EXHIBIT 2015

Original Article

Bendamustine Is Effective Therapy in Patients With Rituximab-Refractory, Indolent B-cell Non-Hodgkin Lymphoma

Results From a Multicenter Study

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BACKGROUND: Bendamustine hydrochloride is a novel alkylating agent. In this multicenter study, the authors evaluated the efficacy and toxicity of single-agent bendamustine in patients with rituximab-refractory, indolent B-cell lymphoma. **METHODS:** Eligible patients (N = 100, ages 31-84 years) received bendamustine at a dose of 120 mg/m^2 by intravenous infusion on Days 1 and 2 every 21 days for 6 to 8 cycles. Histologies included follicular (62%), small lymphocytic (21%), and marginal zone (16%) lymphomas. Patients had received a median of 2 previous regimens (range, 0-6 previous regimens), and 36%were refractory to their most recent chemotherapy regimen. Primary endpoints included overall response rate (ORR) and duration of response (DOR). Secondary endpoints were safety and progression-free survival (PFS). **RESULTS:** An ORR of 75% (a 14% complete response rate, a 3% unconfirmed complete response rate, and a 58% partial response rate) was observed. The median DOR was 9.2 months, and median PFS was 9.3 months. Six deaths were considered to be possibly treatment related. Grade 3 or 4 (determined using National Cancer Institute Common Toxicity Criteria [version 3.0.19]. reversible hematologic toxicities included neutropenia (61%), thrombocytopenia (25%), and anemia (10%). The most frequent nonhematologic adverse events (any grade) included nausea (77%), infection (69%), fatigue (64%), diarrhea (42%), vomiting (40%), pyrexia (36%), constipation (31%), and anorexia (24%). **CONCLUSIONS:** Single-agent bendamustine produced a high rate of objective responses with acceptable toxicity in patients with recurrent, rituximab-refractory indolent B-cell lymphoma. ***Cancer*** **2010;116:106–14.** © *2010 American Cancer Society.*

KEYWORDS: bendamustine, non-Hodgkin lymphoma, B-cell lymphoma, rituximab-refractory, clinical trial.

The anti-CD20 monoclonal antibody rituximab, either as a single agent or, particularly, in combination with chemotherapy, has changed the therapeutic landscape for patients with indolent B-cell lymphoma. In follicular lymphoma, which is the most common indolent non-Hodgkin lymphoma (NHL), rituximab combined with chemotherapy has led to notable improvements in response rates, progression-free survival (PFS), and overall survival (OS).[1-4] Treatment guidelines from the National Comprehensive Cancer Network now recommend a rituximab-based regimen as initial therapy for patients with B-cell lymphoma.[5] Unfortunately, patients tend to become refractory to rituximab over time. Although yttrium-90 ibritumomab tiuxetan and iodine-131 tositumomab have demonstrated activity in patients who are refractory

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to single-agent rituximab, their use has been limited by strict eligibility criteria and other factors.[6,7] Moreover, patients with indolent B-cell lymphoma currently are more likely to be treated with rituximab-chemotherapy combinations than with single-agent rituximab.[8] Consequently, rituximab resistance often develops within the context of generalized chemotherapy resistance, and innovative treatments are needed for this "rituximab-refractory" patient population.

Bendamustine (Treanda; Cephalon, Inc., Frazer, Pa) is a novel alkylator whose mechanisms of action involve induction of apoptosis through activation of DNA-damage stress responses, inhibition of mitotic checkpoints, and induction of mitotic catastrophe.[9] The compound also contains a benzimidazole ring, which may confer purine analogue-like properties in addition to the alkylating properties. In vitro studies indicate that the DNA repair mechanisms that operate after exposure to the drug are different from those evoked by other agents, potentially explaining observed antitumor effects in cell lines that are resistant to other alkylating agents.[10] Several German studies have evaluated its efficacy as a single agent or in combination with chemotherapy and/or rituximab in patients with recurrent, indolent B-cell lymphoma.[11-16] Bendamustine is indicated for the treatment of indolent lymphoma, multiple myeloma, and chronic lymphocytic leukemia (CLL) in Germany and was approved for the treatment of CLL in the United States in March 2008. A recent North American phase 2 multicenter study in patients with recurrent, rituximab-refractory, indolent B-cell lymphoma demonstrated that bendamustine produced durable objective responses with acceptable toxicity.[17] The purpose of the current phase 3 multicenter study was to further evaluate the effects of bendamustine in a larger group of patients with rituximab-refractory, indolent B-cell lymphoma and to provide the pivotal evaluation in this patient population.

MATERIALS AND METHODS

Study Design and Objectives

This multicenter, open-label, single-arm clinical trial was designed to investigate the efficacy and safety of bendamustine in patients with rituximab-refractory, indolent B-cell NHL. Primary endpoints included the overall response rate (ORR) and the duration of response (DOR). Secondary endpoints included progression-free survival (PFS) and the safety profile. The study was performed at 24 centers in the United States and at 4 centers in Canada. The protocol was approved by the institutional review board (IRB) at each site, and an IRB-approved consent form was signed by each patient before study enrollment.

