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A Retrospective Review of the Characterization of Bendamustine

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History and Characterization of Bendamustine

This is the first article in a 4-part series on bendamustine. This article describes the history and characterization of bendamustine. Subsequent articles will discuss the efficacy and safety of bendamustine in registration studies and describe ongoing clinical investigations of bendamustine.

Bendamustine is a bifunctional chemotherapeutic agent with both alkylating and antimetabolite (purine analog) properties, which are discussed in more detail below.[1,2] Bendamustine is known by the trade names Treanda in the United States, where it was initially approved in 2008; Ribomustin in some countries in the European Union (eg, Germany and Switzerland); and Levact in other countries in the European Union, including Austria, Belgium, Denmark, Finland, France, Ireland, Italy, Luxembourg, Norway, Poland, Spain, and the United Kingdom, where it was approved in 2010.[2-5]

The approved indications for bendamustine vary by geographic location. Treanda (bendamustine hydrochloride) for Injection, for IV infusion, is approved in the United States for the treatment of patients with chronic lymphocytic leukemia (CLL), and 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.[3] Levact (bendamustine hydrochloride) is approved for the treatment of CLL in patients who cannot be treated with fludarabine combination therapy; for NHL in patients whose cancer progressed during or within 6 months of treatment with rituximab or rituximab-containing regimens; and for frontline treatment of multiple myeloma (MM) in combination with prednisone in patients older than age 65 years who are not eligible for autologous stem cell transplantation and who cannot be treated with thalidomide or bortezomib due to the presence of clinical neuropathy at diagnosis.[2,5] Ribomustin (bendamustine hydrochloride) was approved for frontline treatment of indolent NHL as part of combination therapy; for advanced MM (Durie-Salmon stage II with progression or stage III) in combination with prednisone; and for CLL.[6]

The use of bendamustine in the United States for indications other than as described above for Treanda is considered to be off-label. Bendamustine is approved in the United States as monotherapy. It is approved in the European Union, as noted, in combination with prednisone for MM.[2,5] Bendamustine has also been used in combination with other agents (**Table 1**[7-11]).

> The use of bendamustine in the US for indications other than as described above for Treanda is considered to be off-label.

Ongoing clinical investigations of bendamustine as monotherapy or in combination therapy in patients with hematologic malignancies or with solid tumors will be discussed in the fourth article in this series.

History of Bendamustine

The observation that nitrogen mustard induced tumor responses resulted in research on the use of alkylating agents to treat cancer.[12] The alkylating agent bendamustine was first synthesized in 1963 in Jena, in the former German Democratic Republic (East Germany), at the Institute for Microbiology and Experimental Therapy.[12] The first use of bendamustine was in 1969 to treat MM.[13] Bendamustine was used primarily in East Germany in patients with CLL, NHL, Hodgkin disease, MM, and lung cancer. Bendamustine was not studied systematically in clinical trials in patients until the 1990s, after German reunification.[9,12] The development of bendamustine in the United States began in the early 2000s.[1]

Table 1. Bendamustine Combination Therapy[7-11]

In Combination With	Treatment
Prednisone	Multiple myeloma
Rituximab	Mantle cell lymphoma and NHL
Obinutuzumab	CLL and indolent lymphomas
Vincristine and prednisone	Indolent NHL
Mitoxantrone	CLL
Mitoxantrone plus methotrexate and prednisone, with idarubicin plus dexamethasone, or with etoposide	Hematologic malignancies
Bortezomib and rituximab	Relapsed/refractory follicular lymphoma
Fludarabine and rituximab	Newly diagnosed CLL
Mitoxantrone and rituximab	Relapsed/refractory CLL and lymphomas

CLL indicates chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

Bendamustine was approved by the FDA for the treatment of CLL on March 20, 2008, and on October 31, 2008, for the treatment of indolent B-cell NHL in patients whose disease progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.[8,12]

> The exact mechanism of action of bendamustine is not known. It is active against both dividing and quiescent cells.

