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ORIGINAL REPORT

# Bendamustine in Patients With Rituximab-Refractory Indolent and Transformed Non-Hodgkin's Lymphoma: Results From a Phase II Multicenter, Single-Agent Study

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## ABSTRACT

### Purpose
Bendamustine hydrochloride is an alkylating agent with novel mechanisms of action. This phase II multicenter study evaluated the efficacy and toxicity of bendamustine in patients with B-cell non-Hodgkin's lymphoma (NHL) refractory to rituximab.

### Patients and Methods
Patients received bendamustine 120 mg/m$^2$ intravenously on days 1 and 2 of each 21-day cycle. Outcomes included response, duration of response, progression-free survival, and safety.

### Results
Seventy-six patients, ages 38 to 84 years, with predominantly stage III/IV indolent (80%) or transformed (20%) disease were treated; 74 were assessable for response. Twenty-four (32%) were refractory to chemotherapy. Patients received a median of two prior unique regimens. An overall response rate of 77% (15% complete response, 19% unconfirmed complete response, and 43% partial) was observed. The median duration of response was 6.7 months (95% CI, 5.1 to 9.9 months), 9.0 months (95% CI, 5.8 to 16.7) for patients with indolent disease, and 2.3 months (95% CI, 1.7 to 5.1) for those with transformed disease. Thirty-six percent of these responses exceeded 1 year. The most frequent nonhematologic adverse events included nausea and vomiting, fatigue, constipation, anorexia, fever, cough, and diarrhea. Grade 3 or 4 reversible hematologic toxicities included neutropenia (54%), thrombocytopenia (25%), and anemia (12%).

### Conclusion
Single-agent bendamustine produced durable objective responses with acceptable toxicity in heavily pretreated patients with rituximab-refractory, indolent NHL. These findings are promising and will serve as a benchmark for future clinical trials in this novel patient population.

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## INTRODUCTION

In recent decades, the most dramatic clinical advance for patients with indolent non-Hodgkin's lymphoma (NHL) has been the anti-CD20 monoclonal antibody rituximab. Rituximab has significant activity as a single agent in both de novo[1] and relapsed/refractory disease[2] and dramatically improves response rates, progression-free survival (PFS), and possibly overall survival when combined with chemotherapy.[3-5] Recent studies also suggest clinical benefit from extended schedules of rituximab[6] and maintenance rituximab after chemotherapy.[7] Indeed, improved overall survival for patients with follicular lymphoma has recently been reported.[8,9] A prospective database in follicular lymphoma suggests that the vast majority of patients in the US are treated at diagnosis with rituximab alone or, more frequently, in combination with chemotherapy.[10]

Despite this success, indolent lymphoma remains incurable with standard therapy and eventually becomes refractory to rituximab, often within 3 years.[11] Both iodine-131 tositumomab and ibritumomab tiuxetan have demonstrated clinical activity in patients refractory to standard single-agent rituximab.[12,13] Current standard treatment programs administer rituximab in combination with chemotherapy; thus, many rituximab-refractory patients are also refractory to standard chemotherapy. No study to date has prospectively evaluated outcomes of subsequent therapies in this growing group of patients.

Bendamustine (Treanda; Cephalon Inc, Frazer, PA) is an alkylating agent, with a unique chemical

structure containing a benzimidazole ring. It shows only partial in vitro cross-resistance with other alkylating agents[14] and is clinically well tolerated. Bendamustine has demonstrated clinical activity in patients with relapsed indolent NHL, including those refractory to other alkylating agents.[15,16] Herein, we describe outcomes of a phase II multicenter study evaluating bendamustine in patients with rituximab-refractory indolent or transformed NHL, including patients refractory to alkylating-agent or purine-analog-based chemotherapy in combination with rituximab. Bendamustine provided a high response rate, including durable responses. This study will serve as a benchmark for future studies evaluating novel agents for indolent NHL refractory to rituximab.