Eligibility

Patients aged $\geq$18 years with a World Health Organization performance status $\leq$2 were eligible for study participation if they had documented rituximab-refractory, indolent B-cell lymphoma. Rituximab-refractory disease was defined as no objective response or documented progression within 6 months of 1) receiving the first dose of a full course of single-agent rituximab ($\geq$4 doses of 375 mg/m^2 weekly), 2) completion of rituximab maintenance therapy or progression before the next scheduled rituximab dose, or 3) completion of a full course of rituximab in combination with chemotherapy. Patients were required to have bidimensionally measurable disease with at least 1 lesion that measured $\geq$2.0 cm in a single dimension. Patients may have received from 1 to 3 previous chemotherapy regimens. Prior autologous stem cell transplantation was permitted. The baseline evaluation included a complete medical history, physical examination, radiographic imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI] studies), bone marrow evaluation, electrocardiogram, and routine laboratory studies, including lactate dehydrogenase (LDH) levels. The following baseline laboratory parameters were required: absolute neutrophil count (ANC) $\geq$1000 cells/mm^3, platelet count $\geq$100,000 cells/mm^3 (or $\geq$75,000 cells/mm^3 in patients who had thrombocytopenia attributable to bone marrow involvement with NHL), creatinine clearance >30 mL per minute, and adequate hepatic function (<2.5 times the upper limit of normal [ULN] range for aspartate aminotransferase and alanine aminotransferase and <1.5 times the ULN for total bilirubin).

Patients were excluded from study participation for the following reasons: chemotherapy, immunotherapy, radioimmunotherapy, or investigational therapy within 28 days before the start of Cycle 1 or failure to recover from adverse events (AEs) associated with prior treatment; myeloid growth factor treatment within 14 days (chronic erythropoietic-stimulating agent was allowed); concurrent treatment with therapeutic doses

of systemic steroids within 14 days; transformed disease; history of prior high-dose chemotherapy with allogeneic stem cell support; concurrent, active malignancy (except nonmelanoma skin cancer, in situ cervical cancer, or localized prostate cancer treated with hormone therapy); central nervous system or leptomeningeal lymphoma; serious infection or another medical or psychiatric condition that might interfere with achieving the study objectives; pregnancy or lactation; or expected survival <3 months.

Treatment

Bendamustine at a dose of 120 mg/m^2 was infused intravenously over 60 to 120 minutes on Days 1 and 2 every 21 days. Treatment was planned for 6 to 8 cycles as long as a response or stable disease (SD) was observed. The development of grade 4 hematologic or grade 3/4 nonhematologic toxicities after any cycle led to a bendamustine dose reduction to 90 mg/m^2 for the subsequent cycle; if grade 4 hematologic or grade 3/4 nonhematologic toxicities were observed at the reduced dose level, then bendamustine was reduced further to a dose of 60 mg/m^2. All dose reductions were permanent. If further toxicity occurred, then study treatment was discontinued.

Subsequent cycles could be administered if nonhematologic toxicities resolved to grade ≤1 and if the ANC recovered to ≥1000 cells/mm^3 and the platelet count recovered to ≥75,000 cells/mm^3 by the time of the next scheduled dose. Dosing was delayed up to 4 weeks until these criteria were met. Patients who did not meet these criteria after a 4-week delay were removed from protocol therapy.

Primary prophylactic use of growth factors was not allowed during Cycle 1. Subsequent filgrastim or pegfilgrastim therapy was allowed for patients who had grade 4 neutropenia that lasted ≥1 week, failure of the white blood cell count to recover to grade ≤1 by the next scheduled dose, or febrile neutropenia in a previous treatment cycle. Low-dose corticosteroids (≤10 mg daily of prednisone or equivalent) were allowed for non-neoplastic disorders; however, other on-study use of corticosteroids was not permitted (with the exception of ≤2 doses per cycle as an antiemetic). Any patient who demonstrated disease progression during therapy was removed from the study.

Criteria for Response and Toxicity

Response was evaluated by contrast-enhanced CT scans or MRI studies at Week 6, Week 12, and every 12 weeks thereafter until the end of treatment. An end-of-treatment scan was obtained within 28 days. Investigators used the International Working Group Response criteria for malignant lymphoma to determine response to treatment.[18] Patients underwent bone marrow aspiration and biopsy to confirm a complete response (CR) if the patient's bone marrow initially had been positive for lymphoma. LDH levels also were measured at each disease assessment. Tumor response was assessed by investigators and also by an independent review committee (IRC) (RadPharm, Princeton NJ). The ORR was defined as the proportion of patients who achieved as their best response a CR, an unconfirmed CR (CRu), and a partial response (PR). DOR was defined as the time from the first documentation of response until disease progression, death, or change of therapy. PFS was calculated as the time from the first dose of bendamustine administered until disease progression or death from any cause. Patients who remained progression free at the end of treatment were evaluated every 3 months until death, disease progression, or the start of a new anticancer therapy up to a maximum of 2 years after treatment. AEs were recorded and their severity was assessed according to the National Cancer Institute' Common Toxicity Criteria for Adverse Events (version 3.0).[19] Serious AEs (SAEs) were defined as those that were life-threatening, required hospitalization, or resulted in significant disability, congenital anomaly of offspring, or death.