Characterization of Bendamustine

Structure and Mechanism of Action

Bendamustine hydrochloride is a bifunctional mechlorethamine derivative with the chemical name 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride, with an empirical molecular formula of $C_{16}H_{21}Cl_2N_3O_2 \bullet HCl$ and a molecular weight of 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent.[3] The structural formula of bendamustine is illustrated in **Figure 1**.

The alkylating activity of bendamustine resides in its mechlorethamine or nitrogen mustard moiety, which resembles the alkylating agents cyclophosphamide and chlorambucil. This is illustrated in **Figure 2**.

Bendamustine has a benzimidazole ring, unlike chlorambucil, which has a benzene ring. The benzimidazole ring resembles some purine analogs; it was included to add antimetabolite effects. Although this structure may add purine analog activity to the molecule, this has not been demonstrated.[3] The exact mechanism of action of bendamustine is not known. It is active against both dividing and quiescent cells.[3] The alkylating activity of bendamustine resembles that of other alkylating agents in that it causes interstrand and intrastrand DNA crosslinks.[3,12] The DNA damage, including DNA double-strand breaks caused by bendamustine, are repaired more slowly than those caused by other alkylating agents. Bendamustine, unlike other alkylating agents, appears to have a unique mechanism of activation of DNA damage stress responses and apoptosis (programmed cell death), and inhibition of mitotic checkpoints. For example, bendamustine causes an increase in the proportion of cells in the S phase of the cell cycle and downregulates genes involved in cell division.[12]

Bendamustine activates a base-excision DNA repair pathway, but unlike other alkylating agents it does not induce an alkyltransferase mechanism of DNA repair. This may result in less susceptibility to drug resistance. The regulation of apoptosis associated with bendamustine is also unlike that

associated with other alkylating agents and appears to be stronger and more rapid.[12] Bendamustine also appears to induce cell death by mitotic catastrophe, a necrotic mechanism, which is distinct from apoptosis. Therefore, even in malignant cells that are missing a functional apoptotic pathway, bendamustine has cytotoxic activity. Other nonapoptotic mechanisms associated with bendamustine-induced cytotoxicity include depletion of adenosine triphosphate, which may make cells more susceptible to metabolic shutdown, and induction of reactive oxygen species stress pathways, which may also affect metabolic equilibrium.[14]

Pharmacology

Dosage and Administration

For patients with CLL, bendamustine is administered by IV infusion at a dose of 100 mg/m^2 over 30 minutes on days 1 and 2 of a 28-day cycle for up to 6 cycles. For patients with NHL, bendamustine is administered by IV infusion at a dose of 120 mg/m^2 over 60 minutes on days 1 and 2 of a 21-day cycle for up to 8 cycles.[3]

Pharmacokinetics

Pharmacokinetic parameters are summarized in **Table 2**.[3,15]

Absorption

The C_{max} of bendamustine hydrochloride occurs at the end of infusion of a single IV dose (dose unspecified).[3]

Distribution

In in vitro studies, 94% to 96% of bendamustine was bound to human serum plasma proteins,[3] primarily albumin. Only the free form is pharmacologically active.[12] This binding was independent of concentration over a range of 1 to 50 µg/mL of bendamustine. There is no evidence that bendamustine displaces or is displaced by highly protein-bound drugs. Bendamustine distributes freely in human red blood cells based on concentration ratios of blood to plasma of 0.84 to 0.86 for bendamustine concentrations of 10 to 100 µg/mL.[3] The role of active transport systems that might affect bendamustine distribution has not been completely evaluated. That P-glycoprotein, the breast cancer resistance protein, and/or other efflux transporters may play a role in bendamustine transport has been suggested by in vitro studies.[3]

Figure 1. Structural Formula of Bendamustine Hydrochloride[3]

