Bendamustine (Treanda) For Chronic Lymphocytic Leukemia

A Brief Overview

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INTRODUCTION

Bendamustine HCl (Treanda, Cephalon, Inc.) is an intravenously administered alkylating agent that was approved by the FDA following a priority review for treating patients with chronic lymphocytic leukemia (CLL). The American Cancer Society estimated that more than 15,000 new cases of CLL would be diagnosed in the U.S. and that approximately 4,400 people would die of CLL during 2008.[1]

Bendamustine was approved for the treatment of CLL on the basis of a randomized, international, multicenter, open-label phase 3 study that compared the drug with chlorambucil (Leukeran, GlaxoSmithKline).[2] Bendamustine has demonstrated clinical activity against various cancers, including non-Hodgkin's lymphoma (NHL),[3,4] multiple myeloma,[5,6] breast cancer,[7] small-cell lung cancer,[8,9] and other solid tumors.[10,11]

The National Comprehensive Cancer Network (NCCN) has updated its Clinical Practice Guidelines in Oncology for NHL to include bendamustine as a single agent for the first-line therapy in patients with CLL. For second-line therapy, it can be used as a single agent or in combination with rituximab (Rituxan, Genentech/Biogen Idec). Although bendamustine is currently approved only for the treatment of CLL, the guidelines also include it as an option for the second-line therapy for follicular lymphoma and mantle-cell lymphoma with a category 2B designation with or without rituximab.[12]

Bendamustine was granted orphan drug status in 2007 and was approved by the FDA on March 20, 2008.[13] On October 31, 2008, the FDA approved bendamustine for treating indolent B-cell NHL that progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.[14]

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CHEMISTRY AND PHARMACOLOGY

Bendamustine is a bifunctional derivative of mechlorethamine with a nitrogen mustard moiety and a benzimidazole ring. The nitrogen mustard group is an alkylating agent that dissociates into electrophilic alkyl groups that form covalent bonds with electron-rich nucleophilic moieties, including single-stranded and double-stranded DNA.

Although the exact mechanism of action is unknown, the covalent linkage with DNA can lead to cell death in both quiescent and dividing cells.[15] In preclinical studies, bendamustine displayed a unique profile compared with other alkylating agents; it exhibits several mechanisms of action, including induction of cell necrosis and apoptosis, activation of DNA repair by base excision, and inhibition of mitotic checkpoints.[16]

PHARMACOKINETICS

Peak plasma concentrations of bendamustine following a single intravenous (IV) administration (100 mg/m^2) are achieved at the end of a one-hour infusion.[17] Bendamustine has a mean steady-state volume of distribution of 25 L and is 94% to 96% bound to serum plasma proteins, primarily albumin, with minimal likelihood of displacement by other highly protein-bound drugs.[17,18]

Bendamustine is distributed freely in blood, with a blood-to-plasma concentration ratio ranging from 0.84 to 0.86 over a concentration of 10 to 100 mcg/mL. The primary route of metabolism occurs via hydrolysis into inactive metabolites. In addition, two active metabolites, M3 and M4, are formed by hepatic cytochrome P450 1A2 at 1/10 and 1/100, respectively, the concentration of the parent compound. M3 and M4 are unlikely to exert significant pharmacological effect. Bendamustine is cleared at a rate of approximately 700 mL/minute, and it is eliminated primarily in the feces (90%). Its mean elimination half-life is 40 minutes.[17]

In preliminary reports, no pharmacokinetic differences were noted in terms of age or mild hepatic or renal sufficiency.[17] No differences in pharmacodynamic parameters were observed in studies of the following patients who received bendamustine 120 mg/m^2:

- patients with renal impairment (N = 31) and a creatinine clearance (CrCl) of 40 to 80 mL/minute or with mild hepatic impairment (N = 26)
- patients with a total bilirubin count at or below the upper limit of normal (ULN)
- patients with aspartate aminotransferase (AST) levels of 1 to 2.5 times the ULN or higher or with alanine aminotransferase (ALT) levels of 1 to 5 times the ULN or higher

Because these results are limited, however, caution should still be used in those patients with renal or hepatic insufficiency.[17]

Although the effect of race on pharmacokinetics has not been established, a study of six Japanese subjects indicated that bendamustine exposure was 40% higher than in non-Japanese subjects. Whether the observed difference significantly affects safety or efficacy in such patients remains unknown.[17]

Disclosure: The authors have no commercial or financial relationships to disclose with regard to this article.

