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Safety of Bendamustine in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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Safety of Bendamustine in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

This is the third article in a 4-part series on bendamustine. While the previous article discussed the efficacy of bendamustine for patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) in the registration studies cited in the US product labeling, this article discusses its safety.[1] The next article in this series will describe ongoing clinical investigations of the agent.

Bendamustine in CLL

As discussed in the previous article in this series, the FDA approved bendamustine hydrochloride (Treanda), an alkylating agent administered IV, on March 20, 2008, for the treatment of patients with CLL. As the basis for its approval, the FDA used the results of a randomized, open-label, parallel-group, multicenter trial comparing bendamustine with chlorambucil as first-line treatment in 301 previously untreated patients (153 on bendamustine and 148 on chlorambucil) with advanced CLL.[1,2] Chlorambucil was chosen as the comparator for this study because it was approved for first-line use in CLL in all participating countries when the pivotal trial was planned in 2001. Patients were randomly assigned to receive either bendamustine 100 mg/m^2 IV on days 1 and 2 every 28 days or chlorambucil 0.8 mg/kg orally on days 1 and 15 every 28 days. Up to 6 cycles were administered to each patient.[1]

Safety Results From the Pivotal CLL Study

Adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 2.0.[3] **Figure 1** shows the abnormal hematologic laboratory test values, indicating the myelosuppressive effects of the drug, seen in this study. Red blood cell transfusions were administered to 20% of patients receiving bendamustine compared with 6% of patients receiving chlorambucil.[1]

Table 1 lists the treatment-emergent AEs, regardless of attribution, that were reported in ≥5% of patients in either treatment group in the randomized CLL clinical study.[1] Worsening hypertension was reported in 4 patients treated with bendamustine and none treated with chlorambucil. Three of these 4 AEs were described as a hypertensive crisis and were managed with oral medications, and all 3 resolved. The most frequent adverse reactions leading to study withdrawal for patients receiving bendamustine were hypersensitivity (2%) and pyrexia (1%).[1]

In the pivotal, randomized CLL clinical study, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Increased grade 3/4 bilirubin occurred in 3% of patients. Increases in AST and ALT of grade 3/4 occurred in 1% and 3% of patients, respectively. The US product label states that "patients treated with bendamustine may also have changes in their creatinine levels."[1]

> Red blood cell transfusions were administered to 20% of patients receiving bendamustine...

Bendamustine in Indolent B-Cell NHL

As discussed in the previous article in this series, the FDA approved bendamustine on October 31, 2008, for the treatment of patients with indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[1] The US product label for bendamustine presents the pooled safety results of a single-arm study of 100 patients with indolent B-cell NHL who had progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen, and those of a previous phase 2 single-arm study in 76 similarly treated rituximab-refractory patients (including 15 patients with transformed disease).[1,4-6] The pooled patient population evaluated was 31 to 84 years of age, 60% were male, and 40% were female. The race distribution was white, 89%; black, 7%; Hispanic, 3%; other, 1%; and Asian, <1%. These patients received bendamustine at a dose of 120 mg/m^2 IV on days 1 and 2 of a 21-day cycle for up to 8 cycles.[1]

Figure 1. Incidence of Hematologic Laboratory Abnormalities in Patients Who Received Bendamustine or Chlorambucil in the Randomized CLL Clinical Study[1]