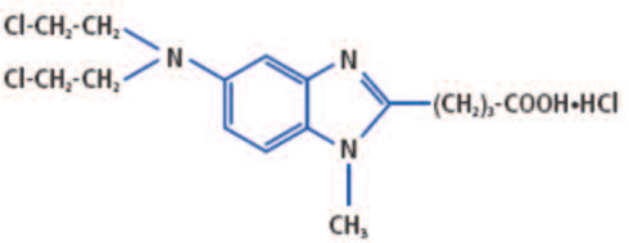
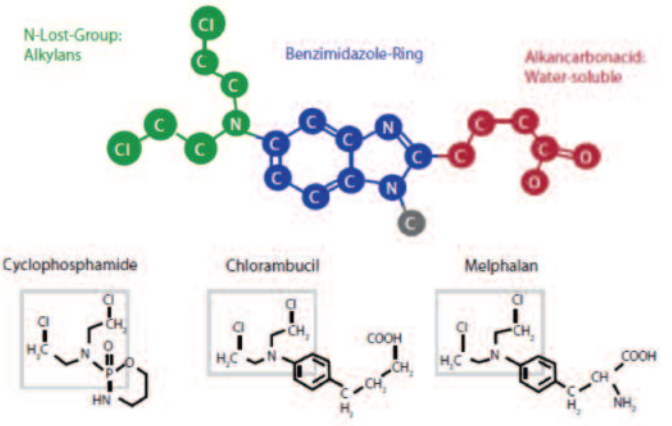


Figure 2. Comparison of the Chemical Structure of Bendamustine With Other Alkylating Agents[14]



Leoni L. The alkylating properties of bendamustine. *Clin Adv Hem Onc*. 2011;9(suppl 19):3-5. Reprinted with permission from *Clinical Advances in Hematology & Oncology*, the copyright holder.

Metabolism

In vitro studies show that bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. Two active minor metabolites, M3 (gamma-hydroxy bendamustine) and M4 (N-desmethyl-bendamustine), are formed via the cytochrome P450 enzyme CYP1A2.[3] M3 is present in plasma at 1/10 the concentration of bendamustine. M4 is present in plasma at 1/100 the concentration of bendamustine.[3] The cytotoxic activity of bendamustine resides primarily in the original, unmetabolized compound.[12] Bendamustine does not inhibit cytochrome P450 enzymes

Table 2. Pharmacokinetic Parameters of IV Bendamustine Hydrochloride[3,15]

Parameter	Value
C_{max}	11.8 µg/mL
AUC	11.7 hr* µg/mL
V_d (volume of distribution)	19.3 L
V_{ss} (steady state V_d)	15.8 to 25 L
Clearance (adults)	639 to 700 mL/minute
Clearance (geometric mean body surface adjusted in pediatric patients)	14.2 L/hr/m^2
t_{max}, mean	29.6 minutes
$t_{½}$ (elimination half-life), mean	28.2 minutes
$t_{½}$ bendamustine (intermediate)	40 minutes for single-dose 120 mg/m^2 bendamustine infused over 60 minutes
$t_{½}$ M3* (mean apparent terminal)	3 hours
$t_{½}$ M4* (mean apparent terminal)	30 minutes

*Minor active metabolite.

CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5 in human liver microsomes in vitro. Bendamustine did not induce metabolism of the cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 in primary human hepatocyte cultures.[3] Inhibitors of CYP1A2 could potentially increase plasma concentrations of bendamustine and decrease plasma concentrations of its active metabolites. CYP1A2 inducers could potentially decrease plasma concentrations of bendamustine and increase plasma concentrations of its metabolites.[3]

When bendamustine is administered on days 1 and 2 of a 28-day cycle, little or no accumulation is expected.