CLINICAL TRIALS

Chronic Lymphocytic Leukemia

The approval of bendamustine was based on results from an unpublished, comparative, phase 3 trial (02CLLIII) of 301 treatment-naive patients with Binet stage B or C CLL.[15,17,19] Data were collected from eight countries (Germany, Bulgaria, Italy, France, Spain, Sweden, Austria, and the United Kingdom) from November 5, 2002, until March 26, 2006. Patients were randomly assigned, in a 1:1 ratio, to receive a continuous IV infusion of bendamustine at 100 mg/m^2 (N = 153) on days 1 and 2 or oral chlorambucil at 0.8 mg/kg (N = 148) on days 1 and 15 of each 28-day cycle for up to six cycles.

The primary endpoints of the study included overall response rate and progression-free survival between treatment groups. The overall response rate was favored in patients who received bendamustine (59%), compared with chlorambucil (26%) ($P < 0.0001$). Similarly, the median progression-free survival rate was superior in the bendamustine group (17.6 months) than in the chlorambucil group (5.7 months) ($P < 0.0001$). Data were insufficient to determine the overall rate of survival.

A secondary endpoint analysis of the duration of response showed a median time of 18.6 months in the bendamustine arm and 6.5 months for the chlorambucil arm. Adverse events occurred at a higher rate in patients receiving bendamustine (89%) than in those receiving chlorambucil (79%); these events most frequently included neutropenia (28%), pyrexia (24%), and thrombocytopenia (23%). The incidence of serious adverse drug events also occurred at a higher frequency with bendamustine (18%) than with chlorambucil (11%).[15,17,19]

Phase 1 and 2 dose-escalation studies for both monotherapy and combination therapies with bendamustine have been reported.[2,20,21] Given as monotherapy in pretreated patients with Binet stage B or stage C CLL or patients with relapsed or refractory disease (N = 31), overall bendamustine response rates of 56% (in 9 of 16 patients) to 60% (9 of 15 patients) were noted.[2,21] In combination therapy with mitoxantrone HCl (Novantrone, Bedford/Ben Venue), an overall response rate of 86% (19 of 22 patients) was noted.[20]

Non-Hodgkin's Lymphoma

The use of bendamustine therapy for NHL has been published in one comparative phase 3 trial conducted in Germany between April 1994 and October 1998.[22] Herold et al. randomly assigned 164 previously untreated patients with follicular lymphoma, mantle-cell lymphoma, or lymphoplasmacytic lymphoma to receive BOP chemotherapy, consisting of bendamustine 60 mg/m^2 plus prednisone 100 mg/m^2 on days 1 to 5 and vincristine (Oncovin) 2 mg on day 1, or to receive a standard COP regimen, consisting of cyclophosphamide 400 mg/m^2 plus prednisone (100 mg/m^2) on days 1 to 5 and vincristine 2 mg on day 1. Drugs were administered by IV infusion over cycles of 21 days for six induction cycles and two consolidation cycles. The primary endpoint was complete remission rate; secondary endpoints included overall survival, toxicity rates, and time to progression and treatment failure.[22]

A complete remission rate of 22% was observed in patients who underwent BOP, compared with a rate of 20% with COP ($P = 0.8$). Overall response rates were also similar between BOP (54/82, 66%) and COP (61/80, 76%; $P = 0.1$). However, the median time to progression was significantly longer for BOP (84 months or more) compared with COP (28 months) ($P = 0.037$).

