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ORIGINAL REPORT

Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients With Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma

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ABSTRACT

Purpose
Bendamustine HCl is a bifunctional mechlorethamine derivative with clinical activity in the treatment of non-Hodgkin's lymphoma. This study evaluated bendamustine plus rituximab in 67 adults with relapsed, indolent B-cell or mantle cell lymphoma without documented resistance to prior rituximab.

Patients and Methods
Patients received rituximab 375 mg/m^2 intravenously on day 1 and bendamustine 90 mg/m^2 intravenously on days 2 and 3 of each 28-day cycle for four to six cycles. An additional dose of rituximab was administered 1 week before the first cycle and 4 weeks after the last cycle. Sixty-six patients (median age, 60 years) received at least one dose of both drugs.

Results
Overall response rate was 92% (41% complete response, 14% unconfirmed complete response, and 38% partial response). Median duration of response was 21 months (95% CI, 18 to 24 months). Median progression-free survival time was 23 months (95% CI, 20 to 26 months). Outcomes were similar for patients with indolent or mantle cell histologies. The combination was generally well tolerated; the primary toxicity was myelosuppression (grade 3 or 4 neutropenia, 36%; grade 3 or 4 thrombocytopenia, 9%).

Conclusion
Bendamustine plus rituximab is an active combination in patients with relapsed indolent and mantle cell lymphoma.

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INTRODUCTION

In 2008, non-Hodgkin's lymphoma (NHL) will be diagnosed in 66,120 patients, and 20,510 patients will die of the disease.[1] Significant gains in response and survival have been achieved with chemoimmunotherapy, particularly with the introduction of rituximab (Rituxan; Genentech, Inc, South San Francisco, CA).[2]

Data from the National LymphoCare Study indicate that, although a variety of regimens are used as initial therapy for follicular lymphomas, rituximab plus chemotherapy is the most frequent choice (51%).[3,4] Given the relapsing nature of indolent lymphomas, patients require re-treatment, and most ultimately become refractory to rituximab and/or various chemotherapies.[5] Thus, despite availability of active therapies, indolent B-cell and mantle cell lymphomas remain incurable for most patients. A significant unmet need remains for effective and well-tolerated treatment.

Mantle cell lymphoma represents approximately 6% of all NHL and is among the more aggressive subtypes, with a response duration of 1 to 3 years after initial treatment and a median survival time of 3 to 5 years.[6] A variety of chemoimmunotherapy approaches have been used in the front-line and relapsed settings, but refractoriness to treatment and the presence of comorbid illness in this typically older population often limit effective therapy.[7]

Bendamustine (Treanda; Cephalon, Inc, Frazer, PA) is a novel agent consisting of a mechlorethamine (nitrogen mustard) group, a benzimidazole ring, and a butyric acid side chain. In vitro studies demonstrate rapid production of DNA cross-links and strand breaks after bendamustine exposure.[8] In addition to direct DNA damage and apoptosis, other mechanisms include inhibition

of mitotic checkpoints and induction of mitotic catastrophe.[9] These characteristics may explain the activity of bendamustine in drug-resistant cancer cells[9] and refractory lymphoma patients.[10] Benzimidazole acts as a purine antagonist in experimental models; the contribution of this structure to the overall antitumor activity of bendamustine is unknown.

In vitro testing in CD20-positive lymphoma cell lines has demonstrated synergy between bendamustine and rituximab, evidenced by a reduction in the bendamustine concentration required to induce apoptosis in 50% of tumor cells after the addition of rituximab.[11] Rituximab has previously been shown to increase the sensitivity of NHL cells to other chemotherapeutic agents.[12] Cross resistance has not been observed between rituximab and chemotherapeutic agents. Considering these findings and the widespread use of rituximab in NHL patients, we evaluated the efficacy and safety of bendamustine plus rituximab in patients with indolent B-cell or mantle cell lymphoma experiencing relapse after chemotherapy or chemoimmunotherapy.