Elimination

In preclinical studies, about 90% of radiolabeled bendamustine is recovered primarily in the feces,[3] and to a lesser extent in the urine. Nonmetabolized particles make up nearly half of the bendamustine that is excreted in urine.[12] Clearance of bendamustine and half-life of bendamustine and minor metabolites M3 and M4 in clinical studies are summarized in Table 2. When bendamustine is administered on days 1 and 2 of a 28-day cycle, little or no accumulation is expected.[3]

Renal Impairment

There have been no formal studies of the effect of renal impairment on the pharmacokinetics of bendamustine.[3] In a population pharmacokinetic analysis of 31 patients receiving bendamustine at a dose of 120 mg/m^2, there was no meaningful effect of renal impairment defined as a creatinine clearance (CrCl) of 40 to 80 mL/minute on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with a CrCl of less than 40 mL/minute. Because of these limited data, bendamustine should be used with caution in patients with mild or moderate renal impairment, and should not be used in patients with a CrCl of less than 40 mL/minute.[3]

Hepatic Impairment

There have been no formal studies of the effect of hepatic impairment on the pharmacokinetics of bendamustine.[3] In a

population pharmacokinetic analysis of 26 patients receiving bendamustine at a dose of 120 mg/m^2, there was no meaningful effect of mild hepatic impairment on the pharmacokinetics of bendamustine. In this study, mild hepatic impairment was defined as total bilirubin no greater than the upper limit of normal (ULN), aspartate aminotransferase (AST) ≥ULN to 2.5 times the ULN, and/or alkaline phosphatase (ALP) ≥ULN to 5.0 times the ULN. Bendamustine has not been studied in patients with moderate or severe hepatic impairment. Because of these limited data, bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate hepatic impairment, defined as AST or ALT 2.5 to 10 times the ULN and total bilirubin 1.5 to 3 times the ULN, or in patients with severe hepatic impairment, defined as total bilirubin greater than 3 times the ULN.[3]

Pharmacodynamics

Age

The pharmacokinetics of bendamustine were similar in patients younger than and at least age 65 years in a study of adults aged 31 through 84 years.[3] In studies in patients with CLL and NHL, there were no clinically significant differences in the safety profile of bendamustine in patients who were at least aged 65 years compared with younger patients.[3]

Bendamustine has been studied in a single phase 1/2 trial in pediatric patients aged 1 to 19 years with acute lymphocytic leukemia (n=27) or acute myeloid leukemia (n=16). The exposures as measured by AUC (area under the concentration time curve from 0 to 24 hours) and C_{max} were similar to those measured in adults at the same dose (120 mg/m^2 IV administered over 60 minutes). Note that the efficacy of bendamustine has not been established in pediatric patients.[3]

Gender

There were no differences in the pharmacokinetics of bendamustine in male and female patients[3] and no differences in safety between male and female patients in studies of patients with either CLL or NHL.[3]

Race

The effect of race on safety and/or efficacy of bendamustine has not been determined. Although a small number (n=6) of Japanese subjects had an average exposure that was 40% higher than that of non-Japanese subjects (number not specified) receiving the same dose, the significance of this difference is not known.[3]

Adverse Events

In adult patients with NHL, there was a correlation between nausea and the C_{max} of bendamustine.[3]

Part 2 in the Series

The next article in this series will present the efficacy data for the registration studies of bendamustine in patients with CLL and NHL. ■

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Stakeholder's Perspective

Julie M. Vose, MD, MBA

Bendamustine has an interesting history that spans more than 50 years. Bendamustine was first synthesized in the early 1960s in the former East Germany. It was first used to treat multiple myeloma and was subsequently extended to patients with chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma. Unfortunately, not much information is available from these original patients treated with bendamustine. It might have been possible to answer some of the questions regarding the long-term effects of bendamustine if these original patients had been followed up and their data recorded. Since bendamustine was first studied in prospective clinical trials in the 1990s, a large amount of information of single-agent and more recently combination therapy has become available.

> Bendamustine should be used with caution in patients with renal and hepatic impairment.

