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ORIGINAL REPORT

Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma

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ABSTRACT

Purpose
Limited data exist regarding the activity of bendamustine in Hodgkin lymphoma (HL). This phase II study evaluated the efficacy of bendamustine in relapsed and refractory HL.

Patients and Methods
Patients with relapsed and refractory HL who were ineligible for autologous stem-cell transplantation (ASCT), or for whom this treatment failed, received bendamustine 120 mg/m^2 as a 30-minute infusion on days 1 and 2 every 28 days with growth factor support. The primary end point was overall response rate (ORR). A secondary end point was referral rate to allogeneic stem-cell transplantation (alloSCT) for patients deemed eligible for alloSCT at the time of enrollment.

Results
Of the 36 patients enrolled, 34 were evaluable for response. Patients had received a median of four prior treatments, and 75% had relapsed after ASCT. The ORR by intent-to-treat analysis was 53%, including 12 complete responses (33%) and seven partial responses (19%). The response rate among evaluable patients was 56%. Responses were seen in patients with prior refractory disease, prior ASCT, and prior alloSCT; however, no responses were seen in patients who relapsed within 3 months of ASCT. The median response duration was 5 months. Five patients (20% of those eligible) proceeded to alloSCT after treatment with bendamustine. Grade $\geq$ 3 adverse events were infrequent and most commonly included thrombocytopenia (20%), anemia (14%), and infection (14%).

Conclusion
This study confirms the efficacy of bendamustine in heavily pretreated patients with HL. These results support current and future studies evaluating bendamustine combinations in relapsed and refractory HL.

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INTRODUCTION

Although the treatment of Hodgkin lymphoma (HL) is highly successful with multiagent chemotherapy, up to 30% of patients will ultimately have either primary refractory or relapsed disease.[1] For these patients, the standard treatment is second-line therapy followed by autologous stem-cell transplantation (ASCT), which cures an additional 50% of patients.[2] Unfortunately, in patients for whom ASCT fails, the outcome is poor, with median survival of only 25 months.[3] Treatment options for this subset of patients are limited and include traditional HL regimens such as MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) or Ch1VPP (chlorambucil, vinblastine, procarbazine, and prednisone), gemcitabine-based regimens, palliative radiotherapy, and investigational agents. Recently, brentuximab vedotin was approved for this specific patient population, but even with this active agent, median progression-free survival was approximately 6 months.[4] Patients who achieve adequate responses to post-ASCT salvage therapies are often referred for an allogenic stem-cell transplantation (alloSCT), which is associated with long-term remission rates ranging from 20% to 59%; however, minimal disease state at the time of transplantation is important for favorable outcome.[5-7]

Bendamustine is a bifunctional alkylating agent with only partial cross resistance to other alkylating agents, making it an attractive agent for use in the relapsed setting.[8] Although it was developed in the 1960s and used in Germany for both HL and non-HL, there is limited published experience with bendamustine in HL. A review by Borchmann et al[9] describes three small studies of

bendamustine in HL conducted in the 1970s and 1980s. One study included 10 patients receiving single-agent bendamustine and demonstrated a response rate of 70%. The other two studies evaluated bendamustine in combination with other chemotherapeutic agents, making assessment of the single-agent activity of bendamustine in HL difficult. Therefore, we carried out a phase II study evaluating the efficacy and toxicity of bendamustine in relapsed and refractory HL. For patients who were potentially eligible for alloSCT, treatment was intended to serve as a bridge to transplantation, provided an adequate response to bendamustine was achieved.

PATIENTS AND METHODS

Patient Eligibility

Patients age ≥ 18 years with biopsy-confirmed relapsed and refractory classical HL were eligible. Failure of ASCT or ineligibility for ASCT was required. Patients were required to have absolute neutrophil count > 1000/μL, platelet count > 100 K/μL, creatinine ≤ 1.5 mg/dL (or creatinine clearance > 60 mL/min), and bilirubin < 2 mg/mL. Seronegativity for hepatitis B, hepatitis C, and HIV was required as well. Previous alloSCT was allowed if relapse was > 6 months from transplantation. Patients with known CNS involvement by HL were excluded, as were patients who were pregnant or breastfeeding. This study was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center, and all patients signed written informed consent. Patients deemed potentially eligible for alloSCT at the time of enrollment (based on absence of comorbidities) were simultaneously offered enrollment onto a parallel intent-to-treat study evaluating alloSCT in relapsed and refractory HL.