PATIENTS AND METHODS

Study Design and Objectives

We conducted this multicenter, open-label, single-arm, phase II clinical trial to determine the overall response rate (ORR) to bendamustine plus rituximab in patients with relapsed indolent B-cell or mantle cell lymphoma. ORR was defined as a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study period. Secondary objectives included safety, progression-free survival (PFS), and duration of response (DR). The institutional review board approved the protocol at each site, and an institutional review board–approved consent form was signed before study participation.

Eligibility

Patients age $\geq$ 18 years with a WHO performance status of 0 to 2 were eligible if they had documented relapsed, CD20-positive mantle cell lymphoma or indolent B-cell (follicular, small lymphocytic, lymphoplasmacytic, or marginal zone) lymphoma. Patients were required to have bidimensionally measurable disease with at least one lesion measuring $\geq$ 2 cm in a single dimension. A maximum of three prior, unique chemotherapy regimens was allowed. Prior rituximab was allowed if the patient was not refractory (disease progression during or within 6 months of the last dose of rituximab or achievement of less than a PR to a rituximab-containing regimen). Adequate hematologic function (absolute neutrophil count $\geq$ 1,000 cells/μL and platelets $\geq$ 100,000 cells/μL) was required unless patients demonstrated more than 50% marrow involvement. Study entry required adequate renal (creatinine clearance $>$ 30 mL/min) and hepatic function ($\leq$ 2.5$\times$ the upper limit of laboratory normal for AST and ALT and $\leq$ 1.5$\times$ the upper limit of laboratory normal for total bilirubin).

Patients were excluded if they were refractory to rituximab, had received prior radioimmunotherapy or prior high-dose chemotherapy with allogeneic stem-cell support, or had concurrent treatment with therapeutic doses of systemic corticosteroids. Patients were also excluded if they had an active malignancy other than lymphoma, malignant effusions, or evidence of serious infection, or had not recovered from prior treatment-related adverse effects.

Treatment

Baseline evaluation included medical history and physical examination, CBC, serum electrolytes and clinical chemistry, bone marrow aspiration/biopsy, and tumor staging using contrast-enhanced computed tomography or magnetic resonance imaging. Patients received rituximab 375 mg/m^2 on day 1, followed by bendamustine 90 mg/m^2 by intravenous infusion over 30 to 60 minutes on days 2 and 3 every 28 days for four cycles. Additional doses of rituximab were administered 7 days before the first cycle and 28 days after the last cycle. Patients could receive up to six cycles if disease regression was evident between the second and fourth cycles. If grade 3 nonhematologic or grade 4 hematologic toxicity occurred, as determined by the Common Terminology Criteria for Adverse Events (version 3.0),[13] the dose of bendamustine was reduced to 60 mg/m^2 in the subsequent cycle. If a similar severity of toxicity occurred at the reduced dose, study treatment was discontinued. Primary prophylactic use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor was discouraged; however, treatment was allowed for prolonged neutropenia (grade 4 leukopenia $\geq$ 1 week, failure of WBCs to recover to at least grade 1 by the next scheduled dose, or febrile neutropenia in a prior treatment cycle). Bendamustine was postponed if toxicities remained at $\geq$ grade 2. Except for patients with more than 50% bone marrow involvement, recovery to absolute neutrophil count $\geq$ 1,000/μL and platelet count $\geq$ 75,000/μL was required before starting the second and subsequent cycles. If recovery was not evident within 2 weeks of a scheduled treatment, the patient was re-evaluated for continued treatment.

Response Criteria

Response was assessed after the second cycle, at the end of treatment (within 8 weeks after the last dose of rituximab), and then every 3 months for a minimum of 2 years until death, disease progression, or alternate treatment. Response and progression were based on International Working Group Response Criteria for NHL,[14] using the same imaging method (computed tomography or magnetic resonance imaging) used to establish baseline tumor measurements.