This article points out the compound structure of bendamustine and its dual mechanisms of action with both alkylating agent activity and purine analog-like activity. Therefore, bendamustine causes cellular death by several mechanisms, including activation of DNA damage stress responses, apoptosis, and inhibition of mitotic checkpoints. When combined with monoclonal antibodies and/or other chemotherapeutic agents, multiple mechanisms of cell death can be combined, thereby increasing malignant cell death. With chemotherapy-resistant malignant cells, this method of attack from multiple mechanisms may be more beneficial.

An interesting aspect of bendamustine is its approval at a number of different doses and for different clinical indications in various areas of the world. With the growing clinical information in a variety of malignancies, extension of the indications for bendamustine seem likely in the United States. Clinically, bendamustine has demonstrated a wide therapeutic usefulness; however, dose reductions in heavily pretreated patients are frequently needed.

The metabolism of bendamustine is primarily through hydrolysis to metabolites. The majority of the elimination is through feces; however, a small amount is excreted in the urine. Bendamustine should be used with caution in patients with renal and hepatic impairment.

This series of articles will discuss data concerning the clinical use of bendamustine in its current indications of CLL and indolent NHL, as well as some of the areas of ongoing investigation in different indications and with a variety of combination therapies. ■

Stakeholder's Perspective

Colleen Ross, RN, MSN, MHA, OCN

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults and is a slowly progressing cancer of the blood and bone marrow. According to cancer statistics, an estimated 16,060 new CLL diagnoses will be made in the United States in 2012.[1] Careful surveillance predicts the time point where treatment becomes necessary. Bendamustine has a unique structure that acts as an alkylating agent, and DNA damage occurs in the cell, causing apoptosis. Bendamustine has been shown to be beneficial as frontline, salvage treatment in CLL, indolent B-cell non-Hodgkin lymphoma, and advanced multiple myeloma. Its mechanism of action may promote less drug resistance in the cell but is not fully understood.

Prior to infusion with bendamustine, the patient is given written information regarding drug delivery and side effects. On the day of treatment, the oncology case manager will review the written information, going over expected treatment side effects. Bendamustine is administered over 60 minutes at doses of 100 mg/m^2 or 120 mg/m^2 on days 1 and 2 of 21- or 28-day cycles.

Adverse reactions to bendamustine include pancytopenia, nausea, vomiting, fatigue, weakness, dry mouth, somnolence, cough, constipation, headache, stomatitis, and skin rash.[2] Careful monitoring of blood counts, usually once per week, is recommended due to the possibility of pancytopenias in week 3. After the first cycle is complete, patient tolerability and blood count trend will be assessed and adjustments in treatment will be made prior to the next cycle.

Along with a complete blood count with differential, a chemistry panel should be done to monitor the patient's renal and liver function, especially in patients with impairments. Due to susceptibility for infection, particularly if the patient has received previous treatment, the usual practice is to start antibiotic prophylaxis. A broad-spectrum antibiotic such as Bactrim DS or another similar antibiotic is prescribed. For an absolute neutrophil count of <500, and/or febrile neutropenia, growth factor support will be ordered at the next cycle. Blood or platelet transfusions are normally not needed, but in the case of significant hematological toxicity, transfusions may be given, and generally a dose reduction for the next cycle will be ordered. For nausea and vomiting prophylaxis, a long-acting antiemetic is given on day 1, and the patient is given a prescription for an oral antiemetic to be used as needed at home.

> The key to successful and safe treatment is close supervision by the physician and reinforcement of patient education.

The probability of tumor lysis mandates precautionary treatment. The patient is started on allopurinol and given ample fluids at the first cycle. There is a possibility of an infusion reaction necessitating emergency medication, which would include an antihistamine, antipyretic, or corticosteroid. If a grade 1 or 2 reaction occurs, subsequent cycles would include routine administration of these medications.