## PATIENTS AND METHODS

### Study Design and Objectives

This multicenter trial was designed to investigate the efficacy and safety of bendamustine in rituximab-refractory patients with indolent or transformed B-cell NHL. The primary end point was overall response rate (ORR).[17] Secondary end points included safety, PFS, and duration of response. The protocol was approved by the institutional review board at each site, and written consent was obtained before enrollment.

### Eligibility

Patients 18 years of age or older with a WHO performance status no greater than 2 were eligible if they had an initial diagnosis of indolent NHL (including follicular, small lymphocytic, lymphoplasmacytoid, and marginal zone lymphoma) or indolent disease that transformed to a more aggressive subtype, as previously described.[18] Patients were required to have received prior rituximab (alone or combined with other treatment) and were considered refractory to (defined as no response, or progression within 6 months of completing therapy) or intolerant of continued rituximab. Patients were allowed a maximum of three prior unique chemotherapy regimens, including autologous stem-cell transplantation (ASCT). A unique regimen was defined as a new combination or agent. Baseline laboratory parameters included an absolute neutrophil count (ANC) of at least 1,000 cells/mm$^3$, platelet count of at least 100,000 cells/mm$^3$, and adequate renal and hepatic function.

Patients were excluded for the following conditions: previous chemotherapy/immunotherapy within 3 weeks before study entry or failure to recover from associated adverse events; investigational treatment within 28 days; hematopoietic growth factor treatment within 14 days (chronic erythropoietin was allowed); therapeutic doses of systemic steroids; allogeneic transplant; concurrent active malignancy (except excised nonmelanoma skin cancer or in situ cervical or bladder cancer); CNS lymphoma; serious infection or other medical or psychiatric condition that might interfere with achieving study objectives; pregnancy or lactation; or expected survival less than 3 months.

### Treatment

Baseline evaluation included a history, physical examination, radiographic imaging, routine laboratory studies, and an EKG. A baseline bone marrow was performed at the discretion of each participating physician. Bendamustine was infused at a dose of 120 mg/m$^2$ intravenously over 30 to 60 minutes on days 1 and 2 every 3 weeks. Patients were treated for six cycles, as long as response or stable disease was observed. Treatment could be continued for up to six additional cycles, until disease progression or unacceptable toxicity occurred. The development of grade 4 hematologic or grade 3/4 nonhematologic toxicities, using National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0, after any cycle led to a dose reduction to 90 mg/m$^2$; if grade 4 hematologic or grade 3/4 nonhematologic toxicities appeared at the reduced dose level, the dose was further reduced to 60 mg/m$^2$. If further toxicity occurred, study treatment was discontinued. Toxicities must have resolved to grade 1 or baseline before beginning the next cycle. ANC must have recovered to at least 1,000 cells/mm$^3$ and platelets to at least 75,000 cells/mm$^3$ by the time of the next cycle.

Concurrent filgrastim or pegfilgrastim therapy was allowed for patients with grade 4 neutropenia lasting 1 week or longer, failure of the WBC to recover to at least grade 1 by the next scheduled dose, or febrile neutropenia in a prior cycle. Primary prophylactic use of growth factors was not allowed.

Treatment was discontinued in patients demonstrating progressive disease, or unacceptable toxicity, or at the discretion of the patient or investigator.

### Criteria for Response and Toxicity

Assessment of response was performed by the investigator after every three cycles of treatment using the same imaging technique used for baseline measurements. Response was defined using the International Workshop NHL criteria.[17] Any patient who otherwise met the criteria for a complete response (CR)/unconfirmed CR (CRu) but did not have a bone marrow biopsy at the time of response was considered a partial response (PR).

PFS was calculated as the number of months from the first dose of study drug to the first documentation of disease progression, death regardless of cause, or change in therapy caused by disease progression, whichever occurred first. Patients who were alive and progression free at the time of final data analysis were excluded at the time of their last assessment. Duration of response was calculated as the number of months from the first documentation of response to documentation of disease progression, death regardless of cause, or change of therapy resulting from disease progression, whichever occurred first. For patients who had not progressed, response duration was measured to the last documented evaluation. If disease progression did not occur by the end of treatment, patients were evaluated every 3 months until progression, up to a maximum of 2 years.