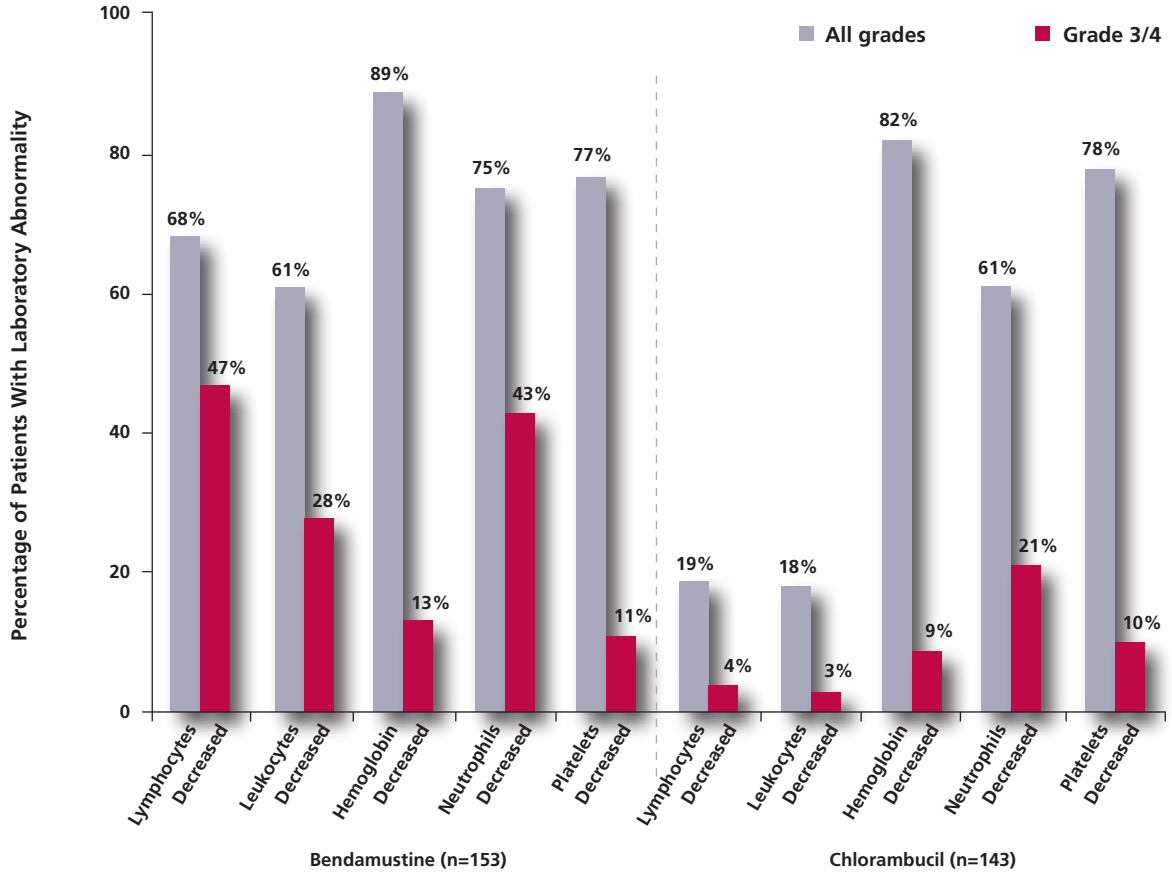
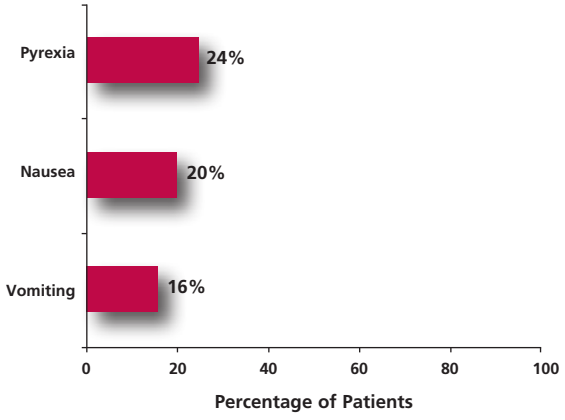


Figure 2. Nonhematologic Adverse Reactions (Any Grade) That Occurred in ≥15% of Patients Who Received Bendamustine in the Randomized CLL Clinical Study[1]



Pooled Safety Results From 2 Indolent B-Cell NHL Studies

In both NHL studies, serious AEs, regardless of causality, were reported in 37% of patients receiving bendamustine. The most common serious adverse reactions occurring in ≥5% of patients were febrile neutropenia and pneumonia.[1]

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single-arm studies combined are shown in **Figure 3**.[1] The median time to a neutrophil nadir was 21 days (range, 1-86 days) and recovery to >1000/μL was 8 days (range, 2-62 days). The median time to platelet nadir was 21 days (range, 1-94 days) and recovery was 14 days (range, 3-63 days). Growth factors or blood products were used in 33% of 901 cycles, and 51% of patients received some growth factor support.[6]

