VOLUME 23 · NUMBER 15 · MAY 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bendamustine Plus Rituximab Is Effective and Has a Favorable Toxicity Profile in the Treatment of Mantle Cell and Low-Grade Non-Hodgkin's Lymphoma

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Submitted August 17, 2004; accepted February 15, 2005.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2315-3383/$20.00

DOI: 10.1200/JCO.2005.08.100

ABSTRACT

Purpose
The aim of this multicenter-study was to evaluate the progression-free survival, response rate and toxicity of the combination of bendamustine and rituximab (BR) in patients with mantle cell or low-grade lymphomas in first to third relapse or refractory to previous treatment.

Patients and Methods
A total of 245 courses (median, four courses per patient) were administered to 63 patients. Bendamustine was given at a dose of 90 mg/m^2 as a 30-minute infusion on days 1 and 2, combined with 375 mg/m^2 rituximab on day 1, for a maximum of four cycles every 4 weeks. Histologies were 24 follicular, 16 mantle cell, 17 lymphoplasmacytoid, and six marginal zone lymphoma.

Results
Fifty-seven of 63 patients responded to BR, corresponding to an overall response rate of 90% (95% CI, 80% to 96%) with a complete remission rate (CR) of 60% (95% CI, 47% to 72%). The median time of progression-free survival was 24 months (range, 5 to 44+ months), and the median duration of overall survival has not yet been reached. In mantle cell lymphomas, BR showed a considerable activity, achieving a response rate of 75% (95% CI, 48% to 93%) with a CR rate of 50%. Myelosuppression was the major toxicity, with 16% grade 3 and 4 leukocytopenia. Thrombocytopenia was rare, with only 3% grade 3 and 4.

Conclusion
These results demonstrate that the BR combination is a highly active regimen in the treatment of low-grade lymphomas and mantle cell lymphomas.

J Clin Oncol 23:3383-3389. © 2005 by American Society of Clinical Oncology

INTRODUCTION

Low-grade non-Hodgkin's lymphoma (lgNHL) consists of a variety of different histologic subtypes based on their putative cell of origin. These malignancies, however, are united by their indolent natural history and the inability to achieve cure through conventional therapeutic approaches. Due to the slow-growing nature of the neoplastic cells, patients with lgNHL can often survive for more than a decade with their disease. During this period, they will be exposed to multiple treatment courses. Typically, patients with low-grade disease are very responsive to frontline chemotherapy, usually with alkylating agents. Unfortunately, multiple relapses are inevitable, and ultimately, no regimen or treatment strategy offers a distinct survival benefit over another.

In contrast, patients with mantle cell lymphomas (MCL) generally experience a more aggressive course, with rapid disease progression. Therapeutic options for this

subgroup are limited, as many patients with MCL quickly become refractory to currently available treatments. Regardless of treatment type, median survival of patients with MCL ranges from 3 to 4 years.

Until treatment strategies that confer a survival advantage are developed, the goal in treating such patients is to prolong remission while minimizing toxicity. One such approach involves the use of monoclonal antibodies. The genetically engineered monoclonal antibody rituximab is directed against the CD20 antigen expressed on the surface of both malignant and normal B cells. The antigen is present in the majority of patients with B-cell NHL (93%), as demonstrated in expression studies. Following administration of rituximab, B cells are rapidly depleted through antigen-dependent cellular cytotoxicity, complement-dependent cytotoxicity, apoptosis, and inhibition of cell growth.[1]

A number of important features unique to rituximab contribute to the rationale using the monoclonal antibody with chemotherapy for the treatment of lgNHL. Direct antitumor effects of rituximab in vitro have been demonstrated, as well as single-agent activity.[2] The potential of combined immunochemotherapy was first evaluated in vitro by Demiden et al in 1997.[3] They demonstrated the sensitizing effect of pretreatment with rituximab in lymphoma cell lines. Thus, lymphoma cells that were once resistant to cytotoxic agents regained responsiveness following exposure to rituximab. Similar results were obtained with the combination of fludarabine and rituximab, demonstrating synergistic effects between these agents in a follicular lymphoma cell line resistant to the cytotoxic activity of either drug alone.[4] Thus, it seemed that immunochemotherapy could enhance the effectiveness of lymphoma treatment. Since then, numerous trials evaluating combination therapy have demonstrated encouraging results.