### Statistical Methods

Sample size was determined using the two-stage methodology of Simon, assuming that bendamustine efficacy would be considered promising at an ORR of at least 35%, and unworthy of further study at an ORR less than 20%.[19] In this two-stage design, accrual continued until at least 22 patients were enrolled. If six or more responses were observed, the second stage began and continued until a total of 72 were enrolled.

The primary analysis was performed on all patients who received any amount of bendamustine (N = 76). Patients were classified according to their best overall response: CR, PR, stable disease, or progressive disease. The number and percentage of patients in each response category were summarized, along with a 95% CI. The median duration of response and the median PFS were assessed using the Kaplan-Meier method. The 95% CI was calculated based on the Greenwood confidence bounds on the Kaplan-Meier estimate.

## RESULTS

### Patient Characteristics

Between September 2003 and February 2005, 77 patients were enrolled at 14 institutions. One patient did not receive treatment and was excluded; characteristics of the 76 treated patients are summarized in Table 1. The median age was 63 years (range, 38 to 84 years). Sixty-one patients had indolent B-cell NHL (46 follicular, 12 small lymphocytic lymphoma (SLL), one lymphoplasmacytoid, two marginal zone), and 15 had transformed disease (including 1 Burkitt's lymphoma). Among patients with transformed disease, a mean ($\pm$ standard deviation) of 22.7 $\pm$ 21.4 months had elapsed since transformed disease was diagnosed. Patients with follicular histologies (n = 46) were categorized according to the Follicular Lymphoma International Prognostic Index (FLIPI) as follows: low (26%), intermediate (30%), and high (33%).[20] Sixty-seven patients had advanced-stage disease. Prior treatments included single-agent rituximab, chemotherapy $\pm$ rituximab; single-agent chemotherapy, radioimmunotherapy, ASCT, and external beam radiotherapy (XRT). Patients received a median of two (range, one to five) unique prior chemotherapies.

**Table 1.** Patient Demographics and Disease Characteristics

| Characteristic | No | % |
|---|---|---|
| No. of patients treated | 76 | |
| Sex | | |
| Males | 41 | |
| Female | 35 | |
| Age, years | | |
| Median | 63.0 | |
| Range | 38.0-84.0 | |
| Time since primary diagnosis, months | | |
| Mean | 64.3 | |
| Standard deviation | 53.2 | |
| Disease stage | | |
| II | 9 | 12 |
| III | 23 | 30 |
| IV | 44 | 58 |
| Histology | | |
| Follicular | 46 | 61 |
| Grade 1 | 17 | 22 |
| Grade 2 | 12 | 16 |
| Grade 3 | 7 | 9 |
| Unknown | 10 | 13 |
| Small lymphocytic lymphoma | 12 | 16 |
| Lymphoplasmacytoid/Waldenström's | 1 | 1 |
| Marginal zone | 2 | 3 |
| Transformed disease* | 15 | 20 |
| No. of unique prior therapies† | | |
| Mean | 2 | |
| Range | 1-5 | |
| Prior treatment | | |
| Single-agent rituximab | 58 | 76 |
| CHOP-like chemotherapy ± rituximab | 41 | 54 |
| CVP ± rituximab | 21 | 28 |
| Purine analogue–based combinations ± rituximab | 18 | 24 |
| Salvage chemotherapy‡ ± rituximab | 10 | 13 |
| Single-agent chemotherapy | 31 | 41 |
| Radioimmunotherapy§ | 9 | 12 |
| External beam radiation | 24 | 32 |
| Autologous transplant | 6 | 8 |
| FLIPI Prognostic risk for follicular histologies (n = 46) | | |
| Low risk (0-1 factor) | 12 | 26 |
| Intermediate risk (2 risk factors) | 14 | 30 |
| High risk (3-5 risk factors) | 15 | 33 |
| Unknown | 5 | 11 |

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; FLIPI, Follicular Lymphoma International Prognostic Index.
*Defined as indolent disease that had transformed to a more aggressive subtype, such as diffuse large B-cell or Burkitt's lymphoma.
†Patients receiving multiple courses of the same regimen were counted once.
‡Salvage chemotherapy included platinum-based combinations.
§All patients received yttrium-90 ibritumomab tiuxetan.

