A retrospective study evaluating the efficacy and safety of bendamustine in the treatment of mantle cell lymphoma

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Abstract

Bendamustine is approved in the United States for relapsed indolent lymphoma. However, it has not been widely studied in mantle cell lymphoma (MCL). We retrospectively reviewed the records of all patients with MCL who were treated with bendamustine at three centers. The primary endpoint was overall response rate (ORR). Thirty patients with MCL received bendamustine, 25 for relapsed disease. After a median follow-up of 12 months, there were 15 complete responses (CRs) with an ORR of 83% (95% confidence interval [CI] 70–97%). Factors significantly associated with longer survival were achieving a CR and classical (versus blastic) variant of MCL. Grade 3 or 4 neutropenia, anemia and thrombocytopenia occurred in 23%, 3% and 20%, respectively. There was one case of progressive multifocal leukoencephalopathy 10 months after therapy completion. Bendamustine in combination with rituximab demonstrated a high response rate in this study of patients with predominantly relapsed MCL.

Keywords

Non-Hodgkin lymphoma; mantle cell lymphoma; chemotherapy; bendamustine; rituximab

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Introduction

In 2011, an estimated 66 000 cases of non-Hodgkin lymphoma (NHL) will be diagnosed in the United States [1], with 6–8% of these cases being mantle cell lymphoma (MCL) [2]. The hallmark of MCL is a translocation between chromosomes 11 and 14, resulting in cyclin D1 overexpression [3]. The natural history of MCL is heterogeneous, with some patients following an indolent course, but in most cases the disease behaves aggressively [4], with over 90% presenting with extranodal disease [5]. As the understanding of this disease has evolved from an indolent to a more aggressive paradigm, the application of more intensive chemotherapy regimens including anthracyclines and high-dose cytarabine has led to improved survival rates in recent years [6].

MCL is generally chemotherapy sensitive, but the induced responses are often short-lived [7]. The usual frontline treatment approach in the USA consists of intensive chemoimmunotherapy [8–10]. The role of transplant in the treatment of MCL, as frontline therapy as well as for relapsed disease, remains controversial, with some investigators showing benefit for autologous hematopoietic stem cell transplant (HSCT) [9] and others for allogeneic HSCT [11].

Bendamustine, which was initially developed in the 1960s in Eastern Europe, has recently evolved as an increasingly used chemotherapeutic agent for diverse lymphomas in the United States and Europe [12]. Bendamustine had been used for decades in East Germany in the treatment of chronic lymphocytic leukemia (CLL), Hodgkin lymphoma disease, non-Hodgkin lymphoma (NHL), multiple myeloma and lung cancer. It is an alkylating agent with a different mechanism of action compared to other alkylating agents [13]. In 2008 the US Food and Drug Administration (FDA) approved its use as a first-line agent for CLL and for relapsed indolent B-cell NHL [14–16].

There have been many studies testing bendamustine in the treatment of indolent lymphoma, but none have focused exclusively on MCL. Kahl *et al.* used single-agent bendamustine and reported a 75% overall response rate (ORR) and a 14% complete response (CR) rate in 100 patients with indolent B-cell lymphoma, primarily follicular type [15]. In a German study, 63 patients with indolent lymphoma (including 16 with MCL) received rituximab plus bendamustine [17]. The MCL group had a progression-free survival (PFS) of 10 months. In one of the initial German trials of bendamustine, Herold *et al.* compared bendamustine, vincristine and prednisone (BOP) to cyclophosphamide, vincristine and prednisone (COP) in 162 patients with indolent lymphomas [18]. Twenty-one of the patients in this study treated with BOP had MCL; in these patients the 5-year survival rate was 43%. Another combination regimen of bendamustine, mitoxantrone and rituximab was studied in 57 patients [19]. Among the 18 patients with MCL, there was an ORR of 78% and a median PFS of 21 months.