In this study, bendamustine, a nitrogen mustard compound, was administered in combination with rituximab. The bendamustine molecule contains a nitrogen mustard group and is therefore chemically related to the alkylating agents chlorambucil and cyclophosphamide. The benzene ring in the chlorambucil molecule is replaced by a benzimidazole ring, which may act as a purine analog. Water solubility is conferred by the addition of a hydrochloride residue to the butyric acid side-chain (Fig 1). Between 1971 and 1992, bendamustine was available in the German Democratic Republic as Cytostasan and was shown to be an effective treatment for chronic lymphocytic leukemia,[5] NHL,[6] Hodgkin's disease,[7] multiple myeloma, and metastatic breast cancer. Bendamustine exhibits similar, if not greater, potency compared with cyclophosphamide, and has been shown in vitro to be active against cell lines that are resistant to other alkylating agents. Its activity profile, when compared with other nitrogen mustards in the National Cancer Institute human 60 cell line assay, appears unique. In addition, no cross-

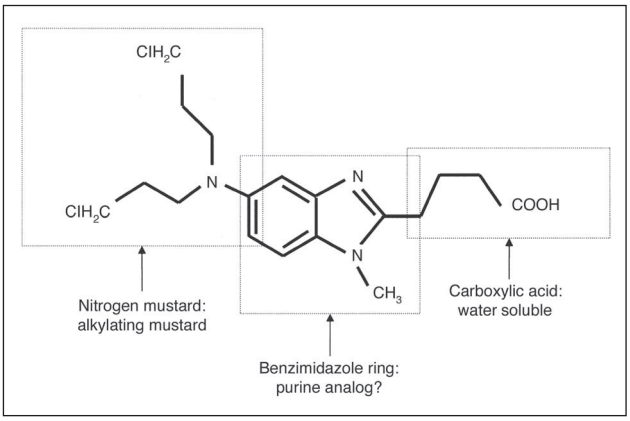

Fig 1. Bendamustine hydrochloride.

resistance with other nitrogen mustards has been observed in NHL cell lines.[8] Preclinical animal models demonstrate a synergistic interaction when bendamustine and rituximab are administered together. Specifically, when both agents were administered to severe combined immunodeficient (SCID) mice with Daudi xenografts, combination treatment had a more profound effect on inhibiting tumor growth than either agent alone.[9] Similar effects were obtained with follicular lymphoma cell lines and in ex vivo cells from patients with B cell chronic lymphocytic leukemia (B-CLL).[10] Furthermore, the in vitro addition of rituximab has been shown to reduce the dose of bendamustine required to induce apoptosis in both the DOHH-2 and WSU NHL cell lines, and ex vivo B-CLL cells.[11]

Based on these results, the present trial was initiated to evaluate bendamustine in combination with rituximab in the treatment of lgNHL and MCL.

PATIENTS AND METHODS

This was an open label, phase II, multicenter trial. It was approved by the ethics committee at the University Hospital of Frankfurt. All patients gave written informed consent. The study was performed in keeping with good clinical practice.

Eligibility Criteria

Patients older than 18 years of age with a WHO performance status of ≤ 2 were eligible if they had a histologically confirmed diagnosis of MCL or lgNHL, including the following subtypes: follicular (grade 1 and 2), lymphoplasmacytoid (Waldenström's macroglobulinemia), and marginal zone. Lymphoid neoplasms were classified according to the WHO classification.[12] All lymph node, bone marrow, and other specimen biopsies were reviewed by one of five German referral centers for hematopathology. Patients were required to have received at least one prior chemotherapy (one to three were allowed) and were permitted to be refractory to previous treatment, which was defined as no response or disease progression following at least three chemotherapy cycles. Prior treatment with rituximab was not allowed. Patients were required to have at least one of the following criteria to demonstrate need for treatment: impairment of hematopoiesis (hemoglobin $<$ 11 g/dL, granulocyte

count $< 1.5 \times 10^9$/L, platelet count $< 100 \times 10^9$/L), presence of "B" symptoms, other disease-related symptoms such as bulky disease with impingement on internal organs, or progressive disease. Patients with inadequate organ function (liver, kidney, or heart) were excluded from the study.