The most common nonhematologic AEs (regardless of severity) in the 2 pooled studies of patients with indolent B-cell NHL are shown in **Figure 4**. The most common nonhematologic grade 3/4 AEs (≥5%) were fatigue (11%), fe-

Table 1. Nonhematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in ≥5% of Patients[1]

	Bendamustine (n=153)		Chlorambucil (n=143)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Total number of patients with at least 1 adverse event	121 (79)	52 (34)	96 (67)	25 (17)
System organ class				
Preferred term				
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10 (7)	0	12 (8)	0
Infection	9 (6)	3 (2)	1 (<1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	11 (7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11 (7)	3 (2)	2 (1)	0
Respiratory, thoracic, and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	12 (8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

brile neutropenia (6%), and pneumonia, hypokalemia, and dehydration (5% each).[1]

The nonhematologic AEs occurring in ≥5% of the NHL patients are listed in **Table 2**. Grade 3/4 AEs were more common in patients aged ≥65 years than <65 years (81% vs 66%, respectively) primarily because of asthenia (16% vs 9%), thrombocytopenia (25% vs 11%), cardiac disorders (11% vs 2%), and infection (24% vs 16%). Patients with previous purine analogue exposure had an increased risk of grade 3/4 neutropenia (41% vs 29%), grade 3/4 infections (26% vs 14%), and herpes zoster reactivation (13% vs 8%). The latter did not occur in patients on prophylactic antivirals, while it occurred in 11% of those not receiving prophylactic therapy. Opportunistic infections were relatively uncommon with bendamustine, with 10% of patients having herpes zoster, 9% candidiasis, 4% herpes simplex, 3% cytomegalovirus, 1% *Pneumocystis jiroveci*, and 1% *Mycobacterium*.[6]

Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at grade 3 or 4 in NHL patients treated in both single-arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).[1]

Key Bendamustine-Related Adverse Reactions and Their Management

Serious drug-related AEs reported in bendamustine clinical trials included myelosuppression, infections (such as pneumonia), infusion reactions, and tumor lysis syndrome.[1]

Myelosuppression

As with other cytotoxic therapies, bendamustine suppresses bone marrow function, which is likely to result in thrombocytopenia, leukocytopenia, neutropenia, and anemia (**Figure 1** and **Figure 3**).[7] In the 2 NHL studies, 3 patients (2%) died of myelosuppression-related AEs; 1 with neutropenic sepsis, 1 with diffuse alveolar hemorrhage with grade 3 thrombocytopenia, and 1 with pneumonia from a cytomegalovirus infection.[1]

In the clinical trials, leukocyte, platelet, hemoglobin, and neutrophil counts were monitored every week initially, and the lowest cell counts typically occurred during the third week after treatment.[7] Myelosuppression was generally reversible.[7] Management strategies for myelosuppression include the administration of colony-stimulating factors and blood product replacement and bendamustine dosage reduction.[7] Grade 3 or 4 neutropenia led to filgrastim or pegfilgrastim therapy in 38% of patients in the larger indolent NHL study.[4] In the CLL study, granulocyte colony-stimulating factors (used at the discretion of the investigator) were administered during 3% (23 of 783 cycles) of bendamustine and 0.3% (2 of 733) of chlorambucil cycles, with erythropoietin administered during 0.5% and 0.3% of cycles.[2] According to the pooled analysis of the rituximab-refractory indolent NHL data, blood products or growth factors were used in 33% of cycles (297 of 901 cycles), with 51% of patients receiving growth factor support.[6] In addition, a higher incidence of grade 3/4 neutropenia (41% vs 29%) was observed in patients with previous purine analogue exposure than in those without this exposure.[6]

Hematologic nadirs may require dose delays if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Before administration of the next cycle of treatment, the absolute neutrophil count should be ≥1000 cells/mL and the platelet count should be ≥75,000 cells/mL.[1] Up-front dosage reductions in the first cycle should be considered for patients who have been heavily pretreated, have a poor performance status, or both. Similarly, this approach may be reasonable to further limit myelosuppression in patients demonstrating a good response.[7]