Of the 76 patients who were treated, 51 were refractory to single-agent rituximab, 18 were refractory to a rituximab-chemotherapy combination, and five were refractory to radioimmunotherapy. Only seven patients were chemotherapy naive. The rituximab-refractory status for two patients could not be confirmed. Twenty-four patients were refractory to their most recent chemotherapy regimen, and 23 to their most recent alkylator-containing regimen.

### *Patient Disposition*

Patients received a median of 5.0 cycles of bendamustine (range, one to nine cycles; Table 2). Thirty-four patients received at least six cycles, and four patients received nine cycles of bendamustine. Forty-three patients discontinued bendamustine treatment before completing six cycles because of adverse events (n = 23), disease progression (n = 14), or patient or investigator decision (n = 6; Table 2). Thrombocytopenia was the most common reason for early study termination.

### *Safety*

Overall, bendamustine was relatively well tolerated in this heavily pretreated population. A total of 19 patients required dose reductions during the study: 15 underwent a dose reduction to 90 mg/m$^2$, and four required an additional dose reduction to 60 mg/m$^2$. Hematologic toxicities, including neutropenia, anemia, and thrombocytopenia were primarily grade 1/2 in severity (Table 3). Five episodes of febrile neutropenia were documented. Additionally, three patients experienced documented grade 3 infections with neutropenia. Table 3 also shows nonhematologic toxicities occurring in more than 20% of patients or at grade 3/4 severity in more than one patient. Grade 3/4 events occurred infrequently. Alopecia and mucositis were not reported.

Secondary malignancies developed in three patients, all of whom eventually died. One patient with normal cytogenetics developed myelodysplastic syndrome (MDS) 6 months after therapy with bendamustine; other therapies included fludarabine and radiotherapy. A second patient developed MDS 7 months after therapy with bendamustine; other therapies included chlorambucil and prednisone, R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), and radiotherapy. The third patient developed

**Table 2.** Patient Disposition

| Characteristic | No. | % |
|---|---|---|
| Patients enrolled | 77 | |
| Patients treated | 76 | |
| Patients completing at least 6 cycles | 34 | 44 |
| Patients completing 1-5 cycles | 43 | 56 |
| No. of cycles completed | | |
| Median | 5 | |
| Range | 1-9 | |
| Reasons for termination (< 6 cycles, n = 43) | | |
| Adverse event | 23 | |
| Thrombocytopenia | 11 | |
| Neutropenia | 2 | |
| Acute renal failure | 1 | |
| Chronic myelomonocytic leukemia | 1 | |
| Fatigue | 1 | |
| Lung congestion | 1 | |
| Pain at IV site | 1 | |
| Shingles | 1 | |
| Anemia | 1 | |
| Hypersensitivity rash | 1 | |
| Postinfusion reaction, systemic | 1 | |
| Xerostomia | 1 | |
| Disease progression | 14 | |
| Patient or investigator decision | 6 | |

