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Rituximab Maintenance Therapy and Bendamustine Containing Treatments may improve the Survival of Mantle Cell Lymphoma: Retrospective Analysis in Single Institute

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Abstract

Introduction: The prognosis for mantle cell lymphoma (MCL) has remained poor despite the current use of autologous transplantation and induction chemotherapy that includes high-dose cytarabine. The introduction of rituximab and bendamustine, however, has led to the improvement of prognosis of diffuse large B-Cell lymphoma and indolent lymphoma. For these reasons, we analyzed the effectivity of rituximab maintenance therapy and bendamustine against mantle cell lymphoma at our hospital.

Methods: We selected 22 cases of MCL for which treatment was initiated between January 2004 and December 2016 at our hospital. We compared the cases based on the use of rituximab maintenance therapy or bendamustine, simplified Mantle Cell Lymphoma International Prognostic Index (sMIPI), staging, and treatment regimens to analyze the effect of rituximab maintenance therapy and bendamustine on prognosis.

Results: Overall five-year survival rate was 67%. Significant difference (P=0.0432) was observed in the 5-year survival rate between the group treated with rituximab maintenance therapy (90.9%) and the group that was not (56.2%). Likewise, significant difference (P=0.0197) was observed in the 5-year survival rate between the group that received bendamustine during the course of treatment (90.9%) and the group that did not (50%). Majority of the cases in the group that received bendamustine, however, had been treated with rituximab maintenance therapy.

Conclusion: Our study showed an improvement in prognosis of MCL due to the treatment with rituximab maintenance therapy and bendamustine. Although the analysis was conducted on a limited number of cases, we believe that rituximab maintenance therapy and treatments that include bendamustine are promising therapies for MCL.

Keywords: Lymphoma; Mantle cell lymphoma; Rituximab; Bendamustine

Introduction

Mantle cell lymphoma (MCL) accounts for approximately 3% of all lymphomas in Japan [1], and 4-9% in Europe and America [2]. Often, aggressive clinical treatment is resorted to, and even if patients respond to initial treatment, the period until relapse is short, with poor prognosis after relapse. Improvement of prognosis has been reported after induction therapy that includes high-dose cytarabine and consolidation therapy by autologous transplantation [3-5]. On the other hand, a study showed that prognosis may not improve despite intensification of treatment [6], indicating that consensus on the matter has not been reached. Recently, studies have shown that rituximab maintenance therapy [7] and chemotherapy that includes bendamustine [8] may improve prognosis among transplant-ineligible MCL patients. We therefore conducted a single-institutional retrospective analysis on MCL treatment outcomes to determine the effect of rituximab maintenance therapy and chemotherapy that includes bendamustine on prognosis of MCL.

Methods

Patients

We selected 22 cases diagnosed with mantle cell lymphoma based on diagnostic pathology and had received initial treatment at Hakodate Municipal Hospital from January 2004 to December 2016. Cases that received initial treatment at other hospitals included those that were not diagnosed at our pathology department, hence, were excluded from this study. A retrospective analysis was conducted on the clinical data, which included whether or not the patients were treated with rituximab maintenance therapy or bendamustine, patient's age at diagnosis, gender, ECOG Performance Status (PS), stage at diagnosis, and simplified MIPI [9].

Study endpoint and statistical analysis

Overall survival (OS), which is the primary endpoint, was defined as the period from start of treatment to death or final day of follow-up, which was discontinued after five years.

Survival curve was determined using Kaplan-Meier method, and comparison between the two groups was performed using log-rank method. In the comparison of the case parameters, Fisher's exact test was used for class variables, and Mann-Whitney U test was used for continuous variables. P-values of <0.05 were considered significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user

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interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics

Median age at diagnosis was 66 (45 to 82 years old), with 68% male patients. Ninety-five percent of the cases were classified as Ann Arbor Stage III or higher, of which 41% were found to have the B-type symptoms. There were no cases with performance status (PS) of 3 or higher, and with respect to sMIPI, 27% of the cases were low risk, 55% were intermediate risk, and 18% were high risk (Table 1).