Infections

The US product label for bendamustine points out that infections, including pneumonia and sepsis, have been reported in adult and pediatric patients in clinical trials and in postmarketing reports, and that infection has been associated with hospitalization, septic shock, and death.[1] Patients with myelosuppression following treatment with bendamustine are more susceptible to infections.[1] Patients receiving bendamustine, especially those with myelosuppression, should be counseled about the potential risk of infection and instructed to immediately report any signs or symptoms of infection.[1]

Infusion Reactions and Anaphylaxis

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy.[1] The US product label for bendamustine points out that patients receiving bendamustine should be monitored clinically and the drug should be discontinued for severe (grade 3/4) reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. In clinical trials, patients who experienced grade ≥3 allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including premedicating with antihistamines and corticosteroids, should be considered in subsequent cycles for patients who have previously experienced grade 1 or 2 infusion reactions, although discontinuation of bendamustine may be necessary in more severe cases.[1,5]

Tumor Lysis Syndrome and Skin Reactions

Tumor lysis syndrome (TLS) is a metabolic disorder that develops as lysed tumor cells release their intracellular contents into the circulation. It is characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia and may lead to acute renal failure, cardiac arrhythmias, or death.[1,8] TLS associated with bendamustine treatment has been reported in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death.[1] TLS occurred in 2 patients with previously untreated CLL who had received their first cycle of bendamustine; these events were not fatal and both patients continued with treatment.[2] In the larger indolent NHL study, 2 patients with disease refractory to rituximab (who had previously been treated with a median of 2 [range, 0-6] chemotherapy regimens) developed TLS (1 grade 3 and 1 grade 4); both episodes resolved with appropriate supportive care, and both patients continued with therapy.[4]

Patients taking bendamustine should be carefully moni-

tored for tumor burden, renal function, and blood chemistry levels (particularly potassium and uric acid levels).[1,7] In high-risk patients (ie, those with large tumor burden [elevated lactate dehydrogenase concentration or circulating tumor cells of >25,000/mm^3], tumors with a high proliferation rate, or tumors with increased sensitivity to cytotoxic therapy), administration of IV or oral fluids is recommended to maintain a high fluid volume.[7] In some cases, allopurinol is administered during the beginning of bendamustine therapy to minimize uric acid production.[7] However, there may be an increased risk of severe skin toxicity (including Stevens-Johnson syndrome [SJS], and toxic epidermal necrolysis [TEN]) when bendamustine and allopurinol are administered concomitantly.[1,7] Another agent, rasburicase, has been suggested as an alternative to allopurinol for the prevention of TLS in patients undergoing treatment with bendamustine for CLL.[7]

A number of skin reactions, including rash, toxic skin reactions, and bullous exanthema have been reported in clinical trials and postmarketing safety reports, although the precise relationship to bendamustine is uncertain.[1] When skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld or discontinued.[1]

Secondary Malignancies

Because bendamustine damages DNA, there is a potential for treatment-induced development of secondary malignancies.[7] The US product labeling states that reports of premalignant and malignant diseases that have developed in patients who have been treated with bendamustine include myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma, but the association with bendamustine therapy has not been determined.[1] One patient in the bendamustine treatment group of the CLL study developed a new malignancy (bronchial carcinoma) 12 months following treatment cessation.[2] In the 2 NHL studies, 9 patients (5%) experienced secondary malignancies: 5 myelodysplastic syndromes, 1 chronic myelomonocytic leukemia, 2 acute myeloid leukemias, and 1 squamous cell carcinoma (deemed not related to bendamustine therapy). Most of the cases of secondary malignancies occurred relatively soon after completion of bendamustine therapy.[6]

Figure 3. Incidence of Hematologic Laboratory Abnormalities in Patients Who Received Bendamustine in the NHL Studies[1]