Abbreviation: IV, intravenous drug administration

**Table 3.** Adverse Events by Severity Grade (N = 76)

| Adverse Event | Grade 1 | | Grade 2 | | Grade 3 | | Grade 4 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % |
| Hematologic* | | | | | | | | | | |
| Neutropenia | 7 | 9 | 17 | 22 | 23† | 30 | 18 | 24 | 65 | 85 |
| Anemia | 27 | 36 | 35 | 46 | 9 | 12 | 0 | | 71 | 94 |
| Thrombocytopenia | 27 | 36 | 18 | 24 | 12 | 16 | 7 | 9 | 64 | 85 |
| Nonhematologic‡ | | | | | | | | | | |
| Nausea | 30 | 39 | 22 | 29 | 3 | 4 | 0 | | 55 | 72 |
| Fatigue | 17 | 22 | 15 | 20 | 5 | 7 | 0 | | 37 | 49 |
| Vomiting | 16 | 21 | 12 | 16 | 3 | 4 | 0 | | 31 | 41 |
| Anorexia/decreased appetite | 18 | 24 | 8 | 10 | 0 | | 0 | | 26 | 34 |
| Diarrhea | 14 | 18 | 8 | 11 | 1 | 1 | 0 | | 23 | 30 |
| Cough | 17 | 22 | 5 | 7 | 0 | | 0 | | 22 | 29 |
| Constipation | 15 | 20 | 4 | 5 | 1 | 1 | 0 | | 20 | 26 |
| Pyrexia without documented neutropenia | 13 | 17 | 4 | 5 | 2 | 3 | 0 | | 19 | 25 |
| Headache | 13 | 17 | 2 | 3 | 0 | 0 | 0 | | 15 | 20 |
| Back pain | 5 | 7 | 5 | 7 | 2 | 3 | 0 | | 12 | 16 |
| Dehydration | 3 | 4 | 4 | 5 | 2 | 3 | 0 | | 9 | 12 |
| *Candida* infection | 3 | 4 | 1 | 1 | 2 | 3 | 0 | | 6 | 8 |
| Hypokalemia | 0 | | 1 | 1 | 3 | 4 | 0 | | 4 | 5 |
| Pneumonia | 0 | | 0 | | 4 | 5 | 0 | | 4 | 5 |

*Severity was determined using the National Cancer Institute Common Toxicity Criteria for Adverse Events, v.3.0 (http://ctep.cancer.gov/reporting/ctc.html).
†Includes 5 patients with febrile neutropenia.
‡Commonly occurring nonhematologic adverse events (occurring > 20% of patients) and all grade 3/4 nonhematologic adverse events occurring in > 1 patient.

chronic myelomonocytic leukemia (CMML) shortly after cycle 3 of bendamustine; prior therapies included CHOP, rituximab, doxorubicin, vincristine, and prednisone.

An infusion reaction syndrome has previously been reported for bendamustine, but it has not been well described.[21,22] We identified seven infusional reactions, based on constellation of symptoms observed and recurrence with rechallenge. These events included fever, hypotension, pain (back or muscle), and chills/rigors occurring within 24 hours after receiving bendamustine. These events most commonly occurred on day 1 of cycle 2 (n = 4 patients), but occurred as late as day 1 of cycle 3 (n = 2). None of the patients experienced grade 4 reactions. Three of these patients exhibited associated transient increases in serum creatinine on day 2 of the cycle. Three patients discontinued bendamustine because of the infusional reaction syndrome. The remaining patients continued treatment with bendamustine with corticosteroid premedication.

### *Response*

Two patients did not have measurable disease at enrollment and are therefore excluded from efficacy analyses. A 77% ORR was observed among 74 assessable patients, which included 11 CRs, 14 CRus (34% CR/CRu), and 32 PRs (43%; Table 4). Among the 45 patients with follicular lymphoma, including almost half with a high-risk FLIPI score, an 82% ORR was documented, including seven CRs, 10 CRus, and 20 PRs. Among 15 patients with transformed disease, two CRus and eight PRs occurred. The median duration of response for responders in the treated population was 6.7 months (95% CI, 5.1 to 9.9; Fig 1); for patients with indolent lymphoma, it was 9.0 months (95% CI, 5.8 to 16.7); and for patients with transformed disease, 2.3 months (95% CI, 1.7 to 5.1). Based on a median follow-up period of 26 months, median PFS was 7.1 months for all patients (Fig 1B), 8.3 months (95% CI, 6.6 to 10.9) for patients