Several studies performed in the USA led to bendamustine approval by the FDA [15,16,20]. Friedberg *et al.* used single-agent bendamustine in the treatment of 76 patients with rituximab-refractory indolent and transformed NHL, yielding an ORR of 77% and a CR rate of 15%. Robinson *et al.* studied rituximab plus bendamustine for relapsed indolent

lymphomas. Of the 66 patients in the study, 11 of the 12 patients with MCL responded to therapy. Recently, other investigators have reported similarly high response rates with bendamustine-containing regimens in small cohorts of patients with MCL [21,22]. Herein we present a multi-institutional series of patients with MCL treated with bendamustine to add to the body of evidence for activity of this agent in MCL.

Patients and methods

We searched our institutions' institutional review board (IRB)-approved lymphoma databases to retrospectively identify all patients with a diagnosis of MCL at Jackson Memorial Hospital and the Sylvester Comprehensive Cancer Center (both in Miami, FL) and the Stanford Cancer Center (in Stanford, CA). We cross-referenced this search with our chemotherapy records to identify patients who had received bendamustine as part of their treatment regimen for MCL since its approval in 2008 until June 2011. The diagnostic specimens of all included patients were reviewed to confirm the immunophenotype, cyclin D1 expression, cytologic variant and lymphoma growth pattern. Patients whose specimens did not fulfill the World Health Organization (WHO) criteria for MCL, without clear overexpression of cyclin D1 or the presence of t(11;14), were excluded [2]. When possible, immunostaining with an antibody to Ki-67 (Dako, Carpinteria, CA) was performed and quantified in the diagnostic specimens.

We collected clinical information, including baseline performance status, serum lactate dehydrogenase (LDH), Ann Arbor stage, extranodal sites of disease, histological subtype of MCL, Ki-67 expression, β_2-microglobulin, peripheral blood lymphocyte count and percentage, and all chemotherapy treatments that the patient had received. The records were also examined for any adverse events that might have been associated with bendamustine and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [23].

The primary endpoint was ORR, defined using the revised International Working Group criteria for response assessment [24]. Secondary endpoints were overall survival (OS), time to treatment failure (TTF) and safety. Survival analysis was performed using the Kaplan–Meier method [25], with significance level for separation of survival curves assessed using the log-rank test. For the analysis of survival according to response to treatment, the landmark method was employed [26].

Results

We identified 30 patients who met the search criteria, with 17 patients treated at the University of Miami, two at Jackson Memorial Hospital and 11 at Stanford Cancer Center. The median age at diagnosis was 58 years and 77% of the patients were male. The most common extranodal site of involvement at diagnosis was the bone marrow (57%), followed by the gastrointestinal (GI) tract (33%). Most patients presented with advanced disease, with 28% and 69% of the patients having stage III and IV disease at diagnosis, respectively. Seven patients (23%) were diagnosed with the blastic variant of MCL. The majority of patients were in the intermediate (55%) or low (41%) MCL International Prognostic Index

(MIPI) risk groups at the time of their initial diagnosis. Of the 25 patients who did not receive bendamustine as front-line therapy, the most widely used regimens were R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; 36%) and R-MACLO-IVAM (rituximab, methotrexate, doxorubicin, cyclophosphamide, vincristine, ifosfamide, etoposide, cytarabine; 28%). Patients had been treated with a median of one chemotherapy regimen prior to receiving bendamustine (range 1–5). Three patients received rituximab as maintenance. Table I summarizes the baseline characteristics of all the patients.

Among the 30 patients studied, 28 had received rituximab with bendamustine, and two had received bendamustine monotherapy. Five patients had received bendamustine with rituximab as initial therapy and the remaining 25 (including two patients who received bendamustine monotherapy) for relapsed disease. The patients who had received bendamustine with rituximab as front-line therapy were not considered to be candidates for more aggressive, multiagent chemo-therapy due to advanced age or comorbidities. Due to the retrospective nature of this study, the dose of bendamustine varied according to the physician's preference. The most common schedule administered was rituximab 375 mg/m^2 on day one and bendamustine 100 mg/m^2 on days one and two of a 28-day cycle, given for a median of six cycles. Daily doses of bendamustine given in prior studies ranged from 90 mg/m^2 [20] to 120 mg/m^2 [19]. The daily doses of bendamustine used in this study were 100 mg/m^2 ($n = 12$), 90 mg/m^2 ($n = 11$) and 80 mg/m^2 ($n = 7$). The most common reason for usage of bendamustine at the dose of 80 mg/m^2 was the presence of renal failure with reduced creatinine clearance. At the start of therapy, the goal was to deliver six cycles. Nineteen patients received six cycles and 11 patients received fewer than six, for reasons including death related to progression of disease ($n = 5$), progressive disease while on therapy after an initial partial response ($n = 2$), adverse effects of therapy ($n = 1$; grade 4 pancytopenia), CR before completion of six cycles ($n = 1$) and treatment ongoing at the time of publication of this study ($n = 1$).

