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Letter to the Editor

Dose-adjusted EPOCH-R in patients with newly diagnosed diffuse large B-cell lymphoma harboring MYC rearrangement

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TO THE EDITOR

Diffuse large B-cell lymphoma (DLBCL) can manifest with phenotypes that vary according to diverse clinical, pathomorphological, immunohistological, and genetic features. Approximately 10% of cases of DLBCL harbor *MYC* rearrangement (*MYC*-R) and this abnormality is associated with a poor prognosis in the rituximab era.[1] In several retrospective studies, the presence of *MYC*-R alone or in combination with *BCL2* and/or *BCL6* translocation (double-hit lymphoma: DHL) was associated with significantly poorer prognosis following standard R-CHOP chemotherapy.[2] However, patients with DHL who were treated using more intensive chemotherapy, such as that for Burkitt lymphoma (BL), had a significantly better outcome than those who received R-CHOP chemotherapy.[3] Recently, Dunleavy *et al*. reported that the intense dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin with rituximab (DA-EPOCH-R) regimen improves the outcome of newly diagnosed BL patients with *MYC* gene rearrangement.[4] Thus, we planned a prospective phase II study of DA-EPOCH-R for newly diagnosed *MYC*-R DLBCL patients (UMIN000015972).

MYC-R was assessed by florescence *in situ* hybridization (FISH) using a breakapart probe. Eligible patients included: those who were newly diagnosed with DLBCL according to the WHO classification; those aged 20-75 years; those diagnosed at any clinical stage according to the American Joint Committee on Cancer based on the Ann Arbor staging system; those with evaluable lesions by CT; those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; and those with no other active malignancies. Patients received chemotherapy consisting of DA-EPOCH-R with pegfilgrastim for 6 cycles.[5] When signs of central nervous system (CNS) invasion were observed, the patient underwent imaging examination and lumbar puncture. If CNS invasion developed, the patient was excluded from the clinical trial. CNS prophylaxis was not performed. According to the WHO classification version 4, all histological sections were reviewed at the Department of Pathology, University of Tokai. The primary study endpoint was the 2-year progression-free survival rate.

Although our initial plan consisted of enrollment of 34 patients between November 2014 and April 2017, only 4 patients were registered because few satisfied the eligibility criteria. The clinical characteristics of all patients included a median age of 62 years (range 51–73), stage III/IV disease in 3/4 (75%), high lactate dehydrogenase (LDH) level in 4/4 (100%), performance status >1 in 0/4 (0%), extranodal site >1 in 2/4 (50%), high-intermediate/high-risk disease in 2/4 (50%) using IPI and high-risk disease in 2/4 (50%) using CNS-IPI (Table 1). As a result of immunophenotyping, CD5 was expressed in 1/4 (25%), BCL2 was expressed in 3/4 (75%) and *MYC* was expressed in 3/4 (75%) of tumors. According to the expression of CD10, BCL6 and MUM1, 2 cases were categorized into the GCB subgroup of the Hans algorithm.[6] By FISH analysis, *BCL2* rearrangement was not observed and *BCL6* rearrangement was observed in one patient. All patients underwent dose adjustment as scheduled. As a result of this treatment, only one patient achieved partial response (PR), and the other three patients developed progressive disease (PD), including two with CNS invasion after 6 cycles. The patient who achieved PR received cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide and rituximab (CHASER), dexamethasone, etoposide, ifosfamide and carboplatin (DeVIC), autologous stem cell transplantation with melphalan, cyclophosphamide, etoposide and dexamethasone (LEED), and irradiation. The patient has maintained complete response (CR) for over 3.5 years since transplantation.

Savage *et al*. reported that there was an increased risk of CNS relapse in cases of DLBCL treated by R-CHOP that harbored *MYC*-R after adjusting for other high-risk factors.[1] On the other hand, García-Suárez *et al*. reported the low incidence of CNS relapse in DLBCL patients treated using DA-EPOCH-like chemotherapy. They hypothesized that rapid tumor reduction together with the use of etoposide (this drug can cross the blood-brain barrier) was sufficient for CNS prophylaxis, thus routine CNS tailored prophylaxis may not be required.[7] Although there was a limited number of patients, our phase II trial demonstrated a high rate of CNS invasion in *MYC*-R DLBCL patients treated using DA-EPOCH-R; therefore, the prevention of CNS invasion of *MYC*-R DLBCL by DA-EPOCH-R alone is insufficient. Recently, Dunleavy *et al*. reported that DA-EPOCH-R improved the prognosis of *MYC*-R DLBCL in a prospective study.[8] The difference from our study was the additional administration of MTX-IT to CNS high-risk patients, thus

Table 1. Patient characteristics and outcomes

No	Age	Cs	LDH	PS	Extranodal site	IPI	CNS-IPI	sIL2R	Outcome	CNS invasion	Survival
1	66	IVB	1691(UNL)	1	>1	High	High	3010(UNL)	PD	+	Dead
2	51	IIIA bulky	379(UNL)	1	0	Low-int	Int	1420(UNL)	PR	-	Alive
3	58	IVA	1523(UNL)	1	>1	High-int	High	6056(UNL)	PD	-	Dead
4	73	IIA	335(UNL)	1	0	Low-int	Int	2197(UNL)	PD	+	Dead

No	Immunohistochemical staining							GC/ nonGC	FISH split		
	CD5	CD10	BCL6	MUM-1	BCL2	MYC	MIB-1		MYC	BCL2	BCL6
1	+	+	-	+	+	+ 80%	+ 90%	GC	+	-	NT
2	-	+ weak	+	+	-	+ 90%	+ 90%	GC	+	-	NT
3	-	-	+	+	+	+ 70%	+ 90%	nonGC	+	-	-
4	-	-	+	+	+	-<5%	+ 90%	nonGC	+	-	+

CS, clinical stage; LDH, lactate dehydrogenase; PS, performance status; IPI, International Prognostic Index; CNS, central nervous system; UNL, upper normal limit; PD, progressive disease; PR, partial response; GC, germinal center; FISH, fluorescence in situ hybridization; NT, not tested.

sufficient CNS prevention may improve the treatment outcome.

CONFLICT OF INTEREST

The authors have no conflicts of interest or funding to disclose.

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