LETTER TO THE EDITOR

Clinical impact of bendamustine exposure on lymphopenia risk after bendamustine and rituximab combination therapy for follicular lymphoma: a single-institute retrospective study

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Dear Editor:

Bendamustine produces long-lasting objective responses in patients with indolent non-Hodgkin lymphoma, including follicular lymphoma (FL) [1]. However, lymphopenia, especially a reduced number of CD4-positive T cells, was reported to potentially lead to lethal infections after bendamustine therapy [2]. Employing bendamustine at cumulative doses ≥ 1080 mg/m^2 might induce delayed CD4-positive T cell recovery [3]. We investigated the effects of bendamustine exposure at cumulative doses < 1080 versus 1080 mg/m^2 on the reduction of CD4-positive T cell counts following bendamustine therapy in patients with FL. This was a retrospective analysis of data from 59 patients with FL who received bendamustine therapy from January 2011 to December 2018 in our institution. The study protocol was approved by the Kyushu Medical Center review board. According to the total dose and number of treatment cycles of bendamustine, we divided the patients into three groups: < 1080 mg/m^2 bendamustine for 4 cycles (group 1, $n = 29$), < 1080 mg/m^2 bendamustine for 6 cycles (group 2, $n = 8$), and 1080 mg/m^2 bendamustine for 6 cycles (group 3, $n = 22$). As presented in Table 1, the mean age was higher in group 2 ($p = 0.043$), and the number of prior chemotherapy regimens was higher in group 1 ($p = 0.039$). Although the number of patients with CD4-positive T cell counts $< 200/\mu l$ at baseline tended to be lowest in group 2 ($p = $ 0.067), which was associated with age < 70 years (vs. ≥ 70; odds ratio [OR] = 8.520, 95% confidence interval [CI] = 2.030–35.80, $p = 0.034$) and 0–1 prior chemotherapy regimens (vs. > 1; OR = 5.160, 95% CI = 1.320–20.10, $p = 0.018$) using multivariate logistic regression analysis, the number of patients with CD4-positive T cell counts $< 200/\mu l$ after 3 months of bendamustine treatment also tended to be lowest in group 2, and this finding was not associated with any patient characteristics (Table 1). Coronavirus disease 2019 (COVID-19) raises specific concerns in terms of morbidity and mortality for patients with FL because of their immunocompromised status induced by the disease or recent exposure to cytotoxic chemotherapy, especially bendamustine and anti-CD20 immunotherapy. Bendamustine appeared to be associated with death, but most patients treated with bendamustine had relapsed/refractory lymphoma [4]. Anti-CD20 treatment within 1 year was not associated with death. Further studies are merited to explore the impact of bendamustine on the evolution of COVID-19. Because the standard dose of bendamustine therapy may be associated with a high mortality risk, our data suggest that for elderly patients receiving bendamustine-based therapy, a reduced initial bendamustine dose (70 mg/m^2) such as that used in the GREEN study for unfit patients with chronic lymphocytic leukemia at the investigator's discretion [5], opposed reduced numbers of chemoimmunotherapy cycles, might explain the decreased risk of serious infections in this population. This study had several limitations, including its single-institute nature and small sample size. Further evaluations for FL are warranted to identify the best dose of bendamustine, notably a reduced initial bendamustine dose, and suitable patients to define the best-tailored treatment at diagnosis.

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Table 1 Characteristics, outcomes, WBC counts, lymphocyte counts, and immune status in patients with follicular lymphoma treated with bendamustine