Study Design and Treatment

This was a phase II single-center study of bendamustine in relapsed and refractory HL. Baseline assessment included computed tomography of the chest, abdomen, and pelvis, [^{18}F]fluorodeoxyglucose–positron emission tomography scan, and bone marrow biopsy within 28 days of beginning treatment. Bendamustine 120 mg/m^2 was administered as a 30-minute infusion on days 1 and 2 of each 28-day cycle. Growth factor support with pegfilgrastim or filgrastim was administered with each cycle of treatment. A total of six cycles of treatment was planned. Adequate hematopoietic recovery was required for each cycle (absolute neutrophil count ≥ 1,000/μL; platelet count ≥ 75 K/μL), and treatment was delayed until these criteria were met. The dose of bendamustine was reduced to 100 mg/m^2 for treatment delays > 5 days because of neutropenia or thrombocytopenia. The dose was further reduced to 70 mg/m^2 for subsequent delays > 5 days for neutropenia or thrombocytopenia. Patients were removed from study for prolonged neutropenia or thrombocytopenia (≥ 21 days). Patients received pneumocystis pneumonia prophylaxis and antiemetics as per institutional guidelines.

Response Criteria

Responses were assessed using the 2007 International Harmonisation Project criteria.[10] Computed tomography and [^{18}F]fluorodeoxyglucose–positron emission tomography scans were repeated after cycles two, four, and six. All scans were reviewed and responses confirmed independently by a single Memorial Sloan-Kettering Cancer Center radiologist assigned to this study. Patients achieving complete response (CR) or partial response (PR) who were eligible for alloSCT were taken off study and referred to alloSCT at the discretion of the treating physician.

Statistics

The primary end point was overall response rate (ORR). A Simon two-stage design was used to determine appropriate enrollment size. Assuming a clinically meaningful ORR of 40% and an unacceptable response rate of < 20%, as well as types I and II error rates of 10%, four responses among the first 17 enrolled patients were required to proceed to stage two. In stage two, 11 responses of up to 37 patients were required to declare bendamustine an effective treatment in relapsed and refractory HL. On enrollment of 36 patients, an adequate number of responses were seen to declare this treatment a success; therefore, the study was closed. Secondary outcomes included toxicity graded according to Common Terminology Criteria for Adverse Events (version 3.0), progression-free survival (PFS), overall survival (OS), and referral rate to alloSCT. PFS and OS were measured from the time of initiation of treatment by the Kaplan-Meier method. Patients taken off study for alloSCT were observed for progression and survival and therefore not censored at the time of transplantation.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	No.	%
Patients enrolled	36	100
Age, years		
Median	34	
Range	21-75	
Sex		
Male	13	36
Female	23	64
No. of prior therapies		
Median	4	
Range	1-17	
Response to last chemotherapy		
Sensitive	18	50
Resistant	18	50
History of autologous transplantation	27	75
Relapse ≤ 3 months after	5	
Relapse > 3 months after	22	
History of allogeneic transplantation	6	17
Disease extent at enrollment		
Nodal only	11	31
Extranodal	25	69
B symptoms at enrollment	7	19

RESULTS

Patient Characteristics

Between July 2008 and December 2010, 36 patients were enrolled (Table 1). The median age was 34 years, and there were 23 women (64%). Patients were heavily pretreated; the median number of prior therapies for HL was four. Seventy-five percent of the patients had relapsed after ASCT, and six patients had relapsed after alloSCT (four of whom had undergone both ASCT and alloSCT). Fifty percent of patients were refractory to their last treatment. The median follow-up for all patients was 19 months (range, 1 to 40 months). Of the 36 patients, two were not evaluable for response. One patient withdrew consent after one cycle of bendamustine because of nausea. She was subsequently monitored and did not require additional treatment for HL until > 1 year later. The second patient died in a car accident after two cycles of bendamustine. She was clinically responding to treatment at the time of her death but never underwent restaging.