Treatment characteristics

Chemotherapies used for the cases in this report are listed in Table 2. Fifteen cases were treated with R-CHOP (rituximab, cyclophosphamide, vincristine, predonine) [10] /R-THP-COP (rituximab, pirarubicin, adriamycin, vincristine, predonine) [11], two cases had BR (bendamustine and rituximab) [8], one case had R-MCD (rituximab, cladribine, mitoxantrone, dexamethasone) regimen [12], while the rest had single-drug chemotherapy of cyclophosphamide (3 cases), and rituximab (1 case). Second-line therapies performed for refractory or relapsed cases were R-CHOP/R-THP-COP for 4 cases, BR for 7 cases, R-MCD for 3 cases, R-ESHAP (rituximab, etoposide, high-dose cytarabine, cisplatin) [13] for 1 case, R-Hyper CVAD/MA (rituximab, cyclophosphamide, vincristine, adriamycin, dexamethasone/high-dose cytarabine, methotrexate) [14] for 1 case, and CHASER (rituximab, cyclophosphamide, high-dose cytarabine, etoposide, dexamethasone) regimen [15] for 1 case. Third-line therapy was performed for 10 cases, and fourth-line therapy for 5 cases. Autologous transplantation was performed for 2 cases, and allogeneic transplantation for 1 case.

n=22		
Age at diagnosis	Median age (range)	66years old (45-82)
	age>65years old (%)	12 (55%)
	Age ≦ 65years old (%)	10 (45%)
Sex, n (%)	male	15 (68%)
	female	7 (32%)
PS	0	18 (82%)
	1	2 (9%)
	2	2 (9%)
Stage, n (%)	Ⅰ	1 (4.5%)
	Ⅱ	0 (0%)
	Ⅲ	1 (4.5%)
	Ⅳ	20 (91%)
B symptoms, n (%)	A	13 (59%)
	B	9 (41%)
simplified MIPI, n (%)	low	6 (27%)
	intermediate	12 (55%)
	high	4 (18%)
Patients who received radiotherapy, n (%)		6 (27%)
Patients who received AutoHSCT, n (%)		2 (9%)
Patients who received AlloHSCT, n (%)		1 (4.5%)

Abbreviations: PS: Performance Status; simplified MIPI: Simplified Mantle Cell Lymphoma International Prognositic Index; AutoHSCT: Autologpus Hematopoietic Stem Cell Transplantation; AlloHSCT: Allogenic Hematopoietic Stem Cell Transplantation

Table 1: Clinical characteristics of the whole patients.

Treatments	**n (%)**	**1st line**	**2nd line**	**3rd line**	**4th line**
		n=22	**n=19**	**n=10**	**n=5**
R-CHOP/R-THP-COP	17 (77)	15 (68)	4 (21)		
EPOCH-R	1 (5)				2 40)
BR	13 (59)	2 (9)	7 (37)	3 (30)	2 (40)
R-MCD	5 (23)	1 (4.5)	3 (16)	1 (10)	
R-FCM	1 (5)		1 (5)		
Etoposide	1 (5)			1 (10)	
Cyclophosphamide	3 (14)	3 (14)		1 (10)	
GV	1 (5)			1 (10)	
Rituximab	2 (9)	1 (4.5)			1 (20)
HD-AraC	3 (14)		3 (16)	1 (10)	
R-MEAM→autoASCT	2 (9)			2 (20)	
BU+CLD+TBI→alloHSCT			1 (5)		

Abbreviations: R-CHOP: Rituximab Cyclophosphamide Vincristine Doxorubicine Prednisolone;

R-THP-COP: Rituximab Cyclophosphamide Vincristine Pirarubicin Prednisolone; EPOCH-R: Rituximab Cyclophosphamide Vincristine Doxorubicine Prednisolone Etoposide; BR: Rituximab Bendamustine; RMCD: Rituximab Cladribine Mitixantrone Dexamethasone; R-FCM: Rituximab Fludarabine Cyclophosphamide Mitoxantrone; GV: Gemsitabine Navelbine; HD-AraC: R-ESHAP, HyperCVAD/MA,CHASER; R-ESHAP: Etoposide Methylprednisolone Cytarabine Ciaplatin Rituximab; HyperCVAD/MA: Rituximab, Cyclophosphamide, Vincristine, Doxorubicine, Dexamethasone/Methotrexate,Cytarabine; CHASER: Rituximab Cyclophosphamide Cytrabine Etoposide Dexamethasone; R-MEAM: Rituximab, Ranimustine, Cytarabine, Etoposide, Melphalan; BU+CLD+TBI: Buslfan+Cladribine+Total Body irradiation

Table 2: Treatments received in the analysis.