**Table 4.** Treatment Response

| Response | No. of Patients | % | | | | |
|---|---|---|---|---|---|---|
| | | CR/CRu | PR* | SD | PD | Unknown/Missing |
| Total | 74 | 34 | 43 | 4 | 17 | 3 |
| Follicular | 45 | 37 | 44 | 4 | 11 | 2 |
| Small lymphocytic | 11 | 36 | 27 | 0 | 36 | 0 |
| Lymphoplasmacytic | 1 | 100 | 0 | 0 | 0 | 0 |
| Marginal zone | 2 | 50 | 50 | 0 | 0 | 0 |
| Transformed disease | 15 | 13 | 53 | 7 | 27 | 0 |

Abbreviations: CR, complete response; CRu, unconfirmed CR; PR, partial response; SD, stable disease; PD, progressive disease.
*PR included patients who met the criteria for CR but did not undergo a confirmatory bone marrow evaluation.

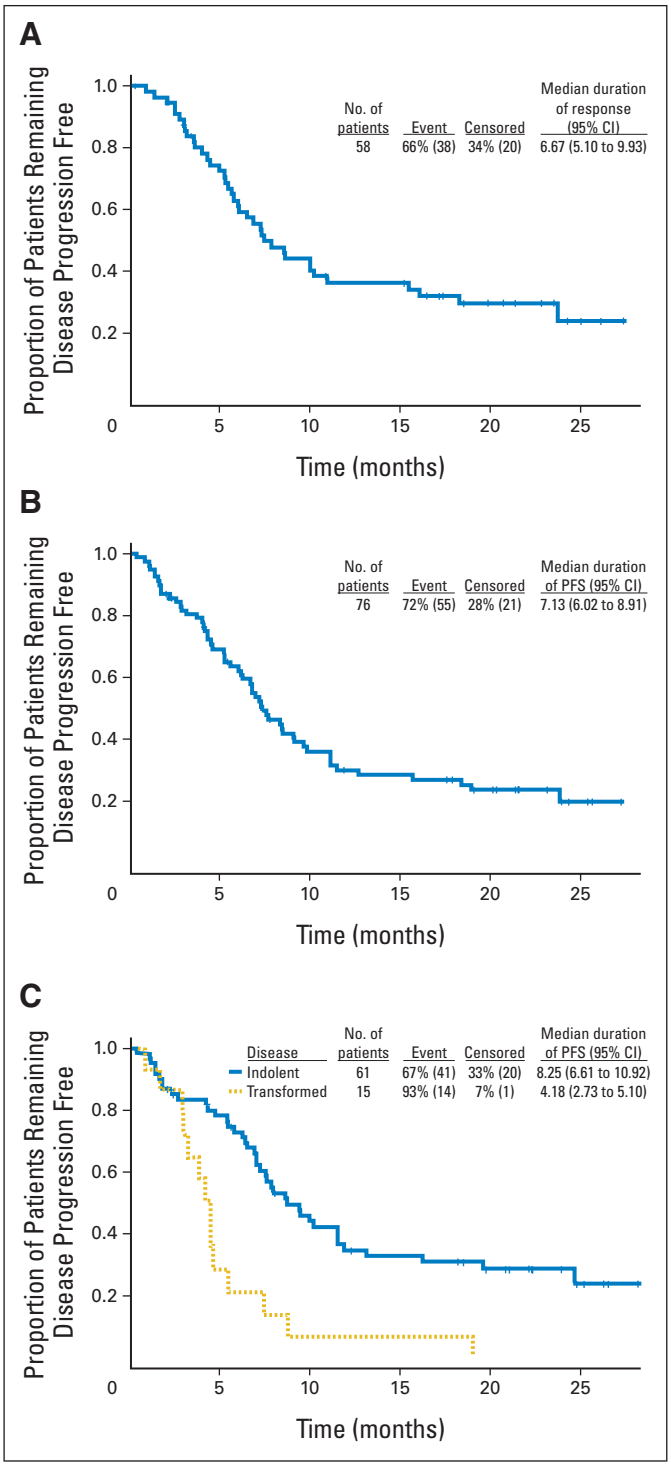


**Fig 1.** Kaplan-Meier curves of (A) duration of response in patients exhibiting a complete, complete unconfirmed, or partial response (n = 58), (B) progression-free survival (PFS) after bendamustine treatment in all treated patients (N = 76), and (C) disease type.

with indolent disease, and 4.2 months (95% CI, 2.7 to 5.1) for those with transformed disease (Fig 1C).