Toxicity and Treatment Reductions and Delays

Adverse events are listed in Table 2. The most common nonhematologic toxicities were fatigue (primarily grade 1) and nausea (primarily grade 1). Thrombocytopenia was the most common hematologic toxicity, with 20% of patients experiencing grade 3 or 4 thrombocytopenia. Five patients experienced serious adverse events deemed

Table 2. Adverse Events in ≥ 5% of Patients

Toxicity	Total (%)	Grade (%) 1	2	3	4
Hematologic					
Thrombocytopenia	50	17	14	17	3
Anemia*	14			14	
Neutropenia*	8			8	
Nonhematologic					
Fatigue	84	64	17	3	
Nausea	50	42	6	3	
Cough	22	22			
Vomiting	22	14	8		
Dyspnea	19	19			
Diarrhea	17	17			
Fever	11	8		3	
Pneumonia	11			8	3
Respiratory infection	9	6		3	
Constipation	8	8			
Mucositis	6	6			
Febrile neutropenia	6			6	
Hematuria	6	3		3	

*Only grade 3 or 4 reported.

Table 4. Efficacy

Parameter	No.	CR No.	CR %	PR No.	PR %	ORR No.	ORR %	P*
Response by intent to treat	36	12	33	7	19	19	53	
Response for evaluable patients	34	12	35	7	21	19	56	
Median No. of prior therapies								1.0
< 4	16	6	38	3	19	9	56	
≥ 4	18	6	33	4	22	10	55	
Response to last chemotherapy								.185
Sensitive	16	9	56	2	13	11	69	
Resistant	18	3	17	5	28	8	45	
Previous ASCT	26	10	38	5	19	15	57	1.0
Relapsed within 3 months of ASCT	5	0	0	0	0	0	0	.011
Previous alloSCT	6	2	33	2	33	4	66	.672

NOTE. Two unevaluable patients: one died in car accident after two cycles of chemotherapy before restaging; one withdrew consent after one cycle of treatment; both had clinical evidence of response to treatment.

Abbreviations: alloSCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; CR, complete response; ORR, overall response rate; PR, partial response.

*Fisher's exact test.

at least possibly related to treatment. These included two patients with febrile neutropenia associated with pneumonia, one patient with grade 4 pneumonia, one patient with self-limited gross hematuria, and one patient with grade 2 vomiting requiring < 24 hours admission for intravenous fluids. Of 120 cycles of bendamustine administered, only 11% of the cycles were delayed and 8% dose reduced (Table 3). The most common reason for dose delay or reduction was thrombocytopenia.

Efficacy and Survival Data

By intent to treat, the ORR for the 36 patients was 53% (Table 4). This included 12 CRs (33%) and seven PRs (19%). Sixty-eight percent of patients achieved tumor reduction (Fig 1). The median response duration for responding patients was 5 months. As summarized in Table 3, a history of ASCT, alloSCT, or refractory disease had no impact on likelihood of responding to bendamustine. However, no responses were seen among the five patients who relapsed within 3 months of ASCT. OS and PFS are shown in Figure 2. The median follow-up for surviving patients was 3 years. The median PFS was 5.2 months.

AlloSCT Outcome

Twenty-five patients were potentially eligible for alloSCT at the time of enrollment, including nine patients who consented to our accompanying intent-to-treat alloSCT protocol. The reasons for ineligibility for alloSCT included prior alloSCT (n = 6) and comorbitities (n = 3). Five patients (20%) ultimately underwent alloSCT directly after treatment with bendamustine. Among the remaining 20 patients, reasons for not undergoing alloSCT included refusal (n = 3), progression of disease despite initial response to bendamustine (n = 5),

Table 3. Dose Delays and Reductions

Delay/Reduction	No.	%
Total No. of cycles administered	120	
Total No. of cycles delayed	13	11
Reason for delay		
Thrombocytopenia	9	
Pneumonia*	2	
Upper respiratory infection	1	
HSV infection	1	
Total No. of cycles reduced	10	8
Reason for reduction		
Thrombocytopenia	7	
Neutropenia	1	
Grade 3 nausea and vomiting	1	
Pneumonia with neutropenic fever	1	

Abbreviation: HSV, herpes simplex virus.
*One associated with neutropenic fever.