Patients were classified by best tumor response (CR, CRu, PR, stable disease, or progressive disease). PFS was calculated as the time from first dose of study drug to first documentation of disease progression or death. DR was calculated as the time from first documentation of best response (CR, CRu, or PR) to first documentation of disease progression or death. Laboratory assessments were performed at baseline and on day 1 of each cycle. The severity of adverse events was determined using Common Terminology Criteria for Adverse Events version 3.0.[13]

Statistical Methods

We hypothesized that bendamustine plus rituximab would produce an ORR $\geq$ 70%.[15] On the basis of prior studies indicating an ORR of 50% after single-agent rituximab,[16] a sample size of 60 patients was planned to yield more than 80% power (using an overall, two-sided, 5% significance level) to detect an increase of 20% in ORR after treatment with bendamustine plus rituximab.

ORR was calculated as the number of patients achieving a best response of CR, CRu, or PR divided by the number of patients treated with at least one dose of bendamustine. Patients without at least one response assessment were treated as nonresponders. A two-sided 95% exact CI for ORR was calculated using the binomial distribution. The Kaplan-Meier method was used to estimate median DR and PFS, and two-sided 95% CIs were calculated using the Brookmeyer-Crowley nonparametric method.[17]

Absolute dose-intensity of bendamustine and rituximab (mg/m^2/wk) was calculated for each patient as the sum of doses administered divided by the number of weeks in the treatment period. Relative dose-intensity for each agent (%) was then calculated as the dose-intensity divided by the weekly intended dose and then multiplied by 100.

RESULTS

Patient Disposition and Characteristics

The study enrolled 67 patients at 22 sites in the United States, Canada, and Australia from April 2004 to December 2005. One patient withdrew consent after the first dose of rituximab, did not receive bendamustine, and was excluded from further analyses. Patient characteristics are listed in Table 1. Fifty-six percent of

Table 1. Patient Demographics and Disease Characteristics

Characteristic	No. of Patients (N = 66)	%
Age, years		
Median	60	
Range	40-84	
Sex		
Male		59
Female		41
Years since NHL diagnosis		
Median	3.4	
Range	0.25-17.0	
Stage		
I-II		18
III-IV		82
WHO performance status		
0-1	63	
2	3	
Histologic subtypes		
Indolent	54	82
Follicular center cell	40	61
Small lymphocytic	10	15
Lymphoplasmacytic/Waldenström	2	3
Marginal zone	2	3
Mantle cell	12	18
Prior chemotherapy or biologic therapy	66	100
Prior chemotherapy	64	97
Prior alkylator	56	85
Prior purine analog	15	23
Prior anthracycline	38	58
No. of prior chemotherapy regimens		
Any	64	100
1	36	56
2	21	33
3	4	6
> 3	3	5
Mean	1.6	
Median	1.0	
Range	1.0-4.0	
Prior rituximab-containing treatment	37	56
No. of prior rituximab regimens		
Any	37	100
1	27	73
2	8	22
3	2	5
Mean	1.3	
Median	1.0	
Range	1.0-3.0	
FLIPI risk category	40	
Low (score = 0-1)	13	33
Intermediate (score = 2)	13	33
High (score > 2)	13	33
Unknown	1	3

Abbreviations: NHL, non-Hodgkin's lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index.

patients had received prior rituximab; 44% were rituximab naive. Sixty-four patients (97%) received prior chemotherapy; these patients received a median of one prior chemotherapy regimen (range, one to four regimens). Two patients (3%) received prior rituximab without chemotherapy. Although three patients received more than three prior chemotherapy regimens, these occurrences did not constitute protocol violations because two patients received repeated treatment with the same regimen and the third patient received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and, later, cyclophosphamide, vincristine, and prednisone, which was counted as one unique regimen.

Safety

Sixty-one patients (92%) received at least four cycles of treatment; 41 patients (62%) received six cycles of treatment (Table 2). Of the total 346 patient-cycles administered, 43 (12%) were delayed; 74% of these delays were ≤ 14 days in duration. The mean relative dose-intensities for bendamustine and rituximab were 93% and 95%, respectively. Six patients discontinued bendamustine treatment before completing four cycles as a result of adverse events (n = 2), disease progression (n = 1), patient/investigator decision (n = 2), or loss to follow-up (n = 1).