No significant difference was noted between the groups in time to treatment failure (27 months for BOP; 21 months for COP; $P = 0.5$), although the five-year overall survival rate was superior in BOP responders than in COP responders who did not receive interferon maintenance therapy (69.7% for BOP vs. 47% for COP; $P = 0.03$). No difference, however, was observed in responders who received interferon therapy (91.7% with BOP vs. 80.4% with COP; $P = 0.7$).

The most frequently observed severe adverse events included leukopenia (55.1% for BOP vs. 63% for COP), thrombocytopenia (15.1% for BOP vs. 9.6% for COP), decreased hemoglobin (40.9% for BOP vs. 45.7% for COP), and nausea and vomiting (29.8% for BOP vs. 27.4% for COP).[22]

Additional trials supporting the use of bendamustine for the treatment of NHL include two phase 1/2 dose-escalation studies involving patients with refractory or relapsed disease.[23–25] Treatment with bendamustine in combination with mitoxantrone and rituximab resulted in an overall response rate of 100% (26/26).[23,24] An overall response rate of 77% (17/22) has also been noted with bendamustine plus fludarabine (Fludara, Bayer/ Ben Venue) combination therapy.[25]

ADVERSE EVENTS

Adverse drug reactions are common and have been reported by 89% of CLL patients receiving bendamustine.[17,26] Of these events, 83% are treatment-related and 58% are considered severe (grade 3 or 4). The most common adverse reactions are presented in Table 1.

Myelosuppression, including neutropenia (28%), thrombocytopenia (23%), anemia (19%), and leukopenia (18%), is common and may be dose-limiting. These events are more common during the first two cycles of treatment, and patients (20%) are likely to require infusions of red blood cells. The most frequently reported nonhematological events include pyrexia (24%), nausea (20%), and vomiting (16%). In clinical trials, adverse reactions, including hypersensitivity (2%) and pyrexia (1%), were the most common cause of withdrawal from treatment.[17,26]

Bullous exanthema, rash, and toxic

Table 1 Adverse Reactions Associated with Bendamustine Therapy

Incidence	Adverse Events, All Grades (Bendamustine/Chlorambucil, %)
>20%	Neutropenia (28/14), thrombocytopenia (23/20), pyrexia (24/6)
11%–20%	Nausea (20/15), anemia (19/11), leukopenia (18/3), vomiting (16/6)
6%–10%	Fatigue (9/6), diarrhea (9/3) rash (8/5), asthenia (8/4), nasopharyngitis (7/8), weight loss (7/3), hyperuricemia (7/1), infection (6/<1), chills (1/<1)
>2%–5%	Hypersensitivity (5/2), cough (4/5)

Data from Treanda (bendamustine), prescribing information.[17]

skin reactions have been reported.[17,26] Patients may also experience infusion reactions, including chills, fever, and pruritus. In rare cases, severe anaphylactic and anaphylactoid reactions may occur during subsequent cycles of therapy. Bendamustine has also been associated with other serious adverse events, such as pneumonia (2%), sepsis (in fewer than 1%), and tumor lysis syndrome (2%).[17,26]

Laboratory abnormalities are common in patients receiving bendamustine and primarily involve hematological parameters that reflect myelosuppression. Decreased levels of hemoglobin (89%), platelets (77%), neutrophils (75%), lymphocytes (68%), and leukocytes (671%) are common. In addition, hyperbilirubinemia (34%) and increased serum creatinine (31%) have been reported.[17,26]

DRUG INTERACTIONS AND CONTRAINDICATIONS

Bendamustine is metabolized by the CYP P450 1A2 enzyme. Coadministration of bendamustine with CYP 1A2 inhibitors, such as ciprofloxacin (Cipro, Bayer) or fluvoxamine (Luvox, Solvay), would increase bendamustine serum levels and decrease the concentration of its active metabolites. Conversely, inducers of CYP 1A, such as smoking, would lead to an increase the serum level of active metabolites. Bendamustine is not likely to inhibit the activity of CYP 450 enzymes or to interfere with metabolism of their substrates.[17,26]

Contraindications include a known hypersensitivity to mannitol or bendamustine. Patients should be closely monitored for reactions or symptoms during the first cycle of therapy. Therapy should be discontinued if severe reactions occur.[17] Because studies examining the effect of renal and hepatic impairment are limited, bendamustine should be used with caution in patients with mild renal or hepatic impairment.

