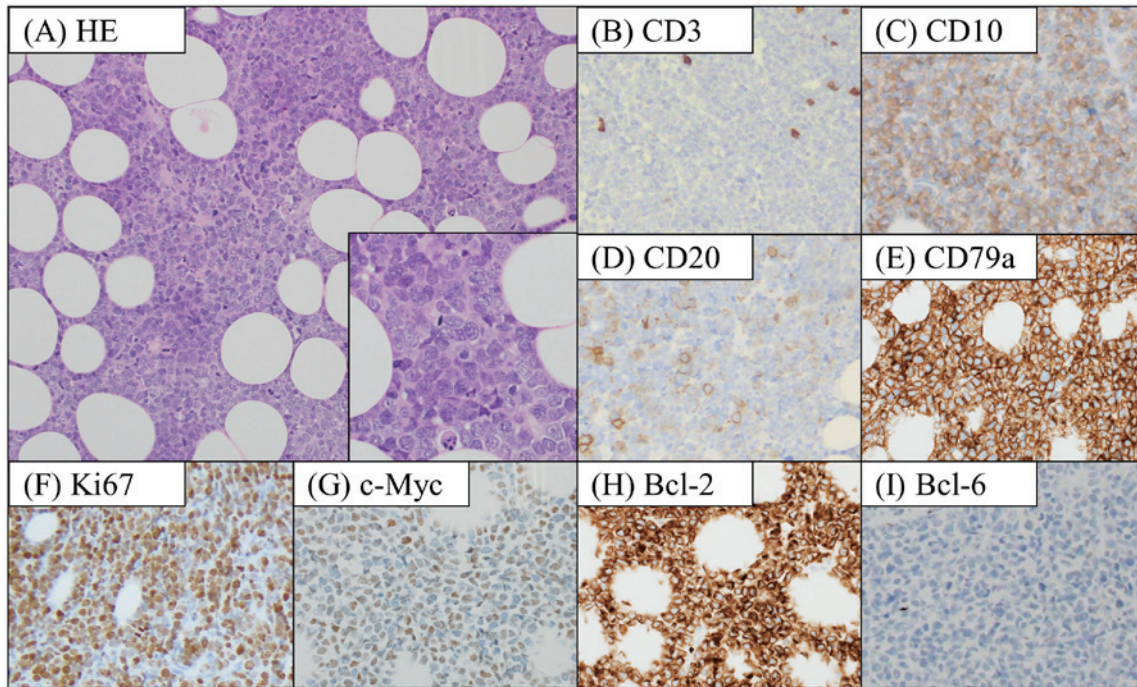


Fig. 2. Pathological images of inguinal lymph node biopsy. Hematoxylin and eosin (H&E) staining images show a diffuse pattern of involvement with medium to large abnormal lymphocytes, with loss of the normal structure of lymphoid follicles (A). Immunostaining images show that the tumor was negative for CD3 (B), negative for CD10 (C), positive for CD20 (D), positive for CD79a (E), positive for Ki67 (positive rate was over 90%) (F), positive for c-Myc (positive rate was over 90%) (G), positive for Bcl-2 (positive rate was over 90%) (H) and negative for Bcl-6 (I).