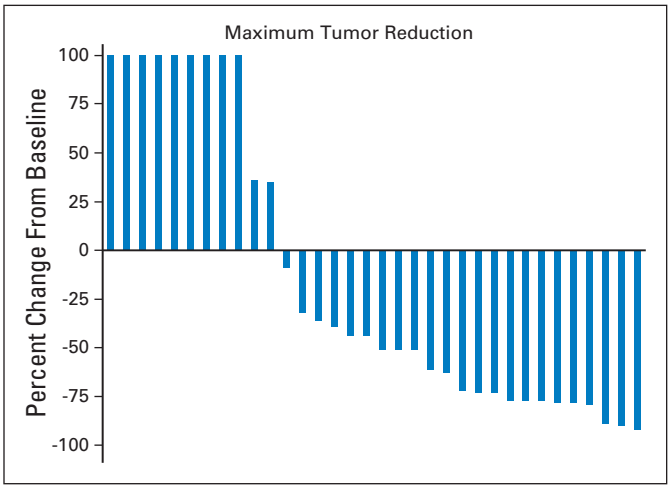

Fig 1. Maximum tumor reduction.

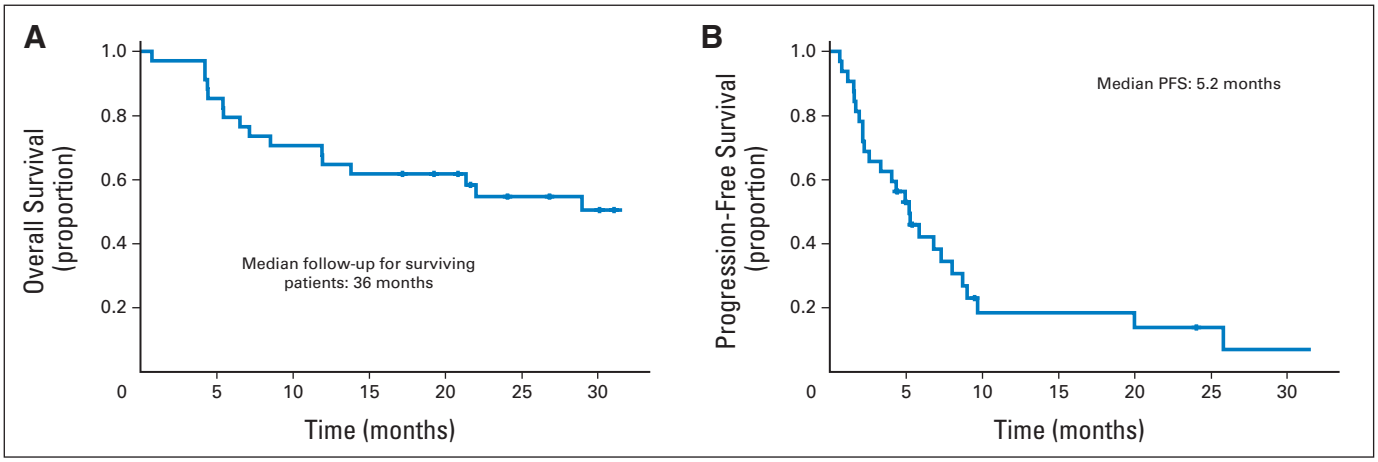

Fig 2. Kaplan-Meier survival curves of (A) overall and (B) progression-free survival (PFS).

disease refractory to bendamustine (n = 8), and toxicity leading to treatment delay and progression of disease (n = 4). The median number of cycles of bendamustine before alloSCT was four. Four patients had achieved CRs and one had achieved PR at time of alloSCT. Since undergoing alloSCT, two patients have remained in remission 19 and 31 months, respectively; the other three patients relapsed at 100 days, 16 months, and 21 months after alloSCT, respectively, and are alive with disease.