Among the 19 cases that had complete or partial remission in the prior treatment, 11 cases were treated with rituximab maintenance therapy, which was carried out by administering rituximab 375 mg/m^2 every 8 to 12 weeks until relapse, until continuation of treatment was possible, or for a total of 12 courses.

Overall survival for all patients

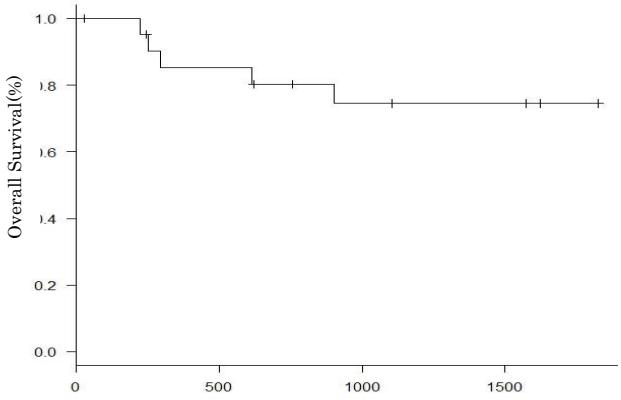
Figure 1 shows the overall survival (OS) for all patients. Seventy-two percent had 3-year survival rate and 67% had 5-year survival rate. The median value of survival period was not reached during the follow-up period.

OS for rituximab maintenance therapy

Rituximab maintenance therapy was carried out for 11 cases. Compared to the other 11 other cases, there were no significant differences between the two groups with respect to gender, age at diagnosis, stage, sMIPI, or whether or not they were treated with bendamustine (Table 3). Five-year survival rate for the group treated with rituximab maintenance therapy (90%) was significantly higher than that of the group that was not (56.2%) (P=0.0432). Both of the groups did not reach median survival within the follow-up period (Figure 2).

OS for bendamustine

Prognosis of the 13 cases that used bendamustine during the treatment process was compared with the other 9 cases that did not. The two groups were compared based on gender, age at diagnosis, stage, sMIPI, and whether or not they were treated with rituximab maintenance therapy. Results showed that many of the cases treated with bendamustine had high sMIPI (P=0.048) (Table 4). Five-year survival rate for the group treated with bendamustine (90.9%) was significantly higher than that of the other group (50%) (P=0.0197). Also, while the bendamustine-treated group did not reach median survival



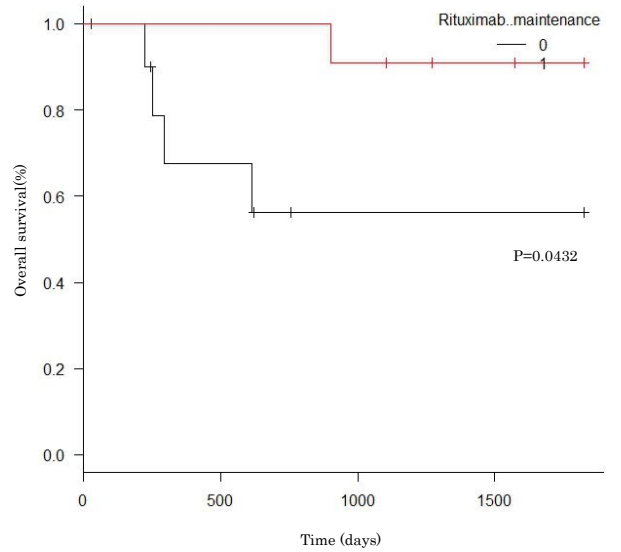
The median of survival was not reached during the follow up period.

Figure 1: Overall Survival (OS) of the all patients.

Rituximab maintenance	Received	Not received	p value
n (%)	11 (50%)	11 (50%)	
Sex (male/female)	05-Jun	10-Jan	0.063
Median age, years (range)	70 (58-78)	60 (45-81)	0.122
Stage, n (%)			1
Ⅰ	0	1(9%)	
Ⅱ	0	0	
Ⅲ	1(9%)	0	
Ⅳ	10 (91%)	10 (91%)	
sMIPI, n (%)		3 (27%)	1
low	3 (27%)	6 (54%)	
intermediate	6 (54%)	2 (19%)	
high	2 (19%)		
Number of patients who received Bendamustine	9 (81.8%)	5 (36.4%)	0.18

Abbreviations: sMIPI: Simplified Mantle Cell Lymphoma International Prognositic Index.

