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No potential conflicts of interest relevant to this article were reported.

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Primary CNS lymphoma: latest updates and a 10-year monocenter experience

TO THE EDITOR: We read with great interest the paper by Qian and colleagues, which described advances in the treatment of newly diagnosed primary central nervous system lymphomas (PCNSLs) [1]. The authors showed the increasing PCNSL incidence rate and the possible correlation of this increase with the increasing number of immunosuppressed patients. This appealing issue was confirmed in a recently published paper that reported a current Swedish scenario in which the increasing trend was mostly observed among elderly individuals [2].

Qian and colleagues extensively analyzed the available treatment options, such as high-dose methotrexate (HD-MTX) alone or as a component of various MTX-based chemotherapy regimens, whole-brain radiotherapy (WBRT), and surgery. We agree with the authors that HD-MTX should be included in the first-line therapy; according to our knowledge, however, the best available evidence suggests that HD-MTX should be administered in association with high-dose cytarabine to improve both progression-free survival (PFS) and overall survival (OS), as previously suggested [3].

An important goal of PCNSL treatment is survival prolongation with minimal toxicity, especially neurotoxicity. The first randomization of the phase II IELSG32 (the International Extranodal Lymphoma Study Group-32) trial was designed to determine whether rituximab and thiotepa could improve the efficacy of first-line treatment comprising HD-MTX plus HD-cytarabine (MATRix regimen). The complete response (CR) rate among patients receiving HD-MTX plus HD-cytarabine (control arm, arm A) was 23%, compared to 30% in the arm receiving rituximab (arm B) and 49% in the arm receiving both rituximab and thiotepa (group C); here, a multivariate analysis confirmed an independent association between the induction arm and CR rate [4]. The recently published second randomization was designed to investigate the efficacy of WBRT or autologous stem-cell transplantation (ASCT) as a consolidation therapy after induction for patients with chemosensitive PCNSL. Out of 122 eligible patients, 118 were randomly assigned to receive WBRT (group D) or ASCT (group E); both strategies were effective and yielded significantly improved CR rates after induction, with 2-year PFS rates of 80% and 69%, respectively [5]. As expected, hematological toxicity was more common in ASCT arm, while neuropsychological tests demonstrated cognitive impairments in attention and executive functions among patients receiving WBRT [5].

ASCT was previously shown to be high effective as a consolidation therapy with manageable toxicity in phase II trials of patients with chemosensitive PCNSL patients; consequently, an international phase III study is ongoing and

will randomize patients to receive ASCT or conventional chemoimmunotherapy [6].

Because the outcomes of PCNSL are relatively worse than those of systemic DLBCL, novel agents are under investigation. The Bruton tyrosine kinase inhibitor ibrutinib was recently shown to be highly effective against relapsed/refractory PCNSL in a phase I trial [7]. Additionally, chimeric antigen receptor-modified T-cell therapy exhibited anti-tumor activity against a heavily pre-treated DLBCL with CNS localization [8].

We would also like to address the important topic of the treatment of elderly patients with PCNSL, who account for an important proportion of the total population of patients with PCNSL. The MATRix regimen is not applicable for patients >70 years old; additionally, WBRT is expected to cause significant neurotoxicity, and a recently reported study demonstrated no improvements in survival in the last decades [9]. A recent meta-analysis confirmed that treatment with a combination of HD-MTX and alkylating agents such as procarbazine or temozolomide was associated with improved survival. Although WBRT may also improve survival, it is associated with a significant risk of early or late neurotoxicity; therefore, previous authors suggested avoiding WBRT or using it only as a strategy for relapsed disease [10]. Among elderly patients with PCNSL, promising results and manageable toxicity were reported with HD-MTX when administered in association with rituximab, procarbazine, and lomustine (lomustine was omitted via protocol amendment because of infectious complications); specifically, 38 (35.5%) and 15 of 107 patients (14%) achieved a CR and PR, respectively, while the 2-year PFS and OS were 37.3% and 47%, respectively [11].

