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LETTER TO THE EDITOR

Reduced bendamustine for elderly patients with follicular lymphoma

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Dear Editor,

As the outcome of follicular lymphoma (FL), the most common subtype of indolent non-Hodgkin's lymphoma, has been improved since the introduction of immunochemotherapy, non-lymphoma-related causes of death, including infections, have become increasingly important [1, 2]. Bendamustine is widely used as one of the key drugs of the standard therapy, and characterized by long-term lymphocytopenia as a frequent adverse event, rendering the patients especially vulnerable to various infections [2, 3]. During a pandemic of COVID-19, the use of bendamustine is not generally recommended due to its highly immunosuppressive property [4, 5]. However, it would be a serious matter that we cannot use one of the most potent therapeutic agents, while the mild epidemic is expected to continue for a long time. To mitigate the immunosuppression, we have reduced the dose of bendamustine to 2/3 for patients > 69 years old when we use obinutuzumab-bendamustine, one of the most potent therapy against both untreated and relapsed FL [2, 6]. In this study, we aimed to clarify the short-term outcome and toxicities of the reduced bendamustine.

We retrospectively analyzed the elecronic records of 18 untreated and 17 relapsed FL patients consecutively started on obinutuzumab-bendamustine at the Department of Hematology & Oncology, the University of Tokyo Hospital from January 2019 to December 2020, with initial lymphocyte counts of more than 500/μL. The baseline characteristics, frequency of adverse effects, and responses are summarized in Table 1. Baseline characteristics were not significantly different between full- and reduced-dose groups except for age. Most patients underwent bendamustine treatment without dose reduction from the original plan. The frequency of grade ≥ 3 non-hematological and grade 4 hematological adverse effects except lymphocytopenia did not differ (Table 1). The reduced-dose group experienced milder lymphocytopenia, as to lowest lymphocyte count (130 ± 70 vs 230 ± 90/μL, $p < 0.001$), while the difference in duration of grade ≥ 3 lymphocytopenia was marginal (median 5.9 vs 2.0 months, $p = 0.183$, Gray's test) (Table 1). Objective response rate and progression-free survival were not different (Table 1). There was no death in both groups (data not shown).

Compared to conventional cytotoxic therapy, little clinical data support the association of dose intensity of bendamustine with the patient outcome as well as toxicities [7–9]. Considering the lack of evidence, treatment decisions whether to use bendamustine and at what dose are difficult since bendamustine is associated with higher mortality in the case of COVID-19, despite its high efficacy [4]. Elderly patients in our cohort showed promising outcomes with a similar rate of toxicities except for lymphocytopenia. Our study had some limitations, in addition to the retrospective nature. A relatively small number of patients with short-term observation periods were included. Our cohorts contain heterogeneous populations including newly diagnosed and relapsed patients, while the profile of response and adverse events was not different (data not shown). However, considering a dearth of evidence regarding optimal dose intensity for different populations, reduced bendamustine can be an attractive option for vulnerable patients, especially under a special condition where immunosuppression should be avoided to the maximum.

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Table 1 Characteristics of the patients

	Full-dose group		Reduce-dose group		
	n = 18		n = 17		p value
Baseline characteristics					
Age (median, range)	61	(37–69)	79	(71–86)	**< 0.001**
Male gender	7	(38.9%)	9	(52.9%)	0.505
Relapsed/refractory (R/R)	9	(50%)	8	(47.1%)	1.000
Median prior regimens of R/R patients	1	(1–4)	1	(1–3)	1.000
Days from diagnosis to treatment (median, range)	92	(8–2475)	61	(30–1966)	0.517
Observation period (days) (median, range)	412	(92–799)	393	(195–731)	0.987
FLIPI					
Low	1	(5.6%)	1	(5.9%)	0.324
Intermediate	6	(33.3%)	2	(11.8%)	
High	11	(55.6%)	14	(82.4%)	
FLIPI2					
Intermediate	8	(44.4%)	5	(29.4%)	0.489
High	10	(55.6%)	12	(70.6%)	
Treatment and adverse effects					
Treatment cycles (mean, S.D.)	5.00	(1.71)	5.18	1.85	0.771
Intervals between cycles (days) (mean, S.D.)	31.91	3.79	31.29	2.73	0.600
Relative dose intensity of bendamustine (mean, S.D.)	0.87	(0.13)	0.60	(0.07)	**< 0.001**
Lowest lymphocyte count (/μL) (mean, S.D.)	130	(90)	230	(70)	**0.001**
Day to lymphocyte recovery to 500 /μL (median, range)	180	(14–424)	62	(0–503)	0.183
Grade 4 lymphocytopenia	12	(66.7%)	1	(5.9%)	**< 0.001**
Grade 4 neutropenia	3	(16.7%)	2	(11.8%)	1.000
Grade 4 thrombocytopenia	0	(0%)	1	(5.9%)	0.486
Grade ≥ 3 non-hematological AEs	4	(22.2%)	3	(17.6%)	1.000
Grade ≥ 3 infections	1	(5.6%)	1	(5.9%)	1.000
Response					
CT					
CR	5	(31.2%)	5	(31.2%)	1.000
PR	10	(62.5%)	9	(56.2%)	
SD	0	(0%)	1	(6.2%)	
PD	1	(6.2%)	1	(6.2%)	
FDG-PET					
CMR	10	(90.9%)	8	(70.6%)	0.724
PMR	0	(0%)	1	(9.1%)	
SMR	0	(0%)	1	(9.1%)	
PMR	1	(9.1%)	1	(9.1%)	
1-year progression-free survival rate (95% CI)	0.929	0.591–0.990	0.878	0.595–0.968	0.685

Factors with *p*-value < 0.05 are indicated in bold

Declarations

Ethical approval All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest Yosuke Masamoto received lecture fees from SymBio Pharmaceutical, Nippon Shinyaku, Eisai, and Chugai Pharmaceutical. Mineo Kurokawa received research funding from Chugai Pharmaceutical, Eisai, and Nippon Shinyaku. Mineo Kurokawa received the advisory fee from Chugai Pharmaceutica. Mineo Kurokawa received the lecture fee from Eisai, Chugai Pharmaceutical, and Nippon Shinyaku.

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