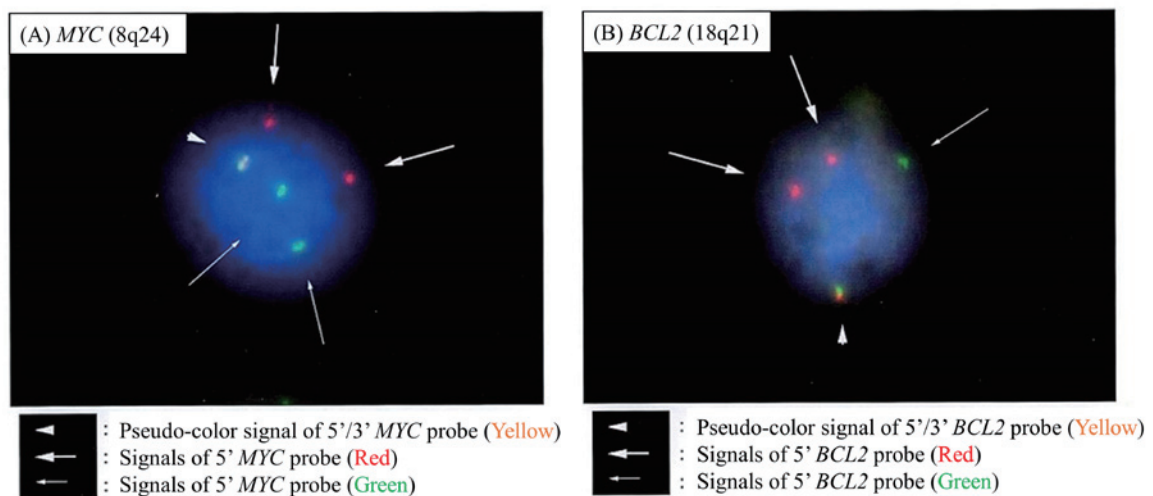


Fig. 3. Fluorescence in situ hybridization (FISH) of inguinal lymph node biopsy. Of 111 cells, 74 (66.7%) showed split signals at 8q24 (*MYC*) and duplication of 5' *MYC* and 3' *MYC* probe signals (A). Out of 104 cells, 68 (65.4%) showed split signals at 18q21 (*BCL2*) and duplication of 5' *BCL2* probe signals (B).

Index was high-intermediate risk.

On the day of admission, right nephrostomy was performed for ureteral obstruction, but Cre improvement was poor, and the patient required emergency hemodialysis from the 4th hospital day. As diagnosis from the preliminary pathological report was diffuse large B-cell lymphoma (DLBCL), we started half-dose CHOP therapy (cyclophosphamide 375 mg/m², day 1; doxorubicin 25 mg/m², day 1; vincristine 0.7 mg/m², day 1; prednisolone 60 mg/m², days 1–5) on the 23rd hospital day. Rasburicase was administered to prevent tumor lysis syndrome. Urinary volume of 1000 mL/day was obtained on the 25th hospital day, but despite this and removal of the ureteral obstruction, Cre and 24-hour urine collection creatinine clearance (Ccr) improved only to 2.4 mg/dL and 37 mL/min, respectively, and right renal dysfunction remained (Figure 4). The patient was weaned off hemodialysis on the 30th hospital day. After the first cycle of half-dose CHOP therapy, the treatment response was stable disease (SD) with 47% tumor reduction (Figure 1). Cre remained approximately 2 mg/dL during treatment.

Pathological examination and FISH revealed the diagnosis of high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements. Although Ccr was as low as 45 mL/min, we started DA-EPOCH-R therapy (rituximab

375 mg/m², day 1; doxorubicin 10 mg/m², days 2–5; vincristine 0.4 mg/m², days 2–5; cyclophosphamide 750 mg/m², day 6; prednisolone 60 mg/m², days 2–6; administered every 21 days) without initial dose reduction on the 38th hospital day because more intensive treatment was considered necessary for DHL/THL. No worsening of renal function was observed during the treatment, and the patient completed the first cycle without any problems. The treatment response was partial response (PR) with 64% tumor reduction, and we decided to continue the DA-EPOCH-R therapy. On the third cycle, grade 4 neutropenia as categorized by the Common Terminology Criteria for Adverse Events (CTCAE) was observed, and we therefore reduced dosages from the fourth cycle onward by 20% in accordance with the protocol for DA-EPOCH-R therapy. The patient completed six cycles of DA-EPOCH-R without any new CTCAE grade 2 or higher adverse events. Ccr remained between 31 and 43 mL/min, with no further exacerbation. Plain CT after six cycles of DA-EPOCH-R therapy showed the response was PR with 65% tumor reduction, although contrast-enhanced CT was not possible due to renal dysfunction, and the accurate evaluation was difficult. There was no indication of tumor enlargement, and we therefore decided to monitor him as an outpatient and he was discharged on the 163rd hospital day.