Table 2. Patient Disposition

Measure	No. of Patients	%
Patients enrolled	67	
Patients treated	66	
No. of cycles completed		
Mean	5.2	
Median	6.0	
Range	2.0-7.0	
Completed No. of cycles		
2	2	3
3	3	5
4	15	23
5	4	6
6	41	62
7	1	2*
Rituximab dose-intensity		
Planned, mg/m^2/wk	93.75	
Absolute, mg/m^2/wk		
Median	93.3	
Range	72.2-95.5	
Relative, %†		
Median	99.3	
Range	76.0-101.5	
Bendamustine dose-intensity		
Planned, mg/m^2/wk	45	
Absolute, mg/m^2/wk		
Median	43.7	
Range	29.6-45.8	
Relative, %†		
Median	97.1	
Range	65.7-101.8	
Reasons for study drug discontinuation in patients receiving < four cycles	6	
Adverse event	2	3
Consent withdrawn	2	3
Disease progression	1	1
Lost to follow-up	1	1

*One patient received an extra cycle of bendamustine in error.
†Relative dose-intensity is a measure of the amount of drug received in an actual treatment period, expressed as a percentage of the amount of drug planned for the realized treatment period.

Table 3. Hematologic Adverse Events in 66 Patients Receiving Bendamustine Plus Rituximab

Event	All Grades		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia	62	94	18	27	2	3
Neutropenia	52	79	15	23	9	14
Febrile neutropenia	4	6	3	5	1	2
Thrombocytopenia	41	62	5	8	1	2
Anemia	51	77	1	2	0	0

NOTE. Severity was determined from postbaseline laboratory results using Common Terminology Criteria for Adverse Events, version 3.0, available at http://ctep.cancer.gov/reporting/ctc.html.

The combination of bendamustine and rituximab was well tolerated (Tables 3 and 4). The primary toxicity was reversible myelosuppression; grade 3 or 4 neutropenia was reported in 24 patients (36%), including four patients (6%) with febrile neutropenia. Other grade 3 or 4 hematologic toxicities included thrombocytopenia (9%) and anemia (2%). Growth factor or blood product support was administered during 43 (9%) of 463 cycles. Ten patients (15%) received RBC growth factors (darbapoetin or epoetin-alfa), and eight patients (12%) received granulocyte growth factors (pegfilgrastim, filgrastim, or sargramostim). Up to cycle 4, growth factor support increased with the number of treatment cycles administered. Four patients (6%) received transfusions of platelets, plasma, or other blood products during the study. There was no clear trend for an increase in the frequency of transfusions administered over time. No secondary malignancies were reported.

Nonhematologic adverse events attributed to bendamustine included (all grades) nausea (70%), infection (64%), fatigue (59%), constipation (44%), diarrhea (36%), headache (36%), and vomiting (29%; Table 4). Most events were grade 1 or 2 in severity. Sixty-two patients (94%) received antiemetics. Ten grade 3 or 4 infections were reported in six patients (diverticulitis, fungal respiratory tract infection, herpes simplex, herpes zoster, neutropenic infection [n = 2], oropharyngeal candidiasis, pneumonia, pseudomonal sepsis, and grade 4 cytomegalovirus infection). Other grade 4 nonhematologic toxicities included compartment syndrome, pulmonary edema, and toxic epidermal necrolysis (one patient each). Events commonly attributed to rituximab by investigators included fatigue (45%) and nausea (30%). There was no evidence of cardiac, renal, or hepatic toxicity. Grade 1 alopecia was reported in one patient (2%).