Of the 30 patients who received bendamustine, 15 had a CR and 10 had a partial response (PR), for an ORR of 83% (95% confidence interval [CI] 70–97%). Of the five patients who received bendamustine for initial therapy, three achieved a CR and the other two had a PR. The response to treatment is summarized in Table II. Of note, one patient who achieved a PR with bendamustine actually had a radiological CR by positron emission tomography (PET) and computed tomography (CT), but was found to have a microscopic involvement of his bone marrow, and therefore was defined as a PR.

Twenty-five patients received bendamustine for relapsed disease, with 15 as second line and 10 as third line or beyond. Of these 25 patients, 12 (48%) had stage IV and eight (32%) had stage III disease at the time of treatment with bendamustine. Among these 25 patients, the median disease-free interval after frontline treatment was 29.8 months (95% CI 26.2–33.4 months). Frontline treatment yielded an ORR of 88% in these 25 patients. Five of these patients had relapsed MCL after an autologous HSCT. Twenty-one of the 23 (91%) patients with the classical variant responded to bendamustine, whereas only four out of seven (57%) with the blastic variant responded ($p = 0.068$, two-sided Fisher's exact test). At the time of this report, five of the seven patients with the blastic subtype have died due to lymphoma.

With a median follow-up of 12 months (range 0.3–37.2 months), the median OS was not reached; the 1-year OS rate was 72%; the 2-year OS rate was 57%. When OS was stratified by response (using a 2-month landmark as the starting point for analysis), patients achieving a CR had a significantly longer survival compared to patients who did not achieve a CR (log-rank $p < 0.001$). The median TTF was 16.2 months. When TTF was stratified by response (again using a 2-month landmark), a statistically significant difference between the two groups was also found; patients who achieved a CR had a significantly longer TTF than patients who did not achieve a CR (log-rank $p = 0.001$). Figure 1 shows the Kaplan–Meier survival curves for TTF and OS stratified by response. The TTF and OS were significantly worse for patients with the blastic variant versus the classical variant, as shown in Figure 2.

The majority of serious adverse events associated with bendamustine use were hematological (Table III). Grade 3 or 4 neutropenia, anemia, thrombocytopenia and neutropenic fever occurred in 23%, 3%, 20% and 7% of patients, respectively. One patient discontinued therapy with bendamustine after two cycles due to grade IV thrombocytopenia and neutropenia. Of note, blood counts were checked monthly on this study. Two patients required hospitalization for infections (folliculitis and pneumonia) while receiving treatment. Common non-hematologic grade 1 or 2 toxicities were fatigue (27%), edema (20%), erythematous rash (20%) and nausea (13%). One patient had a reactivation of dermatomal herpes zoster during therapy. Another patient was found to have new-onset pulmonary nodules approximately 1 month after completing his course of R-bendamustine for relapsed MCL. His symptoms progressed, and he underwent an open lung biopsy, which revealed CD5-negative, cyclin-D1 negative diffuse large B-cell lymphoma (DLBCL), while biopsy at the time of relapse was CD5-positive, cyclin D1-positive MCL without evidence of DLBCL. He expired shortly thereafter.