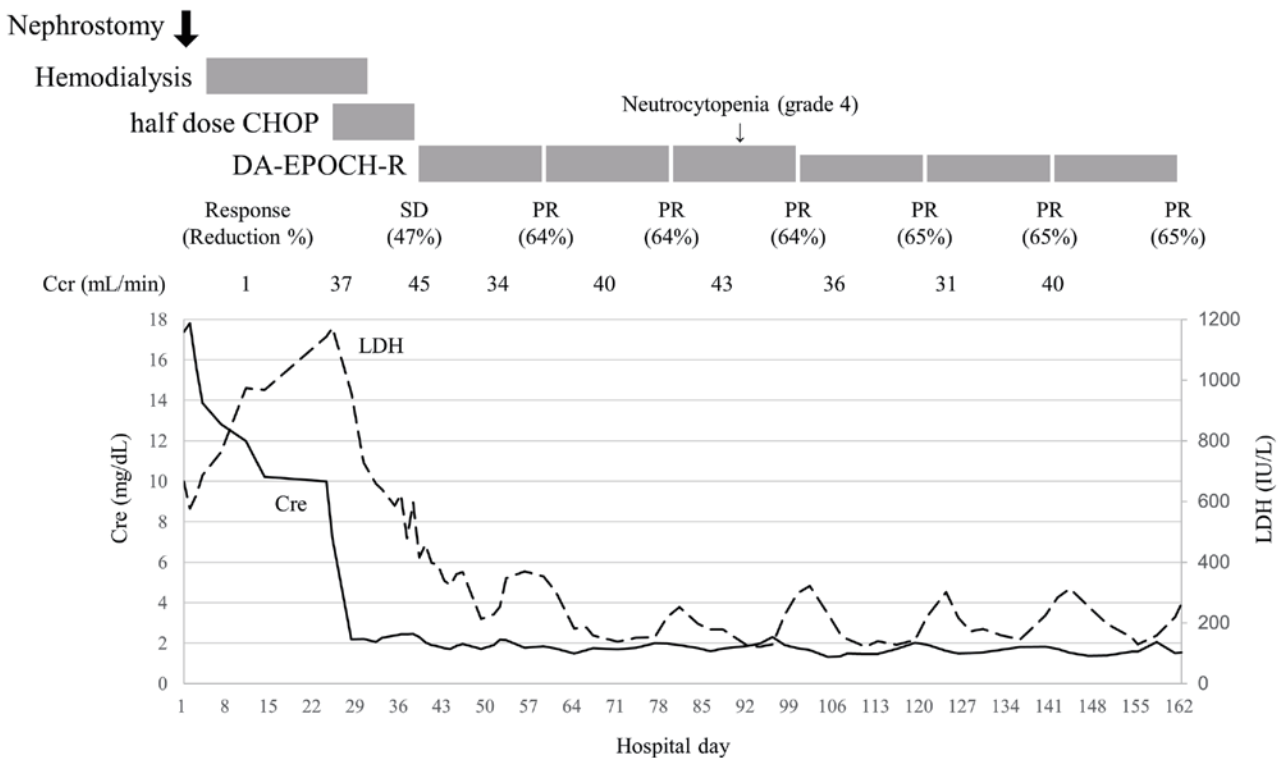


Fig. 4. Treatment and transition of serum lactate dehydrogenase (LDH), serum creatinine (Cre), and 24-hour urine collection creatinine clearance (Ccr) Nephrostomy was performed for ureteral obstruction on the first hospital day. However, Cre did not improve, and we started hemodialysis. We performed half-dose CHOP therapy and the obstruction was removed immediately, although renal dysfunction remained (Cre 2.4 mg/dL, Ccr 37 mL/min). Owing to the confirmed diagnosis of the high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, we decided to use an intensive regimen and started full-dose DA-EPOCH-R therapy. Doses were reduced by 20% from the fourth cycle onward due to Common Terminology Criteria for Adverse Event (CTCAE) grade 4 neutropenia. Six cycles of DA-EPOCH-R therapy were completed without other adverse events greater than CTCAE grade 2. DA-EPOCH-R therapy did not exacerbate renal dysfunction. Cre and Ccr were stable at around 2-3 mg/dL and 30-40 mL/min, respectively, during the treatment.

We scheduled positron emission tomography-computed tomography (PET-CT) after discharge. However, 22 days after discharge he presented diplopia. Head magnetic resonance imaging revealed swellings of the bilateral abducens nerves and the left optic nerve. Cytopathologic examination of lumbar puncture showed an invasion of large abnormal lymphocytes. He was readmitted, and we could not perform PET-CT.

DISCUSSION

We describe a case in which a DHL patient with moderate renal dysfunction (Cre 2 mg/dL, Ccr 30 mL/min) was treated with DA-EPOCH-R therapy according to the protocol without major adverse events, including worsening renal function.