Pretreatment Evaluation

All patients underwent pretreatment screening, which included a physical examination; routine CBC; serum chemistry evaluation; serum immunoelectrophoresis and determination of immunoglobulin levels; chest x-ray; computed tomography scan of the chest, abdomen, and pelvis; sonography of the abdomen; bone marrow aspiration and biopsy. If clinically relevant, endoscopy of the gastrointestinal tract was performed.

Study Design

Patients received four cycles of treatment with bendamustine plus rituximab (BR), with bendamustine administered over a 2-day period, 1 day after rituximab. Cycles were repeated every 4 weeks. In addition, single doses of rituximab were administered 1 week before the first cycle and 4 weeks after the last cycle. Rituximab was given as an intravenous infusion at a dose of 375 mg/m^2 per day according to standard procedure. Bendamustine was administered intravenously at a dose of 90 mg/m^2 per day during a 30-minute time period (Fig 2). No prophylactic antibiotic treatment, including *Pneumocystis carinii* pneumonia prophylaxis was given. Growth factors were permitted, but on a restricted basis.

Criteria for Response and Toxicity

A complete remission (CR) was defined as the disappearance of all measurable disease (lymph node size < 1 cm) and return to normal blood counts. Normal blood counts were defined as hemoglobin greater than 11 g/dL, granulocytes $\geq$ 1,500/mm^3, and platelets greater than 100,000/mm^3. Bone marrow lymphocyte percentage was to be less than 30%, and bone marrow biopsy was to show no evidence of abnormal lymphoid infiltration. Partial response (PR) required a more than 50% reduction of measurable disease and a more than 50% improvement of all abnormal blood counts. Progression was defined as a greater than 25% increase in measurable disease, with one of the following criteria: more than 25% increase in circulating lymphocytes above remission values; corresponding enlargement of lymph nodes, liver, or spleen; appearance of new enlarged lymph nodes; reappearance or increasing infiltration in the bone marrow; or recurrence of B symptoms.

Treatment-related toxicity was evaluated according to WHO criteria. CBCs including differential were performed weekly. Duration of remission was assessed every 3 months until relapse, through clinical, radiologic, and sonographic examinations as well as blood count assessments. Bone marrow biopsy was repeated every 6 months as part of the response evaluation procedure.

Statistical Methods

The primary objective of the study was to conduct a feasibility study and to compare the progression-free survival (PFS) from treatment with BR with the PFS from the patients' previous treatment. Secondary objectives included the overall response rate (ORR) to BR, evaluation of acute and late toxicity, and overall survival (OS).

PFS and OS were calculated from the first day of treatment until disease progression (PFS) or patient death (OS), respectively. Patients who died without evidence of lymphoma were censored at the time of death. Survival curves were estimated by the Kaplan-Meier method, and the log-rank test was applied for comparison. Tests were two-sided, and the level of statistical significance was a P value less than .05.

RESULTS

Patient Characteristics and Disposition

Sixty-three patients were enrolled on the study between July 2000 and July 2003 at 12 participating institutions. The median age of the 40 men and 23 women was 64 years (range, 40 to 81 years). One patient had stage II disease, 12 patients had stage III disease, and 50 patients had stage IV disease. Forty-three patients had received one previous treatment, 12 had received two prior treatments, and eight had three prior treatments. Nineteen of 63 (30%) were refractory to their last treatment. Prior treatment included cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or CHOP-like regimens (25 cases); purine analogs alone or in combination with cyclophosphamide or mitoxantrone (25 cases); chlorambucil plus mitoxantrone plus prednisone (MCP; 17 cases); cyclophosphamide, vincristine, and procarbazine, or chlorambucil (four cases); and radiotherapy (four cases). According to the International Prognostic Index,[13] 46 patients (73%) were in the low or low-intermediate risk group and 17 patients (27%) were in the high-intermediate or high risk group. The 24 patients with follicular lymphoma were also classified according to the Follicular Lymphoma International Prognostic Index[14]:

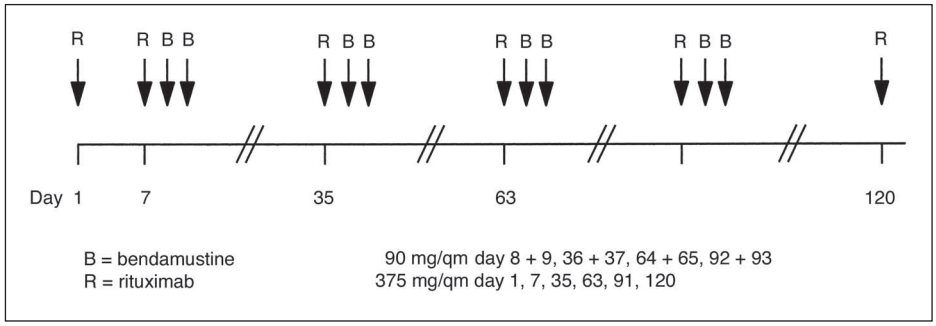

Fig 2. Treatment schedule.

four patients (17%) were in the low-risk group, six patients (25%) in the intermediate-risk group, and 14 patients (58%) in the poor-risk group.

Sixteen patients with MCL, seven of them refractory to previous treatment, were enrolled on the study. Prior treatment included cladribine plus mitoxantrone in four cases; MCP in seven cases; CHOP in five cases; and bleomycin, bendamustine, fludarabine + epirubicin, and COP in one case each. The median age of the 13 men and three women was 66 years (range, 49 to 81 years). Five patients had stage III disease; 11 patients had stage IV disease with bone marrow involvement, and three had additional involvement of the upper and lower gastrointestinal tract.

The characteristics of the 63 patients assessable for response and toxicity are listed in Table 1. A total of 245 cycles of therapy were administered. All but four patients received all four cycles of treatment. Two patients discontinued treatment after two cycles: one owing to ongoing leukopenia and one, who was in partial remission, owing to personal reasons. Two patients received three cycles of treatment. One discontinued due to lack of efficacy and the other for unknown reasons. No dose reductions were required for any patient. Median duration of follow-up is 20 months.

Table 1. Patient Characteristics

	Patients	
	No.	%
Patients	63	
Male-female ratio	40:23	
Age, years		
Median	64	
Range	40-81	
Stages		
II	1	2
III	12	19
IV	50	79
Prior therapy, No. of prior treatments		
1	43	68
2	12	19
3	8	13
Refractory to prior treatment	19	30
Histology		
Follicular	24	38
Mantle cell	16	25
Lymphoplasmacytoid	17	27
Marginal zone (MALT)	6	10
Performance status > 2	1	2
Extranodal involved sites > 1	8	13
LDH > 240 U/L	15	24
Beta-2-microglobulin > 2.0 mg/dL*	30	48
"B" symptoms	33	52
Bone marrow involved	45	71
Gastrointestinal tract involved	4	6
Bulky disease (≥ 5 cm)	35	56
Prognostic groups for all patients (IPI)		
Low-risk (1 risk factor)	14	22
Low-intermediate–risk (2 risk factors)	32	51
High-intermediate–risk (3 risk factors)	9	14
High-risk (4-5 risk factors)	8	13
Prognostic groups for follicular (FLIPI; n = 24)		
Low-risk (0-1 risk factor)	4	17
Intermediate-risk (2 risk factors)	6	25
Poor-risk (3-5 risk factors)	14	58

Abbreviations: MALT, mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase; IPI, International Prognostic Index; FLIPI, Follicular Lymphoma IPI.
*Data assessable for 44 patients.

Response

The ORR in all 63 patients was 90% (95% CI, 80% to 96%), with a CR rate of 60% (95% CI, 47% to 72%) and a PR rate of 30% (95% CI, 19% to 43%; Table 2). Twelve of 16 patients with MCL achieved an ORR of 75% (95% CI, 48% to 93%). CR occurred in eight patients (50%; Table 2).

Median PFS for all patients is 24 months (range, 5 to 44+ months) with 41 patients still in remission. Median PFS is shown for all patients in Figure 3. Sixteen patients have relapsed to date after 5 to 26 months. Median PFS was significantly longer ($P < .0001$) in this study (24 months) as compared with PFS for the patients' previous treatments (9 months). Figure 4 displays Kaplan-Meier graphs depicting both curves. The median PFS for MCL patients was 18 months, with six patients still in remission (range, 6 to 22+ months), whereas the median PFS for patients with follicular and lymphoplasmacytoid lymphomas have not yet been reached.