Two patients developed neurological sequelae during or after treatment with bendamustine. The first patient received six cycles of rituximab plus bendamustine on second relapse and achieved a CR. However, 10 months after completing therapy she began to develop left-sided weakness and dysmetria, along with an ataxic gait. A magnetic resonance imaging (MRI) scan of the brain showed multiple predominantly peripherally enhancing lesions. A stereotactic brain biopsy revealed progressive multifocal leukoencephalopathy (PML) positive for JC virus. At the time of PML diagnosis, she had a low absolute CD4 count of 176 cells/μL (reference range 492–1740), a low absolute CD3 count of 522 (reference range 840–3060) and a normal absolute CD8 count of 368. After 1 year of follow-up, she remains without evidence of relapsed MCL and her neurologic symptoms have gradually improved without therapy, but did not recover completely to baseline. A second patient developed ataxia and incontinence while on bendamustine therapy. Her symptoms continued to progress and she presented to an outside facility 2 months after her last dose of rituximab plus bendamustine. Diagnostic work-up at the time included an unremarkable MRI scan of the brain and spinal cord and negative cerebrospinal fluid cytology. This patient's symptoms were suspicious for PML, but she died before a definitive diagnosis could be established, and autopsy was declined.

Discussion

Bendamustine has been studied for the treatment of indolent lymphoma both as monotherapy [27] and as part of combination therapy, including combination with rituximab, in an attempt to increase the response rate and survival [16,18,20]. These studies have established bendamustine as a valid option for the treatment of indolent lymphoma. However, despite being grouped together with the indolent lymphomas, MCL often behaves more aggressively, and specific studies in patients with MCL are required.

In the present retrospective study, all five patients who received bendamustine in combination with rituximab as frontline therapy responded. The median TTF in this subset was not reached. Based on these limited data for effectiveness, along with the good tolerability of this regimen, rituximab plus bendamustine may be an option for frontline therapy in patients with MCL who are not candidates for more aggressive treatment, but further study is needed.

In relapsed MCL, we observed an ORR of 80% for bendamustine, similar to responses reported in several distinct frontline regimens in patients with MCL [8,10]. Although the median follow-up in relapsed patients is relatively short (12 months) with a median TTF of 13.4 months, at least four patients remained in continued remission for over 2 years after receiving bendamustine. Furthermore, our results are consistent with the previously reported response rates in small cohorts (7–18 patients) of relapsed MCL treated with bendamustine-based regimens (Table IV).

Due to the low prevalence of MCL, there have been few studies specifically evaluating non-transplant treatments in the setting of relapsed and refractory disease. Currently, the proteasome inhibitor bortezomib is the only FDA-approved agent for relapsed MCL, based on its single-agent activity for relapsed and refractory MCL within the PINNACLE trial [28]. In this study of 141 patients, 40% of patients responded to treatment and 8% had a CR. The median OS was 23.5 months and time to progression was 6.7 months, with a median duration of response of 9.2 months [29]. A similar study, with a total of 40 patients, compared relapsed to refractory MCL in their response to bortezomib. The ORR and CR of 47% and 12% were similar to the rates found in the PINNACLE trial [30]. Like bendamustine, bortezomib has a toxicity profile that is favorable when compared to the more intensive regimens used to treat MCL.

Lenalidomide was studied in 15 patients with relapsed or refractory MCL. Responses were seen in 53% of the patients, with a 20% CR. The median PFS was 5.6 months [31]. Fludarabine-based chemotherapy and temsirolimus have also been tested in patients with primary and relapsed MCL, with some evidence of activity [32–35].

Although our data are retrospective, the observed response in our cohort of patients seems to be at least similar to, and may be even better than, the responses reported with bortezomib, lenalidomide and other new drugs, as demonstrated in Table IV. Further prospective studies of bendamustine in patients with relapsed MCL as well as side by side comparisons with alternative currently approved therapies will establish its role in these patients.

While our study included only five patients who received bendamustine after autologous HSCT, bendamustine induced a CR in three and a PR in one other. A fifth patient did not tolerate bendamustine. As of this publication, two of the three patients who had a CR from bendamustine have relapsed. Based on these data, bendamustine appears to demonstrate some activity in patients who experience progression of MCL after transplant. In contrast, our data suggest that bendamustine is ineffective in the blastic variant of MCL, and other novel strategies should be tested in this subtype.