With overall response rates as high as 77% and a reported duration of response from 6 to 12 months, bendamustine is a reasonable treatment and has tolerable toxicity even in pretreated patients. The key to successful and safe treatment is close supervision by the physician and reinforcement of patient education. The goal of treatment is to control disease and maintain a positive quality of life. ■

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Stakeholder's Perspective

Susanne Liewer, PharmD, BCOP

Since the approval of bendamustine, healthcare practitioners have additional treatment options available to patients with specific hematologic malignancies. In the United States, bendamustine was approved for patients with chronic lymphocytic leukemia (CLL) or indolent B-cell non-Hodgkin lymphoma (NHL) who had progressed within 6 months of receiving rituximab-containing regimens. In Europe, bendamustine has also been approved for use in the CLL and NHL populations, and in some countries it has additional approval for use in multiple myeloma (MM) patients in combination with prednisone when other treatments such as autologous transplant or bortezomib are not appropriate options. In addition to its approved uses, bendamustine is being studied in multiple clinical trials as monotherapy or in combination in patients with relapsed or refractory Hodgkin lymphoma, MM, CLL, and as initial therapy in combination in patients with diffuse large B-cell lymphoma.[1]

> The elimination half-life of the parent compound has been reported to be relatively short at 40 minutes.

Although bendamustine has been approved for use in the United States and Europe for only a short period, it has been under investigation for more than 40 years. Structurally, bendamustine has similarities to both alkylating agents and purine analogs, while maintaining an acceptable side effect profile. The structure contains an alkylating group, a benzimidazole ring, and butyric acid side chain. It has been suggested that the benzimidazole ring, which is unique to bendamustine, contributes to its distinct activity.[2] Even though the chemical structure has many similarities to other agents, the mechanism of action of bendamustine has not yet been fully elucidated. The benzimidazole ring is thought to provide stability and accounts for the sustained toxic effects to the DNA, as well as the blunted DNA repair when compared with other alkylating agents. Despite maintaining activity in more resistant malignancies, bendamustine remains reasonably well tolerated. Hematologic side effects are common. Neutropenia, thrombocytopenia, and anemia have been reported to occur in more than 15% of patients.[3] Common nonhematologic toxicities include nausea, vomiting, diarrhea, fatigue, and fever. As with other alkylating agents, secondary malignancies have been reported, but an association with this agent has yet to be determined.

Drug reconstitution and dilution is straightforward and does not require excessive manipulation or specific tubing. In the United States, bendamustine is available in 25- and 100-mg vials that must be reconstituted with sterile water for injection, resulting in a 5-mg/mL solution. This is then further diluted with 0.9% sodium chloride or 2.5% dextrose and 0.45% sodium chloride solution, with a final concentration of bendamustine between 0.2 and 0.6 mg/mL. Bendamustine does not contain an antimicrobial preservative, so it should be used as soon as possible once it has been reconstituted and further diluted. However, the diluted admixture is stable for 3 hours at room temperature and for 24 hours when refrigerated.[3] Since bendamustine is not cell cycle specific, it may be administered as short infusions. Bendamustine is infused over a 30- or 60-minute duration depending on the dose and indication. Infusion-related toxicities have been reported. Caution should be used when infusing bendamustine, as extravasations of this agent have been reported to cause pain, redness, and swelling.[3]

The pharmacokinetic properties of bendamustine have been well described. Despite good oral bioavailability, bendamustine has only been studied in its IV formulation. This agent is highly protein bound, with over 90% of the drug binding to serum plasma proteins. This binding is not affected by lower levels of serum albumin or advancing age.[4]

Bendamustine is metabolized primarily though hydrolysis in the liver into 2 minor active metabolites. The elimination half-life of the parent compound has been reported to be relatively short at 40 minutes. Few drug interactions have been associated with bendamustine. Theoretical drug interactions include concomitant use with strong CYP1A2 agents such as ciprofloxacin or fluvoxamine. These inhibitors could increase the concentrations of bendamustine while decreasing the levels of the minor metabolites. The clinical significance of these potential interactions remains unclear.

Bendamustine provides another option of therapy for patients with specific hematologic malignancies, with a unique mechanism of action, predictable pharmacokinetic profile, and tolerable toxicity profile. ■

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