Infusion-related or injection site reactions were associated with bendamustine and rituximab in 10 (15%) and 13 patients (20%), respectively. These were mostly mild to moderate in severity, consisting of chills, fever, phlebitis, and rash. Two patients

Table 4. Nonhematologic Adverse Events Occurring With a Frequency of ≥ 15% in 66 Patients Receiving Bendamustine Plus Rituximab

Event	All Grades		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nausea	46	70	0	0	0	
Infection*	42	64	5	8	1	2
Fatigue	39	59	3	5	0	0
Constipation	29	44	0	0	0	0
Diarrhea	24	36	2	3	0	0
Headache	24	36	0	0	0	0
Vomiting	19	29	0	0	0	0
Cough	18	27	0	0	0	0
Chills	13	20	0	0	0	0
Rash	13	20	0	0	0	0
Pruritus	12	18	0	0	0	0
Abdominal pain	11	17	0	0	0	0
Stomatitis	11	17	0	0	0	0
Dyspnea	11	17	0	0	0	0
Peripheral edema	11	17	0	0	0	0
Insomnia	11	17	0	0	0	0
Infusion-related reaction	10	15	2	3	0	0
Pyrexia	10	15	0	0	0	0
Asthenia	10	15	2	3	0	0

NOTE. Two deaths occurred that were unrelated to disease progression; one was a result of toxic epidermal necrolysis and was considered to be possibly related to rituximab or bendamustine, and the other death was a result of compartment syndrome and pulmonary edema and was considered to be unrelated to study treatment.
*Grade 3 and 4 infections included diverticulitis, fungal respiratory tract infection, herpes simplex, herpes zoster, neutropenic infection, oropharyngeal candidiasis, pneumonia, and pseudomonal sepsis; one patient also experienced a grade 4 cytomegalovirus infection. The most common grade 1 and 2 infections included nasopharyngitis, sinusitis, herpes simplex, urinary tract infection, pneumonia, and herpes zoster.

Table 5. Treatment Response in All Patients by Pathologic Subtype and by Prior Rituximab Exposure

Pathologic Subtype and Rituximab Exposure Status	No. of Patients	ORR (%)	CR (%)	CRu (%)	PR* (%)	SD (%)	PD (%)
Total	66	92	41	14	38	8	0
Pathologic subtype							
Indolent lymphoma	54	93	41	13	39	7	0
Mantle cell lymphoma	12	92	42	17	33	8	0
Rituximab exposure							
Prior rituximab	37	87	35	14	38	14	0
No prior rituximab	29	100	48	14	38	0	0

Abbreviations: ORR, overall response rate; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease.

experienced grade 3 infusion reactions attributed to rituximab. There were no infusion-related reactions specifically attributed to bendamustine.

Five deaths reported during the study included three attributed to disease progression, one attributed to compartment syndrome and pulmonary edema, and one attributed to toxic epidermal necrolysis. All but the latter event were considered unrelated to bendamustine or rituximab. Toxic epidermal necrolysis was considered possibly related to rituximab or bendamustine, although the patient received multiple other medications that could have contributed.

Efficacy

ORR was 92%, including 41% CR, 14% CRu, and 38% PR (Table 5). Median follow-up time was 20 months (range, 19 to 22 months). Median DR was 21 months (95% CI, 18 to 24 months; Fig 1A). Median PFS time was 23 months (95% CI, 20 to 26 months; Fig 1B). ORR among 37 patients who had prior rituximab exposure was 86% (95% CI, 71% to 95%), and ORR in 29 patients who were rituximab naive was 100% (95% CI, 88% to 100%); corresponding CR rates were 35% (95% CI, 20% to 53%) and 48% (95% CI, 29% to 67%), respectively ($P = .32$). Median DR in 32 patients with prior rituximab exposure (21 months) was similar to the overall population. Among 21 patients who had received two or more previous chemotherapy regimens, the extent of prior treatment did not influence the response rate, and the median DR was 19 months.

Twelve patients with mantle cell lymphoma exhibited an ORR of 92%, including 42% CR, 17% CRu, and 33% PR. Median DR for the mantle cell population was 19 months (95% CI, 12 to 24 months).

