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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.

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