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LETTER TO THE EDITOR

Impact of hematopoietic stem cell transplantation in patients with relapsed or refractory marginal zone lymphoma

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Dear Editor,

Marginal zone lymphoma (MZL) is an indolent lymphoma, which includes extra-nodal MZL of mucosa-associated lymphoid lymphoma (MALToma), nodal MZL (NMZL), and splenic MZL (SMZL) [1, 2]. There are currently several treatment options for patients with relapsed or refractory (R/R) MZL, including high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) [3]. Allogeneic HCT is considered to be an optional therapy for R/R MZL patients, but there is no specific data to support allogeneic HCT for R/R MZL. We retrospectively analyzed the outcomes among R/R MZL patients treated with autologous or allogeneic HCT to identify the potential clinical efficacy of allogeneic HCT. Patient information was derived from the Transplant Registry Unified Management Program database [4, 5], collected by the Japanese Data Center for Hematopoietic Cell Transplantation, and sponsored by the Japanese Society for Hematopoietic Cell Transplantation (JSHCT). This study was approved by the data management committee at the JSHCT and the Institutional Review Board of Kyushu Medical Center.

Patient- and disease-related variables in the R/R MZL patients are shown in Table 1. Seventy patients with R/R MZL (25 MALToma, 31 NMZL, and 14 SMZL) were divided into two groups receiving either autologous HCT ($n = 56$, 19 MALToma, 27 NMZL, and 10 SMZL) or allogeneic HCT ($n = 14$, 6 MALToma, 4 NMZL, and 4 SMZL). The median follow-up times for survivors in patients with MALToma, NMZL, and SMZL receiving autologous and allogeneic HCT were 63, 56, and 59 months and 53, 61, and unevaluable months, respectively. No patients with MALToma died because of non-relapse mortality (NRM) following autologous HCT and no patients developed relapse with MALToma and NMZL at allogeneic HCT. Ten patients who received autologous HCT died of MZL lymphoma (five MALToma, two NMZL, and two SMZL). For allogeneic HCT, three SMZL patients died of lymphoma. This suggested that autologous HCT was safe for MALToma patients, and that allogeneic

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Table 1 Characteristics of patients with refractory or relapsed marginal zone lymphoma receiving autologous or allogeneic hematopoietic cell transplantation