DISCUSSION

Bendamustine is a cytotoxic compound that acts primarily as an alkylating agent inducing extensive and durable DNA breaks. Its benzimidazole ring structure may explain differences between bendamustine and other alkylating agents, such as slower repair of damaged DNA, activity against multidrug-resistant cells, and only partial cross resistance with other alkylating agents.[8] In this study, the response to bendamustine plus rituximab was high, with an ORR of 92% and a CR rate of 41%. These responses were also durable, with a median duration of 21 months. CR occurred less frequently in patients previously treated with rituximab compared with rituximab-naive patients (35% *v* 48%, respectively). One additional notable finding was a high rate of durable responses in the mantle cell lymphoma patients (ORR, 92%; median DR, 19 months).

These results are comparable to those from a German study conducted in a similar population of lymphoma patients receiving

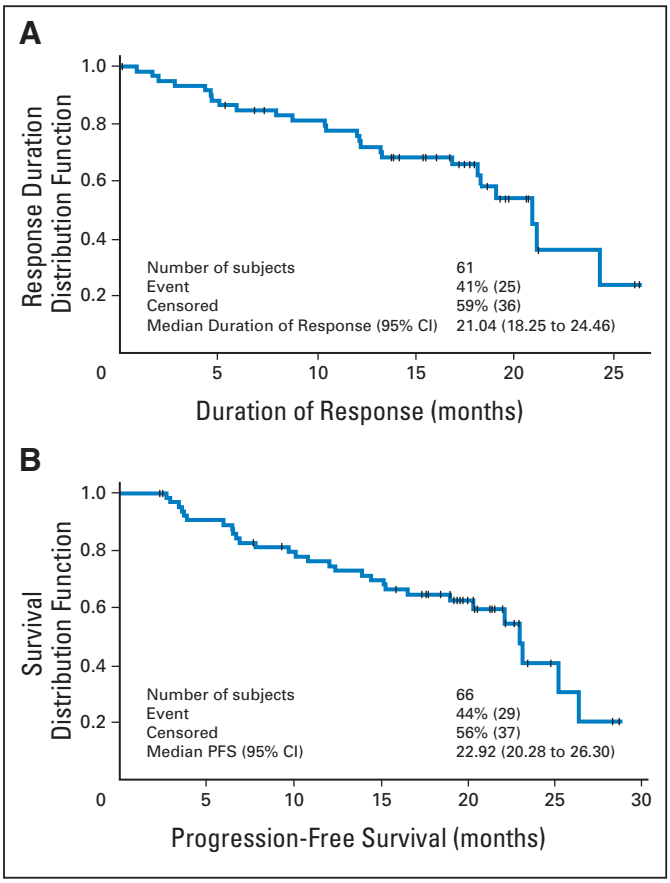

Fig 1. Kaplan-Meier curves of (A) duration of response to bendamustine plus rituximab in patients exhibiting a complete, complete unconfirmed, or partial response (n = 61) and (B) progression-free survival (PFS) in all patients (N = 66) receiving treatment with bendamustine and rituximab. Patients who were alive and without disease progression or lost to follow-up at the time of analysis were censored at the last assessment for tumor response.

bendamustine plus rituximab.[15] In that study, previous rituximab was not allowed, whereas in the present study, 56% of patients received prior rituximab. Otherwise, the overall history of previous treatment was similar in the two study populations. In the German study (N = 63), ORR was 90% (*v* 92% in the present study), with a median PFS time of 24 months (*v* 23 months in the present study). The CR rate was higher in the German study compared with the present study (60% *v* 41%, respectively), possibly because of differences in prior rituximab treatment. The safety profile of combined bendamustine-rituximab was also similar in the two studies, with a relatively low incidence of grade 3 or 4 hematologic and nonhematologic adverse events.

Bendamustine has also been administered in combination with mitoxantrone and rituximab.[18] In a study of 54 patients with relapsed and refractory CD20-positive indolent malignancies, mitoxantrone (10 mg/m^2 on day 1) and bendamustine (90 mg/m^2 on days 1 and 2) were followed by four weekly doses of rituximab (375 mg/m^2); bendamustine and mitoxantrone were repeated every 4 weeks for five additional cycles. Grade 3 or 4 adverse events included anemia (7%), thrombocytopenia (14%), and leukopenia (50%); no cardiotoxicity was reported. ORR was 96%, including a CR rate of 41%, similar to the present study. Among patients with indolent lymphoma, median time to progression had not been reached after a median observation time of 27 months.