Bendamustine is not recommended for patients with severe renal impairment (a CrCl below 40 mL/minute), with moderate hepatic impairment (AST or ALT levels 2.5 to 10 times the ULN, or with total bilirubin levels 1.3 to three times the ULN) or in patients with severe hepatic impairment (total bilirubin levels above three times the ULN).

The use of bendamustine in pediatric patients has not been evaluated.[15,17]

DOSAGE AND ADMINISTRATION

Bendamustine is supplied as a lyophilized powder that must be reconstituted with sterile water and diluted with normal saline prior to infusion. After bendamustine is diluted, it is stable for three hours at room temperature or for 24 hours when it is refrigerated; the medication should be administered during this time frame.

Bendamustine is available in single-use 100-mg vials (bendamustine 100 mg plus mannitol 170 mg). It is recommended that a dose of 100 mg/m^2 as an IV infusion be given over 30 minutes on days 1 and 2 of a 28-day cycle for up to six cycles. Coadministration of allopurinol (Zyloprim, Faro; Aloprim, Bioniche) should be considered as a preventive measure in patients at high risk for the development of tumor lysis syndrome. The use of antihistamines and corticosteroids should also be considered for patients who are susceptible to grade 1 or 2 infusion reactions.[17]

In the event of toxicity, dosing modifications should be made. Subsequent cycles of bendamustine should be delayed in patients who experience grade 4 hematological toxicity or grade 2 or higher nonhematological toxicity until blood counts have increased (an absolute neutrophil count of one or more times 10^9/L, platelets ≥ 75 or more times 10^9/L) or until toxicity has ben reduced to grade 1 or below.

Bendamustine therapy should be reinitiated at a reduced dose of 50 mg/m^2 on days 1 and 2 for subsequent cycles in patients who experienced grade 3 toxicity or higher. The dose should be further reduced to 25 mg/m^2 if grade 3 toxicity or higher recurs. Re-escalation of the bendamustine dose may be considered.[17]

PREGNANCY

Bendamustine is classified as a Pregnancy Category D medication. In studies of rodents, the administration of single intraperitoneal doses during organogenesis resulted in decreased fetal body weights and increased malformations and resorption. Women of childbearing age should consider taking precautions for birth control while receiving bendamustine. No data are available as to whether the drug is excreted in human milk, but mothers should avoid breastfeeding unless the benefits of bendamustine therapy outweigh risks to the infant.[17]

COST

The average wholesale price (AWP) of bendamustine is $4,320 per dose. The AWP for one treatment cycle is $8,640. By contrast, the AWP of chlorambucil is $75 per dose, or $151 per treatment cycle.[27]

CONCLUSION

Bendamustine is a new alternative for the treatment of patients with CLL. Therapy may be useful in patients with refractory disease or in patients who show resistance to other chemotherapeutic regimens. Myelosuppression and gastrointestinal tract–related events are commonly associated with bendamustine therapy. The drug demonstrates only partial cross-resistance with other alkylating agents and has shown superior overall response and progression-free survival rates over chlorambucil for the treatment of CLL.[15]

Similar overall response and progression-free survival rates have been observed between cyclophosphamide and bendamustine regimens in patients with NHL.[22] With the FDA's most recent approval of bendamustine for the treatment of rituximab-resistant, indolent B-cell NHL in late 2008, the drug is likely to be a valuable option for these patients.

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