Although a standard initial treatment for DHL/THL has not been established, it has been reported that intensive regimens such as DA-EPOCH-R therapy, R-HyperCVAD/MA therapy, and R-CODOX-M/IVAC therapy improve progression-free survival (PFS) rates more than R-CHOP therapy.¹¹⁻¹³ A meta-analysis reported that DA-EPOCH-R had lower toxicity and superior PFS and overall survival (OS) than a combined R-HyperCVAD/MA and R-CODOX-M/IVAC treatment (median PFS 22.2 months and 18.9 months, respectively; median OS 31.4 months and 25.2 months, respectively).¹¹ A phase 2 prospective study in DHL also showed a high efficacy of DA-EPOCH-R therapy.¹⁴

Although the efficacy of DA-EPOCH-R therapy as an initial treatment for DHL/THL has been established, in the prospective study mentioned above¹⁴ and in an initial report on DA-EPOCH-R therapy,⁶ patients with renal dysfunction with a Cre >1.5 mg/dL were excluded from the studies. Therefore, the safety of DA-EPOCH-R therapy in patients with renal dysfunction is currently unknown and presents a major question in daily clinical practice. There are few reports regarding DA-EPOCH-R in patients with moderate or severe renal dysfunction, and we could find only two such cases.¹⁵ One case of Burkitt lymphoma with acute kidney injury due to dehydration; this recovered to Cre of 1.73 mg/dL with hydration, and DA-EPOCH-R therapy was subsequently commenced. The second case of Burkitt lymphoma with ureteral obstruction due to the tumor. COP therapy (cyclophosphamide, vincristine, and methylprednisolone) was commenced as the initial treatment, and ureteral obstruction was removed. After improvement of Cre to 1.73 mg/dL, DA-EPOCH-R therapy was started. Both cases completed six cycles of DA-EPOCH-R therapy without exacerbation of renal dysfunction. Considering these reports, DA-EPOCH-R therapy is likely to be safe even in patients with moderate renal dysfunction. For this reason, we selected DA-EPOCH-R therapy instead of CHOP therapy in this case.

According to a report on dose recommendation for anticancer drugs for renal dysfunction,¹⁶ there is no need to adjust doses of rituximab, doxorubicin, vincristine, and cyclophosphamide if the Ccr is 45 mL/min, and a 75% dose of etoposide is recommended. In this case, etoposide was

administered at 100% dose to prioritize efficacy over toxicity. If safety is more important, a 75% reduction in the dose of etoposide may be considered. We could safely administer the DA-EPOCH-R therapy both by preparing a system to resume dialysis at any time if renal dysfunction became exacerbated, and by monitoring the patient with frequent blood tests.

The patient in this case had a retroperitoneal mass and kidney invasion resulting in bilateral hydronephrosis and post-renal acute kidney injury. Cre on admission was 17.37 mg/dL, and it required temporary hemodialysis. Although half-dose CHOP therapy resolved the ureteral obstruction, Cre improved only to approximately 2 mg/dL, and renal dysfunction remained because of kidney lesion. We selected DA-EPOCH-R therapy considering the high risk of recurrence with R-CHOP therapy for DHL/THL, although there was concern regarding decreasing renal function due to high-intensity chemotherapy. We did not select R-CODOX-M/IVAC therapy because high-dose methotrexate therapy has been reported to worsen renal function in a high number of patients with renal dysfunction.¹⁷ We were able to complete six cycles of DA-EPOCH-R therapy according to the protocol and reach remission. Moreover, there was no worsening of renal dysfunction.

Recurrence of central nerve system (CNS) is known to have a high frequency in DLBCL with MYC translocation,² for which CNS prophylaxis is recommended. The same is true for DHL, and a clinical trial showing the efficacy of R-EPOCH for DHL¹⁴ also included CNS prophylaxis with intrathecal methotrexate. In general, high-dose intravenous methotrexate and intrathecal methotrexate are widely used for CNS prophylaxis in NHL.¹⁸ While high-dose intravenous methotrexate has been reported to significantly reduce CNS recurrence,^{19,20} there is no evidence regarding whether intrathecal methotrexate alone significantly reduces or does not prevent CNS recurrence.²¹⁻²³ In this case, intrathecal methotrexate could not be administered because the patient was in poor general condition on admission and could not be positioned for lumbar puncture. High-dose methotrexate therapy could not be administered due to renal dysfunction. Although there is no solid evidence that intrathecal methotrexate significantly suppresses CNS recurrence, the decision not to administer intrathecal methotrexate in this case is a major regret. Whether intrathecal methotrexate alone is useful for preventing CNS recurrence needs to be studied on a larger scale.