Among alkylator-refractory patients, who were defined by a lack of response or disease progression during treatment with an alkylator-containing regimen (n = 23), an ORR of 61% was observed, including three CRs. The median duration of response for alkylator-sensitive (n = 31) and alkylator-refractory (n = 14) patients was 6.5 months (95% CI, 4.7 to 9.9 months) and 7.7 months (95% CI, 4.4 to 16.7 months), respectively. Patients refractory to previous fludarabine (n = 8) demonstrated a 62% ORR. Patients treated with two or more prior chemotherapy regimens (n = 40) had an ORR of 75% (seven CRs, five CRus, 18 PRs); median duration of response for these patients was 5.3 months (95% CI, 3.5 to 14.6 months) compared to 9.0 months (95% CI, 6.1 to not applicable months) in patients receiving one or fewer regimens. Among the nine patients previously treated with radioimmunotherapy, two CRus and six PRs were observed. Six of these patients discontinued bendamustine treatment prematurely because of thrombocytopenia. Among six patients who underwent ASCT before bendamustine, one CR and three PRs were observed, with a median response duration of 2.6 months.

## DISCUSSION

Bendamustine is thought to act primarily as an alkylating agent, by virtue of the presence of a 2-chloroethyl group. The drug is currently approved in Germany for the treatment of NHL, multiple myeloma, and chronic lymphocytic leukemia (CLL). [23]

Several relatively small studies suggest the efficacy of bendamustine in indolent B-cell malignancies. Heider and Niederle[16] published results of a single-institution trial evaluating bendamustine in 52 patients using a dose and schedule similar to the current trial. Details on the histology of these patients and a formal restaging schedule are lacking. The response rate was 73%, including 11% CR. Importantly, the majority of these patients were refractory to previous alkylating-agent–based chemotherapy regimens, and the median duration of response to bendamustine was 16 months, demonstrating activity in a refractory patient population. Bremer[15] reported a trial of 62 patients with various indolent histologies of NHL treated with an alternative regimen of bendamustine 60 mg/m$^2$ daily for 5 days. The ORR with this schedule was 82%, with minimal nonhematologic toxicities. Patients had a longer mean duration of response in this trial (39 months), which again included patients with alkylator-refractory disease. Another small series suggests significant activity as a single agent in refractory CLL.[21]

However, there are few prospective, well-controlled, multicenter published trials of this agent. A European randomized trial compared bendamustine, vincristine, and prednisone (BOP) to cyclophosphamide, vincristine, and prednisone (COP) in 164 previously untreated patients with various histologies of de novo indolent NHL and mantle-cell lymphoma.[24] ORR and survival were equivalent between the two groups; however, BOP-responding patients had a longer time to progression compared with COP-responding patients. Other chemotherapy combinations that have been evaluated in small studies include bendamustine with mitoxantrone or fludarabine.[25,26]

Our current study represents the first evaluation of a chemotherapeutic agent in the rituximab-refractory patient population. As expected, many of these patients had received extensive prior therapy; 26% were also refractory to purine analog therapy, and 30% were refractory to alkylator-based regimens. In general, toxicities were mild, and few patients required hospitalization. No appreciable alopecia or mucositis was observed with this regimen, and nausea was easy to control. An infusional syndrome consisting of systemic illness

occurred in seven patients within 24 hours of receiving bendamustine; this has been previously reported and was self-limited.[27]