At our institution, we have worked for many years in the field of optimal PCNSL management and have retrospectively analyzed a consecutive series of 20 patients diagnosed and treated during the period from 2005 to 2016. Younger and more fit patients received HD-MTX with cytarabine either alone or in combination with rituximab with or without thiotepa (rituximab 375 mg/m^2 days -5 and 0, MTX 3.5 g/m^2 day 1, cytarabine 2 g/m^2×2, days 2–3, thiotepa 30 mg/m^2 day 4; MATRix regimen) every 3 weeks for up to 4 cycles. Elderly and unfit patients received HD-MTX and temozolomide. Induction was followed by WBRT with a minimum dose of 36 Gy or ASCT as consolidation. Responses were assessed after the 2nd and 4th cycles according to the 2005 IPCG Response Criteria [12]; toxicity was defined according to the NCI-CTCAE criteria after each course of treatment. PFS was measured from date of treatment initiation to the date of relapse or progression requiring subsequent treatment, while OS was measured from the date of treatment initiation to the date of death. Statistical

Table 1. Patients' characteristics.

Characteristic	N of Patients (%)
Age:median (range)	61.5 yr (39–76)
Gender	
Men	11/20 (55)
Women	9/20 (45)
ECOG PS	
0–1	7/20 (35)
≥2	13/20 (65)
Elevated LDH	13/20 (65)
Deep lesions	13/20 (65)
IELSG score	
Low	4/20 (20)
Intermediate	14/20 (70)
High	2/20 (10)
Multiple lesions	12/20 (60)
Elevated B2M	10/20 (50)
HBV positive	2/20 (10)

Abbreviations: B2M, beta-2-microglobulin; LDH, lactate dehydrogenase; PS, performance status.

Table 2. Responses to treatment and outcomes.

	N of Patients (%)
Early discontinuation because of PD or toxicity	5/20 (25)
CR after induction	5/15 (33.3)
ORR after induction	10/15 (66.7)
CR after consolidation	9/15 (60)
Consolidation strategy for 10 responders	
WBRT	7/10 (70)
ASCT	3/10 (30)
Relapsed patients	4/10 (40)
Alive patients	6/20 (30)

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete response; ORR, overall response rate; PD, progressive disease; WBRT, whole brain radiotherapy.

Table 3. Treatment toxicity.

	N of Patients (%)
Hematological toxicity	
Neutropenia	20/20 (100)
Grade 3–4	18/20 (90)
Anemia	14/20 (70)
Grade 3–4	7/20 (35)
Thrombocytopenia	20/20 (100)
Grade 3–4	15/20 (75)
Mucositis	8/20 (40)
Grade 3–4	1/20 (5)
Neurotoxicity	5/20 (25)
WBRT	4/5 (80)
Fatal infections	3/20 (15)
Encephalitis	1/20 (5)
Pneumonia	1/20 (5)
Klebsiella KPC	1/20 (5)

Abbreviation: WBRT, whole-brain radiotherapy.

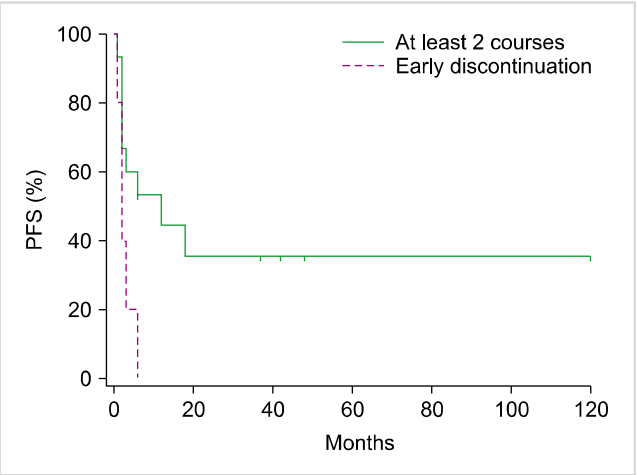

Fig. 1. Progression-free survival (PFS) among primary central nervous system lymphoma (PCNSL) patients receiving ≥2 treatment cycles vs. those who underwent early discontinuation.

analyses were performed using MedCalc software, v2.0 (MedCalc, Ostend, Belgium). Survival was analyzed using the Kaplan-Meier method and the global log-rank test.