The hematological toxicities that we encountered were expected and manageable. They included neutropenia (23%) and thrombocytopenia (20%). One patient withdrew from treatment as a result of these toxicities. There was one confirmed case of PML, which has not previously been described with bendamustine, but this patient was also treated with rituximab, which is associated with PML [36]. This patient currently has no evidence of MCL and is slowly improving from her PML. Another patient with neurological complaints had a clinical suspicion for PML, but expired before biopsy was performed to confirm or rule out this diagnosis. Further reports will clarify whether indeed bendamustine treatment is associated with PML. Despite this concern, compared to other chemotherapy regimens with comparable efficacy in treating patients with MCL, the toxicity profile of bendamustine appears to be favorable. We did not observe an excess of infections during or after therapy as has been reported with the purine analogs such as fludarabine.

Based on the results of this study, bendamustine appears to have a favorable profile as a second-line agent for patients with relapsed MCL. The response rate is at least comparable to that with other therapies, especially when examined in light of the toxicity profile seen with other regimens. This study supports the need for continued investigation of bendamustine as a therapy for patients with MCL in both the frontline and relapsed settings in prospective clinical trials, some of which are currently ongoing.

Acknowledgements

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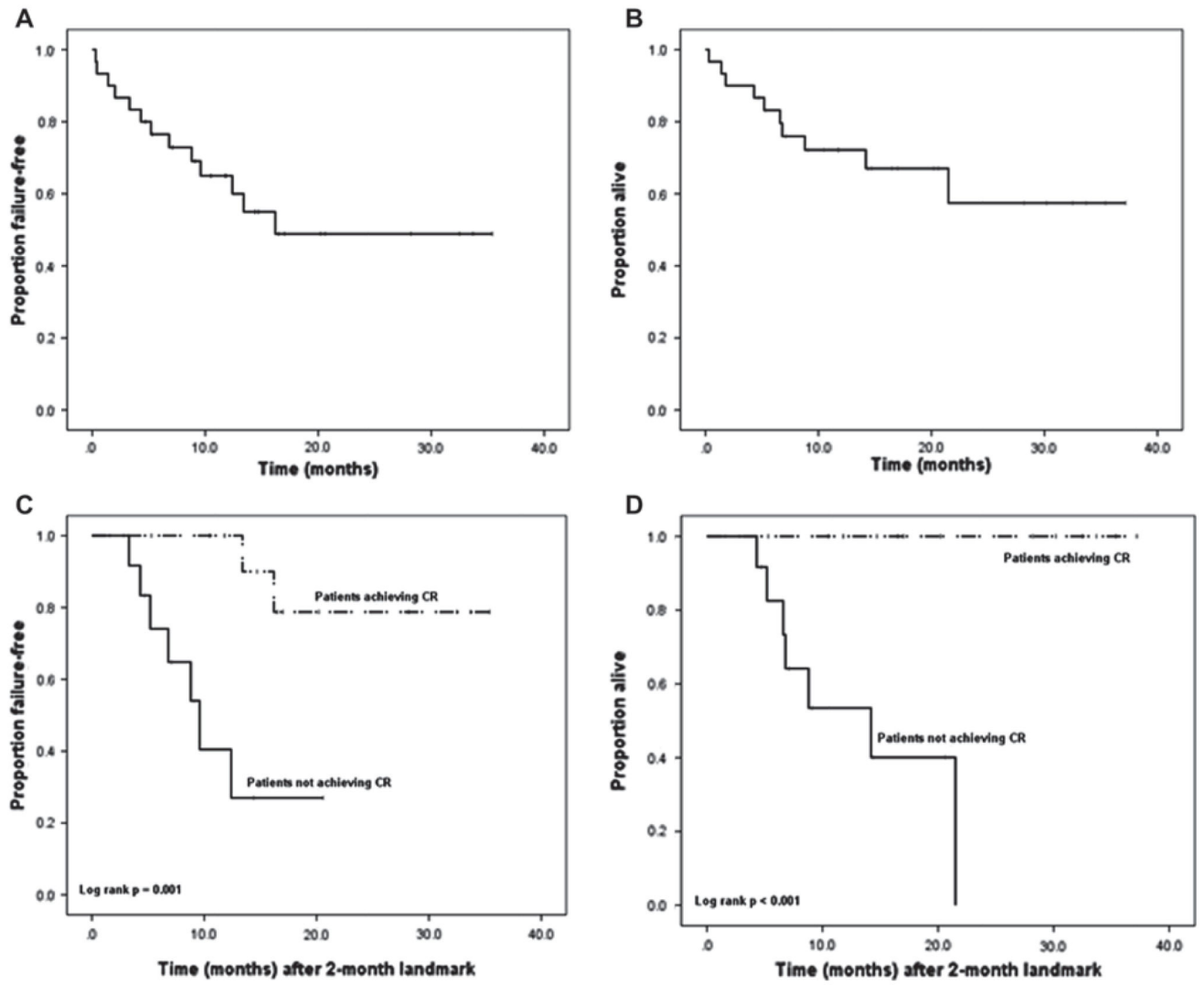
Figure 1.
Kaplan–Meier survival curves showing time to treatment failure in all patients (1A) and stratified by complete response (1C, landmark method); and overall survival in all patients (1B) and stratified by complete response (1D, landmark method).
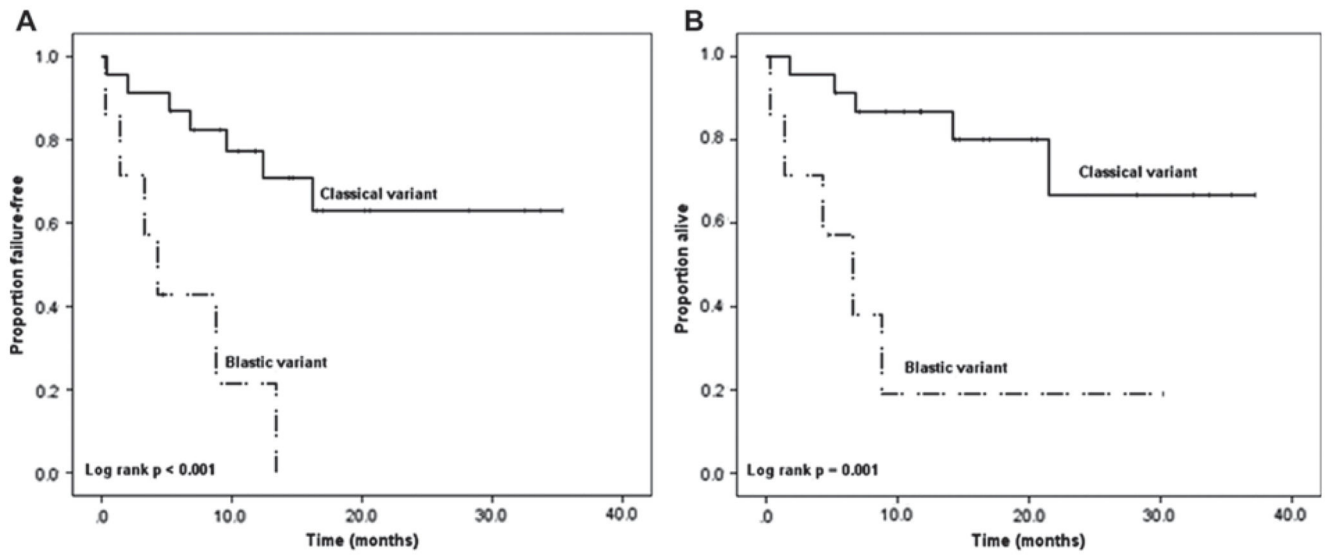
Figure 2.
Kaplan–Meier survival curves showing time to treatment failure (2A) and overall survival (2B) stratified by blastic versus classical variant of mantle cell lymphoma.