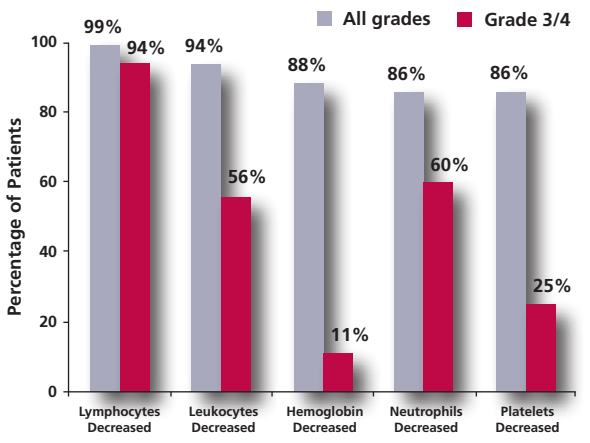
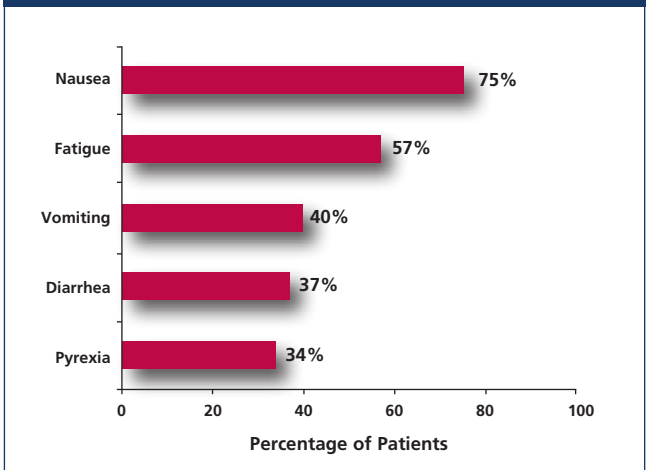


Figure 4. Nonhematologic Adverse Reactions (Any Grade) That Occurred in ≥30% of Patients Who Received Bendamustine in the 2 Pooled NHL Clinical Studies[1]



Summary

The safety of bendamustine in CLL and in indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen has been demonstrated in patients who participated in an actively controlled trial for the treatment of CLL and 2 single-arm studies for the treatment of indolent B-cell NHL. In these studies, the most frequently reported AE was myelosuppression. The most common nonhematologic AEs seen with bendamustine in CLL were pyrexia, nausea, and vomiting, while in NHL, the most commonly reported AEs were nausea, fatigue, vomiting, diarrhea, and pyrexia. Serious drug-related AEs reported in bendamustine clinical trials

Table 2. Nonhematologic Adverse Reactions Occurring in ≥5% of NHL Patients Treated With Bendamustine[1]

	Bendamustine (N=176)	
	All Grades n (%)*	Grade 3/4 n (%)*
Total number of patients with at least 1 adverse event	176 (100)	94 (53)
System organ class		
Preferred term		
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Peripheral edema	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropenia	11 (6)	11 (6)

	Bendamustine (N=176)	
	All Grades n (%)*	Grade 3/4 n (%)*
Infections and infestations (cont)		
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
Psychiatric disorders		
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic, and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3 (2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

*Patients may have reported more than 1 adverse reaction.

included myelosuppression, infections (such as pneumonia), infusion reactions, and TLS. Cases of SJS/TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. Patients should be monitored closely for these reactions after bendamustine treatment for early intervention.

Part 4 in the Series

The next article in this series will describe ongoing clinical investigations of bendamustine. ■

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Safety of Bendamustine in Treatment of CLL and NHL

Colleen Ross, RN, MSN, MHA, OCN

Chronic Lymphocytic Leukemia

Bendamustine is approved for single-agent use in chronic lymphocytic leukemia (CLL) based on the result from a phase 3 trial comparing bendamustine and chlorambucil.[1] Progression-free survival was 18 months in the bendamustine group versus 6 months in the chlorambucil group. Bendamustine 100 mg/m^2 was administered on days 1 and 2 of a 28-day cycle.[1] Overall, bendamustine was well tolerated. The most common hematologic adverse events reported were anemia (89%), thrombocytopenia (77%), and neutropenia (75%). Laboratory values should be monitored on a weekly basis. Hematologic nadir typically occurs during week 3 of treatment. Blood transfusions were required in 20% of patients in the bendamustine arm versus 6% in the chlorambucil arm.[1]

> Overall, bendamustine is effective and generally well tolerated in patients with CLL and NHL.