Eleven patients have died to date: two patients with MCL, one patient with leukemic marginal zone lymphoma, who were refractory to the previous treatment regimens, to BR, and to subsequent salvage therapies; six patients due to progressive disease suffering from recurrent relapses; one 81-year-old male patient due to myocardial infarction with MCL being in partial remission for 14 months; and one 64-year-old male patient due to infectious complications with a pre-existing hypogammaglobulinemia in partial remission for 9 months.

The OS curve for all patients is shown in Figure 5. The median duration of survival has not yet been reached, with an actuarial survival rate of 55% at 48 months. In a univariate analysis, survival was statistically different for age (≤ 60 $v > 60$ years) ($P = .018$), while no statistical difference was observed for lactate dehydrogenase ($\leq$ 240 U/L $v >$ 240 U/L; $P = .18$) and for beta-2-microglobulin ($P = .11$).

Toxicity

Nonhematologic toxicity was generally mild and mainly consisted of WHO grade 1 and 2 events (Table 3). Alopecia was minimal; only two patients experienced grade 1 alopecia. There were no treatment-related deaths. Data on blood counts were available for 216 of 245 administered cycles. Leukopenia was the most common side effect, with grade 3 and 4 events occurring in 35 (16%) of 216 cycles.

Table 2. Treatment Results

Entity	No. of Patients	CR		PR		ORR	
		No.	%	No.	%	No.	%
Follicular	24	17	71	6	25	23	96
Small lymphocytic	17	9	53	8	47	17	100
Mantle cell	16	8	50	4	25	12	75
Marginal zone	6	4	67	1	17	5	83
Total	63	38	60	19	30	57	90

Abbreviations: CR, complete remission; PR, partial response; ORR, overall response rate.

There was no evidence of cumulative myelosuppression based on leukocytes. Two bacterial pneumonias, two localized herpes zoster infections, two events of herpes labialis, and four episodes of diarrhea were observed. Grade 3 or 4 thrombocytopenia and anemia were rare, occurring in 3% and 1% of assessable cycles, respectively. Mild nausea (grade 1) was seen in 43% of cycles; some patients experienced mild but continuous nausea for 1 week following treatment. Besides the one patient with fatal infectious complications in partial remission for 9 months, no further significant infections have been observed since the completion of therapy in patients with an ongoing response, or between cessation of therapy and initiation of salvage therapy in relapsing patients. No growth factor was administered during the study.

DISCUSSION

The present study represents the first study assessing efficacy and toxicity of bendamustine in combination with rituximab. The rationale behind the dosage schedule (Fig 2) was to ensure that patients had high levels of rituximab before chemotherapy, thereby chemosensitizing potentially resistant malignant cells. The rationale for the combined administration of 4 cycles of bedamustine plus rituximab was based on non–cross-resistant mechanisms of action, non-overlapping toxicities, and in vitro synergy between both agents.[11] The treatment duration was limited to four cycles to minimize toxicity in these previously treated patients with possibly impaired bone marrow reserve. The last rituximab infusion was administered to eliminate residual malignant B lymphocytes after having achieved maximal tumor reduction. It is unclear, however, whether such a schedule represents an optimal dosing regimen. Results of ongoing and further studies are required to make this determination.

Bendamustine has been investigated both as a single agent and in combination with other cytotoxic agents in patients with NHL.[15,16] A recent study conducted by Heider et al in 58 patients with relapsed lgNHL studied single-agent bendamustine at a dose of 120 mg/m^2 on days 1 and 2 every 3 weeks until disease progression. The ORR was 73% with