Table 3: Patients characteristics with or without rituximab maintenance therapy.



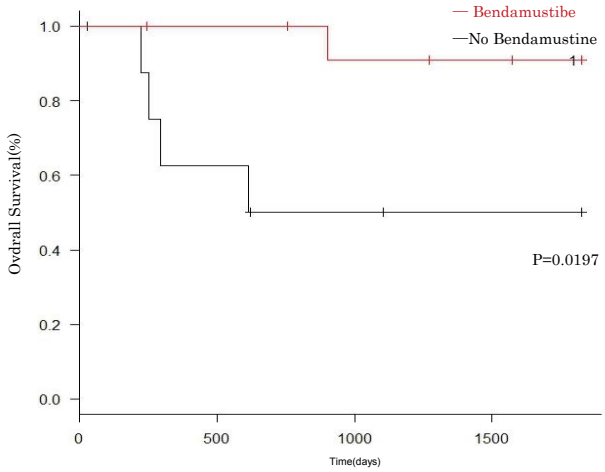
Five-year survival rate for the group treated with rituximab maintenance therapy (90%) was significantly higher than that of the group that was not (56.2%) (P=0.0432).

Figure 2: Overall survival with or without rituximab maintenance therapy.

within the follow-up period, the group not treated with bendamustine had median survival period of 614 days (Figures 3 and 4).

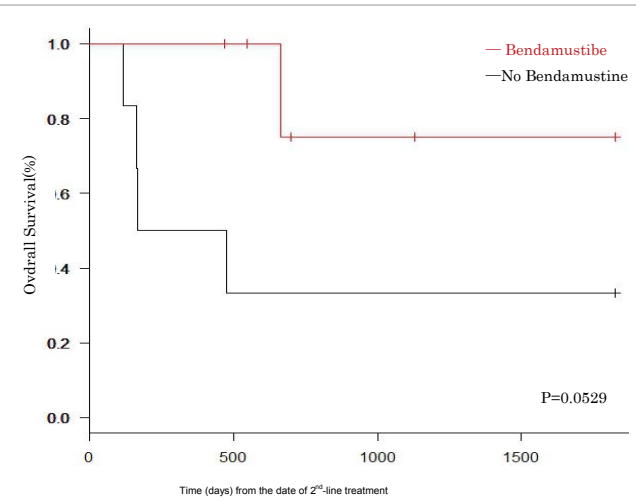
Impact of bendamustine as second-line therapy

To determine the effectiveness of bendamustine for refractory or relapsed cases, we compared the survival period from the start of second-line therapy for the 7 cases that used bendamustine as second-line therapy with the 6 cases that had 2 or more treatment regimens from among the 9 cases that did not use bendamustine. The two groups had no significant differences in terms of gender, age at diagnosis, stage, and sMIPI. Many of the cases treated with bendamustine were also treated with rituximab maintenance therapy (P=0.029). Further, for second-line therapy cases, 100% of the bendamustine-treated group went into either partial remission (PR, 29%) or complete remission (CR, 71%), while only 50% (PR, 50%) went into remission for the group not treated with bendamustine (P=0.038). Five-year survival rate



Five-year survival rate for the group treated with bendamustine (90.9%) was significantly higher than that of the other group (50%) (P=0.0197).

Figure 3: Overall survival with or without treatments including bendamustine.



Five-year survival rate from the start of second-line therapy was 75% for the bendamustine-treated group and 33.4% for the other group; but the difference was not significant (P=0.0529).

Figure 4: Overall survival of patients who received with or without bendamustine as the 2nd-line treatments.

Bendamustine	Received	Not Received	p value
n (%)	13 (59)	9 (41)	
Sex (male/female)	08-May	07-Feb	0.648
Median age, years (range)	66 (56-81)	67 (45-78)	0.592
Stage, n (%)			0.662
Ⅰ	0	1 (11%)	
Ⅱ	0	0	
Ⅲ	1 (8%)	0	
Ⅳ	12 (92%)	8 (89%)	
sMIPI, n (%)			0.048
low	6 (46%)	0 (0%)	
intermediate	6 (46%)	6 (67%)	
high	1 (8%)	3 (33%)	
Number of patients who received Rituximab maintenance	9 (69.2%)	2 (22.2%)	0.08

Abbreviations: sMIPI: Simplified Mantle Cell Lymphoma International Prognositic Index.