Our experience, combined with the conclusions of the two cases mentioned above, suggests that DA-EPOCH-R therapy may be safely administered even if Cre is below 2–3 mg/dL or Ccr is above 30–40 mL/min, although no definite reference values for Cre and Ccr can yet be set. There have been few reports of DA-EPOCH-R therapy administered to patients with renal dysfunction, and an appropriate treatment regimen for DHL/THL patients with renal dysfunction has not been established. We therefore recommend carrying out more case studies to continue the evaluation of the safety and efficacy of DA-EPOCH-R therapy for patients with renal

dysfunction.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

- 1 Johnson NA, Savage KJ, Ludkovski O, *et al.* Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood.* 2009; 114 : 2273-2279.
- 2 Savage KJ, Johnson NA, Ben-Neriah S, *et al.* MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood.* 2009; 114 : 3533-3537.
- 3 Kawamoto K, Miyoshi H, Yoshida N, *et al.* MYC translocation and/or BCL 2 protein expression are associated with poor prognosis in diffuse large B-cell lymphoma. *Cancer Sci.* 2016; 107 : 853-861.
- 4 Tomita N, Tokunaka M, Nakamura N, *et al.* Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. *Haematologica.* 2009; 94 : 935-943.
- 5 Swerdlow SH, Campo E, Pileri SA, *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016; 127 : 2375-2390.
- 6 Wilson WH, Grossbard ML, Pittaluga S, *et al.* Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood.* 2002; 99 : 2685-2693.
- 7 Miyazaki K. Treatment of Diffuse Large B-Cell Lymphoma. *J Clin Exp Hematop.* 2016; 56 : 79-88.
- 8 Kojima M, Amaki J, Ogiya D, Ando K, Nakamura N. Dose-adjusted EPOCH-R in patients with newly diagnosed diffuse large B-cell lymphoma harboring MYC rearrangement. *J Clin Exp Hematop.* 2020; 60 : 60-61.
- 9 Thomas DA, O'Brien S, Faderl S, *et al.* Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol.* 2010; 28 : 3880-3889.
- 10 Mead GM, Sydes MR, Walewski J, *et al.* An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol.* 2002; 13 : 1264-1274.
- 11 Howlett C, Snedecor SJ, Landsburg DJ, *et al.* Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol.* 2015; 170 : 504-514.
- 12 Petrich AM, Gandhi M, Jovanovic B, *et al.* Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood.* 2014; 124 : 2354-2361.
- 13 Landsburg DJ, Falkiewicz MK, Maly J, *et al.* Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. *J Clin Oncol.* 2017; 35 : 2260-2267.
- 14 Dunleavy K, Fanale MA, Abramson JS, *et al.* Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. *Lancet Haematol.* 2018; 5 : e609-e617.
- 15 Ross S, Eisenman K, Maloney KW. Successful Use of EPOCH-R in 2 Young Adult Patients With Burkitt Lymphoma and Acute Kidney Injury. *J Pediatr Hematol Oncol.* 2019; 41 : 498-500.
- 16 Krens SD, Lassche G, Jansman FGA, *et al.* Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol.* 2019; 20 : e200-e207.
- 17 May J, Carson KR, Butler S, *et al.* High incidence of methotrexate associated renal toxicity in patients with lymphoma: a retrospective analysis. *Leuk Lymphoma.* 2014; 55 : 1345-1349.
- 18 Hill QA, Owen RG. CNS prophylaxis in lymphoma: who to target and what therapy to use. *Blood Rev.* 2006; 20 : 319-332.
- 19 Abramson JS, Hellmann M, Barnes JA, *et al.* Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer.* 2010; 116 : 4283-4290.
- 20 Kuitunen H, Kaprio E, Karihtala P, *et al.* Impact of central nervous system (CNS) prophylaxis on the incidence of CNS relapse in patients with high-risk diffuse large B cell/follicular grade 3B lymphoma. *Ann Hematol.* 2020; 99 : 1823-1831.
- 21 Arkenau HT, Chong G, Cunningham D, *et al.* The role of intrathecal chemotherapy prophylaxis in patients with diffuse large B-cell lymphoma. *Ann Oncol.* 2007; 18 : 541-545.
- 22 Chua SL, Seymour JF, Streater J, *et al.* Intrathecal chemotherapy alone is inadequate central nervous system prophylaxis in patients with intermediate-grade non-Hodgkin's lymphoma. *Leuk Lymphoma.* 2002; 43 : 1783-1788.
- 23 Eyre TA, Kirkwood AA, Wolf J, *et al.* Stand-alone intrathecal central nervous system (CNS) prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity. *Br J Haematol.* 2019; 187 : 185-194.