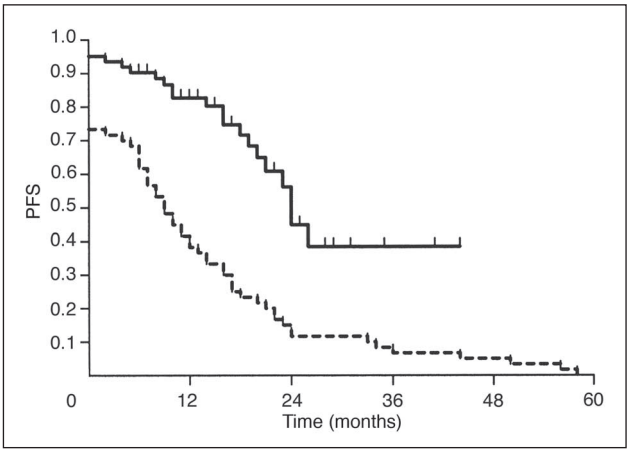

Fig 4. Comparison of progression-free survival (PFS) with bendamustine plus rituximab (BR) and previous treatment for all patients. Median PFS for BR 24 months, median PFS for previous treatment 9 months ($P < .0001$).

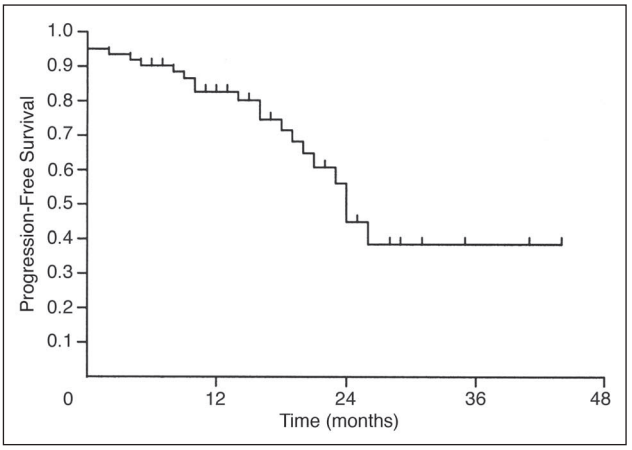

Fig 3. Progression-free survival for all patients.

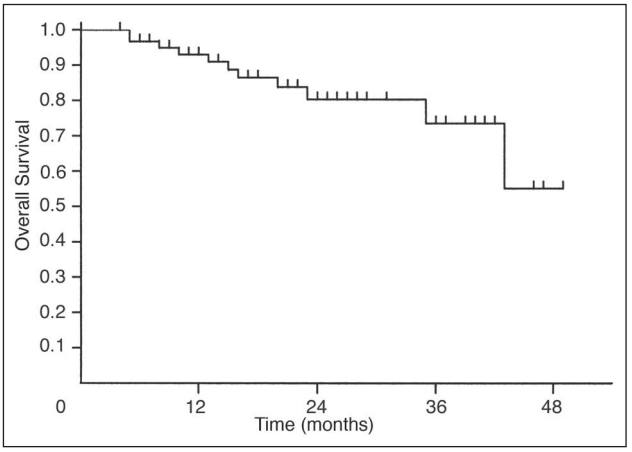

Fig 5. Overall survival for all patients.

Table 3. Toxicity Based on Number (and percentage) of All Cycles

	WHO Grade					
	0	1	2	3	4	3/4 (%)
Leukocytes (n = 216)	87	47	47	32	3	16
Thrombocytes (n = 214)	173	19	15	6	1	3
Anemia (n = 199)	169	23	5	2	—	1
Nausea/vomiting	136	102	—	—	—	
Allergic reaction	230	9	—	—	—	
Cardiotoxicity	239	—	—	—	—	
Neurotoxicity	239	—	—	—	—	
Alopecia	235	4	—	—	—	

NOTE. All data are No. of cycles except where indicated.

11% CRs. The median duration of response was 16 months. Toxicity was generally mild with only three patients experiencing grade 3 leukopenia and no grade 4 events.[17]

Many chemoimmunotherapy combinations have been conducted since the approval of rituximab. The first such trial, conducted by Czuczman et al, studied the combination of CHOP chemotherapy with rituximab (R-CHOP) in 38 patients with lgNHL, of whom 31 patients were previously untreated. The ORR was 95% with 55% CRs.[18] The median duration of remission has not been reached after 50 months of follow-up.[19] More recently, a randomized multicenter study conducted by Hiddeman et al reported an ORR of 97%, with 21% CRs for 201 patients with previously untreated follicular lymphoma treated with R-CHOP. Follow-up was too short to report a median response duration; however, the time to treatment failure was 2.6 years in the CHOP arm, whereas it was not yet reached for R-CHOP.[20]