Table I

Baseline patient characteristics at diagnosis, *n* = 30.

	n (%)
Male	23 (77)
Age (median)	58 (range 39–86)
ECOG Performance Status	
0	17 (63)
1	10 (37)
Extranodal site	
GI tract	10 (33)[*]
Bone marrow	17 (57)
Ann Arbor stage	
III	8 (28)
IVA	11 (38)
IVB	9 (31)
Histological subtype	
Blastic	7 (23)
Classical	23 (77)
Ki-67 (for 18 cases)	
<10%	1 (6)
10–30%	6 (33)
>30%	11 (61)
β_2-Microglobulin (for 13 cases) (mg/L)	
<3	4 (31)
>3	9 (69)
LDH exceeding upper limit of normal	10 (42)
MIPI score (for 22 cases)	
Low	9 (41)
Intermediate	12 (55)
High	1 (5)
Frontline therapy prior to bendamustine	
R-CHOP	9 (36)
R-MACLO-IVAM	7 (28)
Other[†]	9 (36)
Number of treatments prior to bendamustine	
One	15 (60)
Two	8 (32)

ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, predni sone; R-MACLO-IVAM, rituximab, methotrexate, doxorubicin, cyclophospha mide, vincristine, ifosfamide, etoposide, cytarabine; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; R-DHAP, rituximab, dexamethasone, ara-C, cisplatin.

Table II

Response to therapy.

	n (%)
Received bendamustine as frontline therapy (n = 5)	
CR	3 (60)
PR	2 (40)
Received bendamustine for relapsed disease (n = 25)	
CR	12 (48)
PR	8 (32)
SD	3 (12)
PD	2 (8)
All patients (n = 30)	
CR	15 (50)
PR	10 (33)
SD	3 (10)
PD	2 (7)
Overall response rate	83% (95% CI 70–97)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

Table III

Adverse events during bendamustine treatment ($n = 146$ cycles).

	Grade 3–4, n (%)
Hematological	
Neutropenia	7 (23)
Neutropenic fever	2 (7)
Anemia	1 (3)
Thrombocytopenia	6 (20)
Leukopenia	5 (17)
Lymphopenia	6 (20)
Non-hematological	
Fatigue	1 (3)
Infection	3 (10)
Fever	1 (3)
Near-syncope	1 (3)
Headache	1 (3)
Acute renal failure	1 (3)
Edema	0
Erythematous rash	0
Dyspnea	0
Night sweats	0
Cough	0
Pain	0
Blurred vision	0
Insomnia	0
Pruritus	0
Nausea	0
Anorexia	0
Diarrhea	0
Constipation	0
Hypocalcaemia	0
Hypokalemia	0

Table IV

Summary of studies examining treatment of relapsed mantle cell lymphoma.

Year	Author	Experimental treatment	n	ORR	Median TTF (months)	Median OS (months)
2010	Ohmachi	Bendamustine	11	100%	NR	NA
2005	Rummel	B-R	16[*]	75%	18 (PFS)	NR
2008	Robinson	B-R	12	92%	19.0 (DOR)	NA
2011	Warsch[†]	B-R	25	80%	13.4	NR
2007	Weide	B-R-mitoxantrone	18	78%	21.0 (PFS)	31
2011	Friedberg	B-R-bortezomib	7	71%	NA	NA
2001	Cohen	FC	30[‡]	63%	4.8 (FFS)	17.5
2004	Forstpointer	R-FCM	52	52%	8.0 (PFS)	NR
2005	Witzig	Temsirolimus	35	38%	6.5 (TTP)	12
2009	Hess	Temsirolimus	54[§]	22%	4.8 (PFS)	12.8
2009	Habermann	Lenalidomide	15	53%	5.6 (PFS)	NA
2008	O'Connor	Bortezomib	40	47%	5.3 (PFS)	NA
2009	Goy	Bortezomib	141	40%	6.7 (TTP)	23.5

MCL, mantle cell lymphoma; B-R, bendamustine, rituximab; FC, fludarabine, cyclophosphamide; R-FCM, rituximab, fludarabine, cyclophosphamide, mitoxantrone; ORR, overall response rate; TTF, time to treatment failure; NR, not reached; PFS, progression-free survival; DOR, duration of response; NA, data not available; FFS, failure-free survival; TTP, time to progression; OS, overall survival.

[*] Seven of the 16 patients in this study had refractory MCL.

[†] Present study.

[‡] Twenty of the 30 patients in this study had relapsed/refractory MCL.

[§] Outcomes shown for the 54 patients allocated to 175/75 mg dosing schedule.