The most common gastrointestinal adverse events included nausea (20%), vomiting (16%), diarrhea (9%), and weight loss (7%). Other nonhematologic adverse events included drug-related fever (24%), fatigue (9%), asthenia (8%), rash (8%), hyperuricemia (7%), nasopharyngitis (7%), chills (6%), hypersensitivity reactions (5%), pruritus (5%), and herpes simplex (3%).[1]

Adverse reactions and hypersensitivity reactions after the first infusion have been reported. Premedications such as antiemetics and steroids are given prior to infusions. Prophylaxis with antifungal, antiviral, and antibiotic therapy during treatment will help to prevent the possibility of fungal and herpes infections and pneumocystis pneumonia.

Dose reduction perimeters for grade 3/4 hematologic or nonhematologic adverse events are as follows: for the first occurrence, decrease the dose from 100 mg/m^2 to 50 mg/m^2. If the adverse events require a treatment delay, the same guidelines pertain and treatment is held until resolution of the grade 3/4 adverse event. If a second dose reduction is required, 25 mg/m^2 would be given.[1]

Non-Hodgkin Lymphoma

Bendamustine is also approved as a single-agent therapy for patients with non-Hodgkin lymphoma (NHL) in whom rituximab or a rituximab-containing regimen has failed during or within 6 months of treatment.[1] Safety results are from a single-agent therapy trial of 100 participants that produced a 74% overall response rate and median response of 9.2 months. The recommended dose of bendamustine for the treatment of NHL is 120 mg/m^2 administered on days 1 and 2 of a 21-day cycle. Hematologic nadir is usually seen during week 3 of treatment, and weekly laboratory surveillance is recommended.[1]

In a study by Cheson and colleagues, growth factors or blood products were used in 31% of 903 cycles; growth factor alone was used in 51% of patients.[2] Growth factor should be given after an episode of febrile neutropenia, not as prophylaxis.

The most common nonhematologic adverse events reported are nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), pyrexia (34%), constipation (29%), weight loss (18%), stomatitis (15%), herpes zoster (10%), and urinary tract infection (10%).[1] Grade 3/4 adverse events were more common in patients aged ≥66 years than in younger patients (88% vs 66%, respectively).[2] Protection from infection required placing the patient on antibacterial, antifungal, and antiviral prophylactic therapy. If dose reduction or dose delays for grade 3/4 adverse events is necessary, decrease the dose from 120 mg/m^2 to 90 mg/m^2 on days 1 and 2. If treatment delays or recurring grade 3/4 adverse events continue, the dose should be reduced to 60 mg/m^2 on days 1 and 2.[1]

Overall, bendamustine is effective and generally well tolerated in patients with CLL and NHL. With diligent surveillance, side effect management, and patient education about the most commonly seen side effects, patients can receive documented benefit from bendamustine, with longer disease-free survival. ■

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Toxicity of Bendamustine Therapy

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Bendamustine is an active chemotherapy agent approved by the FDA for the treatment of patients with chronic lymphocytic leukemia (CLL) and for specific populations of patients with non-Hodgkin lymphoma (NHL). While bendamustine has been reported to be very effective in treating these malignancies, its tolerable toxicity profile has made it a useful agent in a variety of patient populations.

Bendamustine, like many other cytotoxic therapies, is associated with hematologic adverse events including neutropenia, anemia, and thrombocytopenia. Myelosuppression associated with bendamustine therapy is generally reversible. The median time to neutrophil and platelet nadir is approximately 21 days, with recovery occurring in 8 and 14 days, respectively.[1] Management strategies for patients experiencing bone marrow suppression include blood product transfusions, colony-stimulating growth factors, and dose reductions for future bendamustine cycles. Further cycles of bendamustine should be delayed until the absolute neutrophil count is ≥1000 cells/mL and the platelet count is ≥75,000 cells/mL.

Since myelosuppression has been reported in trials in which bendamustine was used as either monotherapy or in combination therapy, patients are at an increased risk for infectious complications. Prophylactic antimicrobials were not routinely administered to patients enrolled in bendamustine trials. Commonly reported infections when bendamustine was given as monotherapy include pneumonia, herpes zoster, and *Candida* infections. When bendamustine was given in combination with rituximab, viral infections such as cytomegalovirus, herpes simplex, and herpes zoster were reported, as well as fungal infections, pneumonia, and bacterial sepsis.[2] All patients experiencing myelosuppression during bendamustine therapy should be counseled to immediately report all symptoms of infection.