Characteristics		MALToma			NMZL			SMZL		
		Autologous HCT $n = 19$	Allogeneic HCT $n = 6$	P	Autologous HCT $n = 27$	Allogeneic HCT $n = 4$	P	Autologous HCT $n = 10$	Allogeneic HCT $n = 4$	P
Median age (range) at HCT, years		54 (39–69)	53 (16–57)	0.424[c]	58 (36–67)	45 (37–47)	0.051[c]	54 (39–66)	58 (54–64)	0.310[c]
>60 years of age at HCT, *n* (%)		3 (16)	0	0.303[a]	11 (40)	0	0.112[a]	4 (40)	2 (50)	0.742[a]
Median age (range) at diagnosis, years		53 (36–68)	45 (16–51)	0.103[c]	55 (27–66)	37 (31–43)	*0.019*[c]	51 (37–66)	55 (47–63)	0.776[c]
Sex, *n* (%)	Male	8 (42)	1 (17)	0.364[b]	14 (52)	3 (75)	0.385[b]	7 (70)	3 (75)	0.852[b]
	Female	11 (58)	5 (83)		13 (48)	1 (25)		3 (30)	1 (25)	
ECOG PS at HCT, *n* (%)	0	11 (58)	5 (83)	*0.046*[a]	18 (67)	2 (50)	0.565[a]	6 (60)	2 (50)	0.441[a]
	1	8 (42)	0		7 (26)	2 (50)		4 (40)	1 (25)	
	0	0	1 (17)		2 (7)	0		0	1 (25)	
ECOG PS at diagnosis, *n* (%)	0	12 (63)	4 (67)	0.848[a]	16 (59)	2 (50)	0.855[a]	3 (30)	4 (100)	0.105[a]
	1	6 (32)	2 (33)		7 (26)	2 (50)		3 (30)	0	
	≥2	1 (5)	0		4 (15)	0		4 (40)	0	
Ann Arbor stage at diagnosis, *n* (%)	1	2 (11)	2 (33)	0.405[a]	2 (7)	0	0.250[a]	0	0	0.341[a]
	2	5 (26)	2 (33)		3 (11)	2 (50)		0	1 (25)	
	3	4 (21)	0		8 (30)	1 (25)		2 (20)	0	
	4	8 (42)	2 (33)		14 (52)	1 (25)		8 (80)	3 (75)	
IPI at diagnosis, *n* (%)	Low	10 (53)	6 (100)	0.109[a]	9 (33)	2 (50)	0.757[a]	4 (40)	2 (50)	0.913[a]
	Low-intermediate	7 (37)	0		12 (44)	2 (50)		1 (10)	0	
	High-intermediate	2 (11)	0		5 (19)	0		2 (20)	1 (25)	
	High	0	0		1 (4)	0		3 (30)	1 (25)	
No. of nodes at diagnosis, *n* (%)	0	4 (21)	3 (50)	0.303[a]	13 (48)	3 (75)	0.794 [a]	4 (40)	1 (25)	0.733[a]
	1	8 (42)	3 (50)		6 (22)	1 (25)		1 (10)	1 (25)	
	≥2	7 (37)	0		8 (30)	0		5 (50)	2 (50)	
B symptoms at diagnosis, *n* (%)		1 (5)	0	0.566[a]	4 (15)	0	0.409[a]	5 (50)	1 (25)	0.580[a]
LDH elevation at diagnosis, *n* (%)		5 (26)	0	0.160[a]	8 (30)	1 (25)	0.849[a]	5 (50)	2 (50)	0.999[a]
HBV infection, *n* (%)		1 (5)	0	0.566[a]	2 (7)	1 (25)	0.349[a]	2 (20)	2 (50)	0.520[a]
HCV infection, *n* (%)		0	0	–	2 (7)	0	0.574[a]	0	0	–
No. of regimens before HCT, median (range)		2 (1–10)	3 (1–17)	0.323[c]	3 (1–13)	4 (2–7)	0.366[c]	2 (1–3)	4 (3–5)	*0.0038*[c]
Median time (range) from diagnosis to HCT, M		26 (4–148)	*75 (15–104)*	*0.025*[c]	28 (5–121)	93 (10–131)	0.140[c]	22 (2–105)	42 (4–86)	0.396[c]
Disease status at HCT, *n* (%)	CR	14 (74)	1 (17)	*0.033*[a]	17 (63)	0	*0.032*[a]	5 (50)	1 (25)	0.255[a]
	PR	1 (5)	2 (33)		5 (19)	2 (50)		4 (40)	1 (25)	
	PIF	0	0		2 (7)	2 (50)		1 (10)	1 (25)	
	Relapse	4 (21)	*3 (50)*		3 (11)	0		0	1 (25)	
Year at HCT, *n* (%)	2002–2006	6 (32)	0	0.170[a]	10 (37)	2 (50)	0.214[a]	2 (20)	1 (25)	0.153[a]
	2007–2011	8 (42)	1 (17)		8 (15)	1 (25)		5 (50)	2 (50)	
	2012–2016	5 (26)	5 (83)		9 (33)	1 (25)		3 (30)	1 (25)	
HCT-CI at HCT, *n* (%)	0	19 (100)	2 (33)	*0.001*[a]	24 (89)	3 (75)	0.446[a]	0	1 (25)	*0.011*[a]
	1	0	3 (50)		3 (11)	1 (25)		10 (100)	3 (75)	
	2	0	1 (17)		0	0		0	0	
Median (range) follow-up of survivors, months		63 (12–134)	53 (31–93)	0.500	56 (36–136)	61 (65–150)	0.379	59 (52–138)	–	–

Variables in the two groups were compared using [a] Pearson's χ^2 test, [b] Fisher's exact test, or the [c] Mann–Whitney *U* test. All effects were statistically significant at the 0.05 significance level (p value were italized)

MALToma mucosa-associated lymphoid tissue lymphoma; *NMZL*, nodal marginal zone lymphoma, *SMZL* splenic marginal zone lymphoma, *HCT* hematopoietic cell transplantation, *N* total number of patients assessed, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *IPI* international prognostic index, *LDH* lactate dehydrogenase, *HBV* hepatitis B virus, *HCV* hepatitis C virus; *M* month, *CR* complete remission, *PR* partial remission, *PIF* primary induction failure, *HCT-CI* HCT-specific comorbidity index

HCT might be suitable for patients with MALToma and NMZL to cure R/R MZL.

The main findings of this study indicated that both autologous and allogeneic HCT may be acceptable for patients with chemo-sensitive MALToma and NMZL, but the results of allogeneic HCT for chemo-resistant MALToma (data not shown) and SMZL were disappointing, probably reflecting the low chance of being salvaged by allogeneic HCT. Secondary primary malignancy (SPM) was observed in two NMZL patients after autologous HCT, but not after allogeneic HCT. The choice between autologous and allogeneic HCT remains controversial because of the risk of NRM and SPM.

In conclusion, the parameters for choosing between autologous and allogeneic HCT for R/R MZL have not been defined, and strategies aimed at improving the selection of R/R MZL patients for autologous HCT and excluding R/R chemo-resistant MALToma patients may allow us to identify individual R/R MZL patients who are at high risk of death after both autologous and allogeneic HCT. Selecting suitable R/R SMZL patients for allogeneic HCT might reduce NRM. The introduction of novel therapies [6, 7] before and after receiving allogeneic HCT could improve outcomes among R/R SMZL patients.

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Compliance with ethical standards

This study was approved by the data management committee at the JSHCT and the Institutional Review Board of Kyushu Medical Center. All procedures performed in studies involving human participants were in accordance with 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 The authors declare that they have no conflict of interest.

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