Statistical Methods

The primary efficacy and safety analyses were performed on all patients who received treatment with bendamustine (the primary analysis set). Patients were classified according to their best overall response at the completion of therapy. Response assessments were made by the investigator and an IRC, and the latter assessment informed the primary endpoint analysis. The number and percentage of patients in each response category (CR, CRu, PR, SD, or progressive disease [PD]) were summarized along with a 2-sided binomial exact 95% confidence interval (95% CI) for ORR.

The statistical criterion for success relative to the response outcome was evidence of a true response probability >40% with the trial powered for a response probability ≥60%. Therefore, the trial tested the null hypothesis that the true response probability was ≤40% with a planned trial size of 100 patients who had no major screening or eligibility violations.

Table 1. Patient Demographics and Disease Characteristics

Characteristic	No. of Patients (%)
No. of patients treated	100
No. of men/women	65/35
Median age [range], y	60 [31-84]
Disease stage	
I	8 (8)
II	16 (16)
III	33 (33)
IV	43 (43)
Histology	
Follicular	62 (62)
Grade 1	33 (33)
Grade 2	16 (16)
Grade 3	8 (8)
Unknown	5 (5)
Small lymphocytic lymphoma	21 (21)
Lymphoplasmacytic lymphoma	1 (1)
Marginal zone	16 (16)
Follicular Lymphoma Prognostic Index, n = 62	
Low risk: 0-1 risk factor	18 (29)
Intermediate risk: 2 risk factors	26 (42)
High risk: 3-5 risk factors	18 (29)

Table 2. Previous Therapies

Variable	No. of Patients (%)
No. of previous chemotherapy regimens	
0	1 (1)
1	41 (41)
2	36 (36)
3	14 (14)
>3	8 (8)
Median [range]	2 [0-6]
Type of previous therapy	
Single-agent rituximab	1 (1)
CHOP-like chemotherapy rituximab	37 (37)
CVP ± rituximab	38 (38)
Purine analogue-based combinations±rituximab	44 (44)
Radioimmunotherapy	24 (24)
External beam radiotherapy	20 (20)

CHOP indicates combined cyclophosphamide, doxorubicin, vincristine, and prednisone; ±, with or without; CVP, combined cyclophosphamide, vincristine, and prednisone.

The median DOR and PFS were assessed using the Kaplan-Meier method.[20] If the patient did not experience disease progression, death, or change of therapy at the time of the computation of the DOR or PFS, then the patient had a censored observation at the date of the most recent progression-free visit. The criterion for success with respect to the duration of response was demonstrating that the DOR was not significantly less than 6 months (defined as the lower end of the 95% CI for the median DOR of >4 months).

RESULTS

Patients

Between October 2005 and July 2007, 102 patients were enrolled at 28 institutions. Two patients did not receive treatment and were excluded from the study analysis. One hundred patients received at least 1 dose of bendamustine, and these patients comprise the current primary analysis set. Demographics and baseline characteristics of the 100 patients in the primary analysis set are summarized in Table 1. The median age was 60 years (range, 31-84 years), and 76% of patients had advanced-stage disease at enrollment. Histologies included follicular lymphoma (n = 63), small lymphocytic lymphoma (n = 21), lymphoplasmacytoid lymphoma (n = 1), and marginal zone lymphoma (n = 16). The patients who had follicular histologies were categorized according to the Follicular Lymphoma International Prognostic Index (FLIPI) as follows: low risk, 29%; intermediate risk, 42%; and high risk, 29%. Table 2 summarizes prior treatment history for all patients. The median number of prior chemotherapy regimens was 2 (range, 0-6 regimens). One patient had not received prior chemotherapy (having received only single-agent rituximab), and 8 patients had received >3 prior chemotherapy regimens. These 9 patients were in violation of the protocol, which mandated at least 1 but not more than 3 prior chemotherapy regimens. They were included in the primary analysis, consistent with prespecified analysis conditions. Prior treatments included single-agent rituximab, chemotherapy with or without rituximab, single-agent chemotherapy, radioimmunotherapy, and external beam radiation. Thirty-six patients (36%) had disease that was refractory to their most recent chemotherapy.

Tolerability and Safety

The median number of cycles completed was 6 (range, 1-8 cycles). Sixty patients (60%) received at least 6 cycles of bendamustine. Forty patients discontinued treatment early for the following reasons: AEs (n = 27), disease progression (n = 10), patient decision (n = 1), bone marrow transplantation referral (n = 1), and an excessive treatment delay (n = 1) (Table 3). Twenty-four patients (24%) had dose reductions because of AEs: Twenty

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