Nonhematologic toxicities have also been reported with bendamustine therapy. Gastrointestinal effects such as nausea and vomiting can affect up to 40% of patients.[1] Most studies report that the majority of patients experience grade 1/2 toxicities that do not require dose adjustment of bendamustine. Bendamustine is considered a moderately emetogenic agent by the National Comprehensive Cancer Network in the 2013 guidelines for antiemesis.[3] It is recommended that each patient receives a serotonin antagonist prior to each dose. Patients should also be given prescriptions for antiemetic agents to be used as needed after chemotherapy. Follow-up prior to each cycle of chemotherapy is suggested to determine if the antiemetic therapy needs adjustment.

Monitoring patients during and after bendamustine infusions is very important. Tumor lysis syndrome has been reported, so tumor burden, electrolytes, and renal function should be evaluated prior to the first cycle. For high-risk patients, agents such as allopurinol or rasburicase with further laboratory monitoring may be necessary. Infusion-related reactions have also occurred during bendamustine therapy. These reactions generally occur during or shortly after the completion of the infusion. Fever, chills, pruritus, shortness of breath, hypotension, and rash have been reported and are more commonly associated with the second or subsequent cycles of therapy. Rarely, anaphylactic reactions have occurred with bendamustine administration. Patients experiencing severe reactions may need to discontinue therapy. However, for less severe reactions, patients may be rechallenged if premedicated with antihistamines and corticosteroids.[4] Finally, long-term follow-up of bendamustine patients is essential. Premalignant and secondary malignancies have been reported in patients who have received bendamustine therapy. Most of these cases occurred soon after the completion of bendamustine therapy.[5] While concerning, a direct association with bendamustine therapy cannot be made at this time.

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Bendamustine has demonstrated it is an active agent in patients with CLL and specific populations of NHL. Even though this agent is generally well tolerated, a discussion of potential and serious side effects should occur with both patient and caregivers prior to the initiation of therapy. Patients and caregivers should be given an opportunity to ask questions. Also, written information regarding side effects and provider contact information can be a helpful resource for patients. As the clinical experience with bendamustine matures, it will be important to document the long-term safety

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Safety of Bendamustine in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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The previous articles have outlined the clinical outcomes of clinical trials evaluating bendamustine in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). The third in the series of articles discusses the short-term toxicities of bendamustine from these clinical trials.

Patients with CLL are always a challenge to treat due to their underlying immune suppression. Compared with chlorambucil, patients receiving bendamustine had higher rate of grade 3/4 neutropenia – 43% versus 21%. Grade 3/4 thrombocytopenia was almost identical – 10% for chlorambucil and 11% for bendamustine, and the infection rate was similar in the 2 arms. Nonhematologic toxicities were also similar between the arms. With similar toxicities but an improved response rate, bendamustine has become a frequently used alternative for patients with CLL.

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In patients with indolent NHL, the pooled safety data showed the most common serious adverse events to be febrile neutropenia and pneumonia. Other grade 3/4 adverse events of note were fatigue (11%), hypokalemia (5%), and dehydration (5%). Varicella zoster reactivation was seen in 11% of patients who did not take antiviral prophylaxis but was controlled in those who did take it. Patients with prior purine analogue therapy had an increased risk of grade 3/4 neutropenia (41% vs 29%). Appropriate prophylactic antibiotics do need to be used in patients receiving bendamustine.

Infections are common in patients with CLL and NHL despite aggressive supportive care such as neupogen or neulasta and prophylactic antibiotics. If a patient has been heavily pretreated, has a lower neutrophil count, or has a bad performance status, a first-cycle dose reduction of bendamustine should be considered. A high level of suspicion for cytopenias and infectious complications should be maintained for patients receiving bendamustine. Other more rare complications include infusion reaction, rash, or tumor lysis. Because bendamustine does damage DNA, there is the potential for secondary malignancies as well. However, when weighing the risk/benefit ratio, bendamustine is a beneficial drug for many patients with CLL and NHL. ■

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profile of this agent. Long-term follow-up of patients and submission of adverse events to the manufacturer will help define the role and toxicity profile of bendamustine in these patient populations. ■

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