Results from the present study compare favorably with other established treatments for relapsed indolent lymphoma, including rituximab monotherapy and radioimmunotherapy.[19,20] A recent phase III study of CHOP versus rituximab plus CHOP (R-CHOP) in 474 patients with relapsed/refractory follicular lymphoma showed an ORR of 85% for R-CHOP and a CR rate of 29%.[21] PFS for patients treated with R-CHOP was longer than in the present study, but the comparison is complicated by the use of rituximab maintenance after the completion of R-CHOP and because prior treatment with rituximab was not allowed.

The efficacy outcomes associated with bendamustine and rituximab in the subgroup of patients with mantle cell lymphoma are particularly good for this relatively poorly responsive population after initial relapse. Although the number of patients treated is small (n = 12), the ORR of 92% and median PFS time of 23 months compare favorably with the ORR of 58% and median PFS time of 8 months reported for 24 relapsed mantle cell patients treated with rituximab plus fludarabine, cyclophosphamide, and mitoxantrone regimen.[22]

Given the efficacy of bendamustine demonstrated in the relapsed setting, Rummel et al[23] are currently comparing the bendamustine plus rituximab combination and R-CHOP as initial therapy in a multicenter, randomized phase III trial. Interim results in 315 assessable patients with indolent (80%) and mantle cell (20%) lymphomas show similar rates of response (ORR, 93% for bendamustine plus rituximab *v* 94% R-CHOP) between treatments. After a median 18-month observation period, median PFS time is 39 months for R-CHOP–treated patients and has not been reached for bendamustine/rituximab-treated patients. Bendamustine plus rituximab, compared with R-CHOP, was associated with lower incidences of myelosuppression (grade 3 or 4 leukopenia, 16% *v* 41%, respectively), infection (23% *v* 41%, respectively), and alopecia (0% *v* 94%, respectively).

Tolerability of treatment is an important consideration for patients with relapsed lymphoma. Large studies of alternative combination regimens, such as rituximab plus fludarabine, cyclophosphamide, and mitoxantrone[22]; R-CHOP[21]; and rituximab plus cyclophosphamide, vincristine, and prednisone,[24] demonstrate frequencies of nonhematologic toxicities similar to the bendamustine and rituximab combination with two exceptions. First, severe nausea and vomiting were not observed in the present study but were reported for a small proportion of chemotherapy-naive patients receiving R-CHOP for follicular NHL.[25] Whether this difference is meaningful is not clear because antiemetic use may differ between protocols. A second major difference was in the incidence of alopecia. This was reported for only one patient in the present study (grade 1), whereas the majority of patients receiving R-CHOP experience grade 3 or 4 alopecia.[25]

The hematologic toxicities observed in the present study seem similar to those reported for other rituximab plus chemotherapy combinations, although no comparative studies have been conducted. The observed incidence of grade 3 or 4 neutropenia and thrombocytopenia is lower than in the previous study of bendamustine monotherapy in rituximab-refractory indolent NHL patients.[10] This finding may be related to a higher dose-intensity of the monotherapy regimen (120 mg/m^2 on days 1 and 2 every 21 days) and a more heavily pretreated population with more advanced disease. However, the incidence of grade 3 or 4 lymphopenia was higher with combined bendamustine-rituximab compared with bendamustine alone, likely reflecting the contribution of rituximab to the combination regimen.

Results of this study support the efficacy of combined bendamustine and rituximab for patients with relapsed indolent and mantle cell NHL. This combination elicited durable responses without evidence of additive toxicity and a low incidence of severe and life-threatening events. High response rates were observed in all subgroups; response rates and PFS for patients with mantle cell lymphoma were similar to those in patients with follicular NHL. This combination represents an effective and tolerable treatment option in patients with relapsed indolent and mantle cell NHL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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