Table 4: Patients characteristics with or without bendamustine.

Bendamustine	Used in the 2nd-line chemotherapy	Not received	p value
N	7	6	
Sex (male/female)	04-Mar	6/0	0.192
Median age, years (range)	67 (45-75)	63 (56-81)	0.774
Stage, n (%)			NA
Ⅰ	0	0	
Ⅱ	0	0	
Ⅲ	0	0	
Ⅳ	7 (100%)	6 (100%)	
sMIPI, n (%)			0.217
low	2 (29%)	0	
intermediate	5 (71%)	4 (67%)	
high	0	2 (33%)	
Number of patients who received Rituximab maintenance	6 (85.7%)	1 (16.7%)	0.029

Abbreviations: sMIPI: Simplified Mantle Cell Lymphoma International Prognositic Index.

Table 5a: Patients characteristics in 2nd-line treatments including or not including bendamutstine.

2nd-line treatment	Including bendamustine	Not including bendamustine	p value
Clinical Response	5 (71%)	0	0.038
CRu	2 (29%)	3 (50%)	
PR	0	1 (17%)	
SD	0	2 (33%)	
PD			

Abbreviations: CRu: Complete Remission undetermined; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease.

Table 5b: Clinical response of 2nd-line treatment.

from the start of second-line therapy was 75% for the bendamustine-treated group and 33.4% for the other group; but the difference was not significant (P=0.0529). While the bendamustine-treated group did not reach median survival during the follow-up period, the group not treated with bendamustine had median survival of 319 days.

Discussion

Prognosis of mantle cell lymphoma has remained poor despite current methods of treatment, which include induction chemotherapy, autologous transplantation, and maintenance therapy. Good prognosis was reported to result from intensified treatment by adding high-dose cytarabine, etc. in addition to the conventional therapies [16]. Martin et al., however, reported in a retrospective study that prognosis was not different between R-CHOP and intensification therapies such as R-HyperCVAD, against MCL [16]. Also, there have been reports of improvement in prognosis MCL from autologous transplantation. The European MCL Network Younger Trial, however, showed that minimal residual disease (MRD) negativity, which was 37% before autologous transplantation, increased to 60% after transplantation [4], but even after the autologous stem cell transplantation, the survival curve did not reach plateau [5], pointing to the difficulty of preventing relapse [16].

Meanwhile in the SWOG Study S1106, no difference in response was found between R-HyperCVAD and BR regimens [17]. Likewise Rummel et al. also reported no difference in outcomes between BR and R-CVP/R-CHOP regimens against MCL, including indolent lymphomas [18,19]. Likewise in our department, as shown in this study, albeit retrospective, the use of bendamustine or rituximab maintenance therapy may improve prognosis, and that bendamustine is also highly effective as a second-line therapy.

As shown in the BRIGHT study, however, secondary malignancies occur in patients who received bendamustine. Also, as previously reported by our department, combination with rituximab and bendamustine tends to cause reduction in CD4/CD8-positive lymphocytes particularly among patients treated with rituximab maintenance therapy, sometimes resulting in severe infections. These results indicate that administering bendamustine from the beginning is unsuitable in consideration of secondary malignancies. Likewise, the continuation of rituximab maintenance therapy until relapse is also unsuitable from the standpoint of immune deficiency. For these reasons, in our department, we use R-CHOP or R-THP-COP for initial treatment and use therapies that include bendamustine for relapsed or refractory cases. Also, we administer rituximab maintenance therapy in 12 courses, within the coverage of Japan's national health insurance system. Out of the 22 cases in this study, however, 19 were switched to second-line therapy, wherein relapse occurred in almost all cases, indicating that problems remain with induction chemotherapy (Table 5).

Conclusion

Our study showed that rituximab maintenance therapy is effective for MCL, which had shown good response from induction chemotherapy. In addition, it was also shown that prognosis may improve even for relapsed or refractory cases using treatments that include bendamustine. Large cohort, prospective studies are needed in the future.

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