Characteristics	Bendamustine exposure			P
	< 1080 mg/m^2		1080 mg/m^2	
	Cycle			
	4 ($n = 29$)	6 ($n = 8$)	6 ($n = 22$)	
Age, median (range) years	68 (53–88)	81 (59–84)	67 (51–81)	0.039
> 70 years old, n (%)	13 (45)	7 (88)	10 (45)	0.100
Sex, n (%)				
Male	12 (41)	2 (25)	9 (41)	0.688
Female	17 (59)	6 (75)	13 (59)	
Number of prior chemotherapy regimens, median (range)	2 (1–4)	1 (0–3)	1 (0–3)	0.043
> 1 regimen, n (%)	16 (55)	1 (13)	7 (32)	0.053
Total bendamustine exposure, median (range) (mg/m^2)	720 (480–960)	780 (720–900)	1080	
Rituximab, n (%)	23 (79)	6 (75)	19 (86)	0.724
Rituximab maintenance, n (%)	2 (7)	2 (25)	3 (14)	0.273
Median (range) follow-up (month)	105 (96–114)	96 (46–104)	42 (19–66)	< 0.001
Baseline				
WBC (/µl), median (range)	4600 (1900–8100)	5550 (3000–8600)	4650 (2700–8800)	0.738
Lymphocyte (/µl), median (range)	1050 (387–2436)	1353 (792–3440)	1071 (429–2964)	0.522
CD4-positive T cell (/µl), median (range)	255 (76–730)	436 (189–1032)	304 (94–1188)	0.051
CD4-positive T cell < 200/µl, n (%)	13 (44)	1 (12)	4 (18)	0.067
IgG (mg/dl), median (range)	933 (167–1626)	1126 (700–1780)	862 (433–1436)	0.126
After 3 months of bendamustine exposure				
WBC (/µl), median (range)	3210 (1300–7500)	4400 (2400–5600)	3250 (1700–7700)	0.424
Lymphocyte (/µl), median (range)	558 (100–2829)	1131 (295–3080)	598 (177–2000)	0.133
CD4-positive T cell (/µl), median (range)	73 (10–282)	126 (29–1170)	59 (18–360)	0.227
CD4-positive T cell < 200/µl, n (%)	27 (93)	5 (62)	20 (90)	0.081
IgG (mg/dl), median (range)	717 (128–1729)	850 (575–1390)	755 (263–1846)	0.424
After 1 year of bendamustine exposure				
WBC (/µl), median (range)	3800 (2400–7300)	4150 (2400–5900)	3400 (1900–7100)	0.657
Lymphocyte (/µl), median (range)	975 (96–1776)	1022 (465–1813)	860 (240–1846)	0.585
CD4-positive T cell (/µl), median (range)	180 (23–532)	238 (79–715)	186 (28–577)	0.425
CD4-positive T cell < 200/µl, n (%)	17 (58)	3 (37)	12 (54)	0.631
IgG (mg/dl), median (range)	715 (143–1630)	850 (500–1552)	810 (250–1380)	0.924

WBC, white blood cell; *CD*, cluster of differentiation; *IgG*, immunoglobulin G

Continuous variables were expressed as the median and range, and differences between groups were assessed using the Mann-Whitney U test. Intergroup differences in categorical variables were expressed as numbers and percentages, and differences between groups were assessed using the chi-squared test

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W, Study group indolent Lymphomas (StiL) (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority t0rial. Lancet 381:1203–1210

2. Gafter-Gvili A, Polliack A (2016) Bendamustine associated immune suppression and infections during therapy of hematological malignancies. Leuk Lymphoma 57:512–519

3. Martínez-Calle N, Hartley S, Ahearne M, Kasenda B, Beech A, Knight H, Balotis C, Kennedy B, Wagner S, Dyer MJS, Smith D, McMillan AK, Miall F, Bishton M, Fox CP (2019) Kinetics of T-cell subset reconstitution following treatment with bendamustine and rituximab for low-grade lymphoproliferative disease: a population-based analysis. Br J Haematol 184:957–968

4. Lamure S, Duléry R, Di Blasi R, Chauchet A, Laureana C, Deau-Fischer B, Drenou B, Soussain C, Rossi C, Noël N, Choquet S, Bologna S, Joly B, Kohn M, Malak S, Fouquet G, Daguindau E, Bernard S, Thiéblemont C, Cartron G, Lacombe K, Besson C (2020) Determinants of outcome in Covid-19 hospitalized patients with lymphoma: a retrospective multicentric cohort study. EclinicalMedicine 27:100549

5. Stilgenbauer S, Leblond V, Foà R, Böttcher S, Ilhan O, Knauf W, Mikuskova E, Renner C, Tausch E, Woszczyk D, Gresko E, Lundberg L, Moore T, Morris T, Robson S, Bosch F (2018) Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Leukemia 32:1778–1786