The median age was 61.5 years; additionally, 13 of 20 patients (65%) had an Eastern Cooperative Oncology Group Performance score of ≥2 and 4, 14, and 2 patients had low, intermediate, and high International Extranodal Lymphoma Study Group scores, respectively, as shown in Table 1. Five of 20 patients (25%) discontinued treatment early (after 1 cycle) because of disease progression or toxicity and were analyzed separately in survival curves. Fifteen patients received at least 2 courses of treatment; among them, 10 were responders (66.6%) and 5 (33.3%) achieved a CR, as reported in Table 2. Two patients older than 70 years who received HD-MTX and temozolomide experienced progressive disease (PD). Grade 3–4 hematological toxicity was reported in all cytarabine-treated cases, and fatal infections were observed in 3 of 20 patients (15%) as presented in Table 3. All 10 responders received WBRT (7 patients) or ASCT (3 patients) as consolidation; 3 patients receiving WBRT and 1 receiving ASCT exhibited improved responses from PR to CR. Neurotoxicity was reported in 5 patients (4 received WBRT). The median PFS and OS improved among patients receiving at least 2 courses of treatment, compared to the early discontinuation group (12 vs. 2 mo, P=0.03; 10 vs. 4 mo, P=0.01). In the first group, the estimated 5-year PFS (Fig. 1) and OS were 35% and 38%, respectively.

Our study had some limitations, most notably the retrospective study design and small sample size, although these were comparable to previously published experiences [13, 14]. Although our cohort of 20 patients could not adequately represent the general population, our 10-year experience may help to confirm the difficulties experienced in clinical daily practice regarding the adequate treatment for PCNSL because of issues related to age, diagnostic delays, and a poor performance status. In conclusion, the presented data have led us to confirm that the treatment outcomes in real-life practice are somewhat different from those in clinical trials. We suggest that the optimal induction therapy should include HD-MTX, HD-cytarabine, rituximab, and thiotepa in younger and fit patients, while WBRT and ASCT are both effective as consolidation therapies.

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Acetate moderately attenuates the generation of neutrophil extracellular traps

TO THE EDITOR: It has been suggested that short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which are produced by the microbial fermentation of dietary fiber in the gut, exhibit several immunologic or metabolic effects. For example, SCFAs can modulate neutrophil migration [1, 2], induce the differentiation of regulatory T cells [3], and inhibit tumor necrosis factor-α production from macrophages [4, 5].

Recently, Vieira *et al.* [6] reported that treatment with acetate accelerated the resolution of inflammation in experimental mouse models of gout. The effects of acetate were shown to be mediated by accelerated neutrophil apoptosis, enhanced efferocytosis, reduced nuclear factor-κB activity, and an enhanced production of anti-inflammatory mediators including interleukin-10, transforming growth factor-β, and annexin A1.

Neutrophils exert their anti-microbial functions through the formation of neutrophil extracellular traps (NETs), the production of reactive oxygen species, and the secretion of several proteases such as elastase, lactoferrin, and lysozyme. NETs are composed of decondensed chromatin fibers coated with antimicrobial proteins such as myeloperoxidase, neutrophil elastase, and α-defensin [7]. However, NETs contribute to organ damage including acute lung injury, thrombosis formation, autoimmune pathologies, metastasis of malignant tumors, and atherosclerosis [7]. In this study, we investigated the effects of acetate on the formation of NETs.

The following methods were utilized. Heparinized peripheral blood was collected from healthy volunteers after obtaining their written informed consent. Neutrophil separation (>90% purity) was performed as reported previously [8]. This study was approved by the Ethics Committee of Himeji Dokkyo University (12-01, 17-08).

Phorbol myristate acetate (PMA), bovine serum albumin, nuclease from *Staphylococcus aureus*, ethylene glycol tetraacetic acid, diphenylene iodonium (DPI), and acetate were purchased from Sigma-Aldrich (St. Louis, MO, USA). SYTOX

Table 1. Lambda DNA was measured using SYTOX Green.

Acetate	Lambda DNA 0 ng/mL		1 ng/mL		3 ng/mL		5 ng/mL	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 mM	4,278	386	166,649	14,119	403,841	58,468	576,097	42,468
25 mM	4,344	445	164,181	14,809	419,319	51,839	576,772	68,383
50 mM	4,466	547	157,233	10,602	423,093	40,819	579,226	85,789

The linearity was unaffected by the addition of 25 or 50 mM acetate. No statistically significant difference was observed between the data with and without acetate addition (N=6).
Abbreviation: SD, standard deviation.