Other combination regimens, such as those with fludarabine plus rituximab, have reported similar high response rates, though at the cost of unexpected significant hematologic toxicity, in particular neutropenia and prolonged cytopenia. Czuczman et al reported the results of a study of 40 patients with previously untreated lgNHL treated with fludarabine in combination with rituximab. They observed a 93% ORR with 80% CR; however, 40% of patients experienced grade 4 neutropenia, and 15% experienced febrile neutropenia.[19] Fewer studies with combined immunochemotherapy have been reported in the relapsed indolent population. Forstpointner et al reported a 79% ORR using rituximab in combination with fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in 66 patients with relapsed follicular lymphoma or MCL.[21] Of note, the ORR was 58% in 24 patients with MCL. Patient characteristics of this cohort treated with R-FCM were comparable to those in the present study of BR, with a median age of 64 years in both studies, and 80% of patients had a remission to prior therapy in the R-FCM group, versus 70% in the BR group. Other prognostic parameters did also not differ significantly, with a bone marrow infiltration in 64% and 71%, and an elevated LDH in 25% and 24% of the R-FCM and the BR group, respectively. Considering the achieved median PFS of 16 months for all 66 patients, and 8 months for the subgroup of 24 MCL patients treated with R-FCM,[21] our presented data with BR are very encouraging, demonstrating a median PFS of 24 months for all patients and 18 months for the patients with MCL.

The subset of patients with MCL have uniformly proven to be more refractory to therapy. With R-CHOP, Howard et al achieved an ORR of 81%, with 33% CRs in 40 patients with previously untreated MCL; however, the median progression-free survival was only 16 months.[22] Similar results were reported recently by Lenz et al in 62 patients with untreated MCL treated with R-CHOP, achieving an ORR of 94%, with a median PFS of 19 months.[23] Romaguerra et al have achieved better results with their single-institution experience using the combination Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen with rituximab. They report a CR rate of 88% but at the cost of severe hematologic toxicity (60% grade 4) and a high incidence of infection.[24]

Taken in this context, the results of the current study evaluating the combination of bendamustine and rituximab compare favorably with these historic results. The patient population consisted of patients with both relapsed lgNHL and MCL. The ORR was 96% with 71% CRs in those patients with follicular lymphomas, and for patients with relapsed MCL the ORR was 75% with 50% CRs. These high response rates were achieved with minimal toxicity and only four cycles of chemotherapy. Only 16% of cycles were complicated by grade 3 or 4 leukocytopenia, demonstrating a favorable toxicity profile in comparison to the R-FCM regimen, with 54% grade 3 or 4 leukocytopenia being observed.[21] Only two cases of serious infection (pneumonia) were observed—one in a patient 6 months after completion of therapy. No patients experienced alopecia, a toxicity that is severe with other alkylator- or anthracycline-containing regimens, and of particular importance, no organ toxicity has been observed. The responses were also durable, with a median duration of PFS of 24 months, which was significantly longer than that experienced by these patients with their prior chemotherapy.

The BR combination therefore offers the potential for an effective new regimen without the toxicity associated with other chemoimmunotherapy combinations. Further studies, however, need to be performed to replicate these findings. Several ongoing multicenter trials are underway that intend to confirm and extend these observations. A phase II trial is being conducted in the United States and Canada studying the BR combination in a population of patients similar to that of this trial. A second phase II trial explores the efficacy and safety of single-agent bendamustine in rituximab-refractory patients.

Based on the encouraging results obtained with BR in this phase II study, we initiated two phase III trials that compare BR with established chemoimmunotherapy

regimens. One trial compares BR versus *R*-CHOP in patients with previously untreated lgNHL or MCL. The objective of this ongoing trial is to demonstrate a noninferiority of BR in comparison to *R*-CHOP with respect to efficacy, but to show a more favorable toxicity profile. The second ongoing trial compares the BR combination to fludarabine/rituximab in patients with relapsed lgNHL or MCL. These studies should provide considerable guidance for the appropriate role of bendamustine in the treatment of lgNHL and MCL.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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