Hematologic adverse events were the most frequent events resulting in delay of therapy or withdrawal from the trial. Our inclusion criteria allowed patients with platelet counts of at least 100,000/mm$^3$; patients with relative thrombocytopenia at baseline, indicative of decreased marrow reserve, had difficulty tolerating a full dose-intensity of the prescribed regimen. Interestingly, six of nine patients who had received prior radioimmunotherapy discontinued study treatment because of thrombocytopenia. Retrospective trials have suggested that patients receiving radioimmunotherapy can tolerate subsequent therapy,[28,29] but to our knowledge, this is the first prospective trial including an appreciable number of patients with prior radioimmunotherapy. Additional study is required to determine the degree to which radioimmunotherapy contributes to subsequent thrombocytopenia, or whether it is simply a surrogate for extensive prior therapy. Of note, eight of these nine patients responded to bendamustine. Alterations of dose and schedule or the addition of prophylactic growth factors may therefore be appropriate for this group; a recently closed study of bendamustine and rituximab used a lower dose of bendamustine (90 mg/m$^2$) on a 4-week schedule with promising initial results.[30]

Two cases of MDS and one of CMML have been reported in the present study to date, all in patients with prior therapy including alkylating agents, purine analogs, or radiotherapy. The incidence of secondary myelodysplasia in patients with indolent lymphomas is highest after ASCT,[31] but may approach 5% cumulatively after standard chemotherapy[32-34] or radioimmunotherapy.[35] As expected for secondary MDS with a known poor prognosis, all of these patients died. It is unclear what contribution bendamustine had to the development of these malignancies.

Treatment options for rituximab-refractory indolent NHL are limited. Two published trials demonstrated the efficacy of radioimmunotherapy in this setting. Unlike the current study, these trials did not include patients who were refractory to rituximab-chemotherapy combinations. Our trial included 18 such patients. The reported response rate and median response duration in patients refractory to single-agent rituximab treated with ibritumomab tiuxetan are 74% and 6.8 months, respectively,[13] and with iodine-131 tositumomab, 65% and 10.4 months, respectively.[12] It is difficult to compare these results to our results given different patient populations.

Moreover, our trial included patients with transformed indolent lymphoma. Historically, the outcome of such patients treated with conventional chemotherapy was poor unless they had very favorable clinical characteristics.[36,37] Despite a reasonably high response rate in our series, the time to progression of patients with transformed lymphoma was short, suggesting that single-agent bendamustine at this dose and schedule is inadequate therapy for this subgroup. Alternative approaches for patients with rituximab-refractory, transformed indolent lymphoma include ASCT for younger patients[18] and radioimmunotherapy.[38]

In the present trial, the results of bendamustine therapy for patients with refractory disease without evidence of transformation are quite promising. Additionally, the agent is reasonably well tolerated, without appreciable alopecia or mucositis. Activity in patients refractory to purine analogs and other alkylating agents (including the R-CHOP regimen) makes this a potentially attractive therapeutic option for this group of patients who are not candidates for intensive approaches like ASCT. A pivotal trial of single-agent bendamustine for patients with rituximab-refractory, indolent lymphoma is ongoing to confirm these results. In addition, phase II trials in rituximab-sensitive indolent lymphoma using bendamustine with rituximab suggest high response rates with excellent tolerability.[30,39] A study in Germany is prospectively comparing the bendamustine/rituximab combination against CHOP/rituximab for de novo indolent lymphoma. Results of these ongoing studies, including exploration of an ideal dose and schedule, will further define the optimal role for this promising agent in the treatment of indolent NHL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Employment or Leadership Position:** Ling Chen, Cephalon Inc (C) **Consultant or Advisory Role:** Jonathan W. Friedberg, Cephalon Inc (C); Michael E. Williams, Cephalon, Inc (C); Jennifer W. Oliver, Cephalon Inc (C) **Stock Ownership:** Jennifer W. Oliver, Cephalon Inc **Honoraria:** None **Research Funding:** Jonathan W. Friedberg, Cephalon Inc; Michael E. Williams, Cephalon Inc.; Richard H. van der Jagt, Cephalon Inc; Andres Forero-Torres, Cephalon Inc; Luis E. Fayad, Salmedix; Elber S. Camacho, Cephalon Inc.; Philip Cohen, Cephalon Inc **Expert Testimony:** None **Other Remuneration:** None

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