DISCUSSION

In this heavily pretreated group with relapsed and refractory HL, which included 75% of patients with previous ASCT, 17% patients with previous alloSCT, 11% with previous ASCT and alloSCT, and over 50% with more than four previous treatments, bendamustine is an active drug inducing responses in 53% of patients. This response rate is comparable to those of multiagent regimens used in this setting, such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin), for which an ORR of 70% was observed in a less heavily pretreated group.[11] Furthermore, the activity compares favorably to those of other single agents tested in this setting, such as panobinostat (ORR, 27%) and lenalidomide (ORR, 19%).[12,13] Responses to bendamustine were seen in patients for whom ASCT and alloSCT failed and in patients refractory to their last treatment; however, among the small subset of patients who had relapsed within 3 months of ASCT, no responses were seen. Because ASCT conditioning regimens routinely incorporate high-dose alkylator therapy, it is not surprising that patients refractory to high-dose therapy seem unlikely to respond to bendamustine as well. Nonalkylating-based therapies may offer more promise for these patients. For all other heavily pretreated patients with relapsed and refractory HL, bendamustine was likely to induce responses and was well tolerated at a dose of 120 mg/m^2, with only 11% and 8% of cycles delayed and reduced, respectively.

Although the response rate was high, the number of patients proceeding to alloSCT after this treatment was disappointing. The principal reason why more patients did not proceed to alloSCT was lack of durable response with bendamustine. The median response duration was only 5 months, and many patients progressed while receiving treatment despite demonstrating initial responses at the 8-week restaging. Therefore, bendamustine may better serve as an initial debulking agent that could be followed by a non–cross-resistant agent to maintain the response. Furthermore, combining bendamustine with other agents may improve both the rate and duration of response, enabling more patients to proceed to consolidation.

We have previously reported the outcomes for patients with relapsed and refractory HL at our institution for whom ASCT failed. The prognosis for this group is, as expected, poor, with a median survival of 25 months.[3] The one factor that improved prognosis after ASCT failure was treatment with a second transplantation, most commonly alloSCT. Clearly, patients who can undergo a second transplantation represent an inherently more favorable group, at least in part because they must demonstrate chemosensitivity and response durability before transplantation; therefore, it is difficult to determine whether alloSCT truly improved outcomes in this setting. Nevertheless, multiple series have demonstrated long-term remission with alloSCT and responses to donor leukocyte infusion, thus supporting the role for alloSCT in patients for whom ASCT has failed.[14]

Because a minimal disease state seems important for alloSCT to be successful, novel agents or novel combinations are needed to improve the referral rate to alloSCT.[7] One of the most promising active drugs currently available is brentuximab vedotin (BV), which is approved for relapsed and refractory HL based on a response rate of 75% in this population.[4] Studies are ongoing aiming to incorporate BV into front-line treatment, pre-ASCT salvage, and post-ASCT maintenance; therefore, it may not be long before most patients relapsing after ASCT will have already received BV. Other options include gemcitabine-based regimens, lenalidomide,[13] everolimus,[15] and other investigational agents.

With a response rate of 53% in heavily pretreated patients, bendamustine is a good option for patients with relapsed and refractory HL who could proceed to consolidative SCT. Studies evaluating bendamustine in combination with other agents are warranted to improve response duration and referral rate to alloSCT. Current bendamustine combinations under investigation in relapsed and refractory HL include bendamustine plus gemcitabine (NCT01535924) and bendamustine plus lenalidomide (NCT01412307). Other promising agents for HL, such as everolimus

and histone deacetylase inhibitors (eg, panobinostat and entinostat), warrant evaluation either in combination with or as maintenance after bendamustine.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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