Bendamustine: Rescue of an Effective Antineoplastic Agent From the Mid-Twentieth Century

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Although the alkylating agent bendamustine was developed in Germany in the mid-twentieth century, it has only recently come to the forefront in the rest of the world as an effective chemotherapeutic agent for the treatment of several hematologic malignancies. Based on the activity demonstrated in single-arm and randomized trials, this nitrogen mustard is approved by the US Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukemia and rituximab-refractory indolent non-Hodgkin lymphoma. The unique structural and mechanistic features of bendamustine differentiate it from other alkylating agents, providing increased stability and potency in DNA cross linking and subsequent cytotoxicity. Due to its unusual development, few studies have closely examined the mechanisms of action for this nitrogen mustard and many unanswered questions remain. Additionally, phase I and pharmacokinetic studies are limited, although increased understanding of the clinical pharmacology of bendamustine led to development of dosing recommendations by international experts based on the available data. The clinical activity of bendamustine as a single agent and in combination with other chemotherapeutic and immunotherapeutic drugs, coupled with its potential lack of cross-resistance with many other chemotherapy agents, make bendamustine an attractive therapy for patients with newly diagnosed and refractory hematologic malignancies. This review will discuss the development of bendamustine, its structural and pharmacologic characteristics, and current data regarding the optimal dosing of this agent in specific clinical settings.
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DEVELOPMENTAL HISTORY OF BENDAMUSTINE

Bendamustine was synthesized by Ozegowski and colleagues in the early 1960s at the Institute for Microbiology and Experimental Therapy in the former East German Democratic Republic.[1] At that time, the nitrogen mustards were becoming an important class of anticancer agents, and the intent was to synthesize a novel anticancer agent that would have superior pharmacologic properties compared to other nitrogen mustards such as cyclophosphamide, chlorambucil, and carmustine. In particular, the goal was to reduce toxicity without sacrificing antitumor activity. Ozegowski and colleagues synthesized a series of benzimidazole mustard compounds, which contained the benzimidazole ring structure common to many purine analogues (eg, cladribine).[1] One of these compounds, known as bendamustine hydrochloride, with the chemical name 4-(5-[bis(2-chloroethyl)amino]-1-methyl -2-benzimidazolyl) butyric acid hydrochloride, had the nitrogen-mustard group at position 5 on the benzimidazole ring (Figure 1).[2,3] This unique structure, originally known as IMET3393, is more stable than other nitrogen mustards, resulting in more sustained DNA damage.[3] Combining the nitrogen-mustard group with the benzimidazole ring also created a potentially bifunctional compound that could have some antimetabolite properties in addition to being a potent alkylating agent.

From 1971 to 1992, bendamustine was marketed in the former East German Democratic Republic as Cytostasan (Volkseigener Betrieb/VEB Jenapharm) for the treatment of chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), Hodgkin disease, multiple myeloma (MM), and breast cancer. Beginning in 1993, it was produced and marketed in Germany by Ribosepharm GmbH and later by Fujisawa Deutschland GmbH

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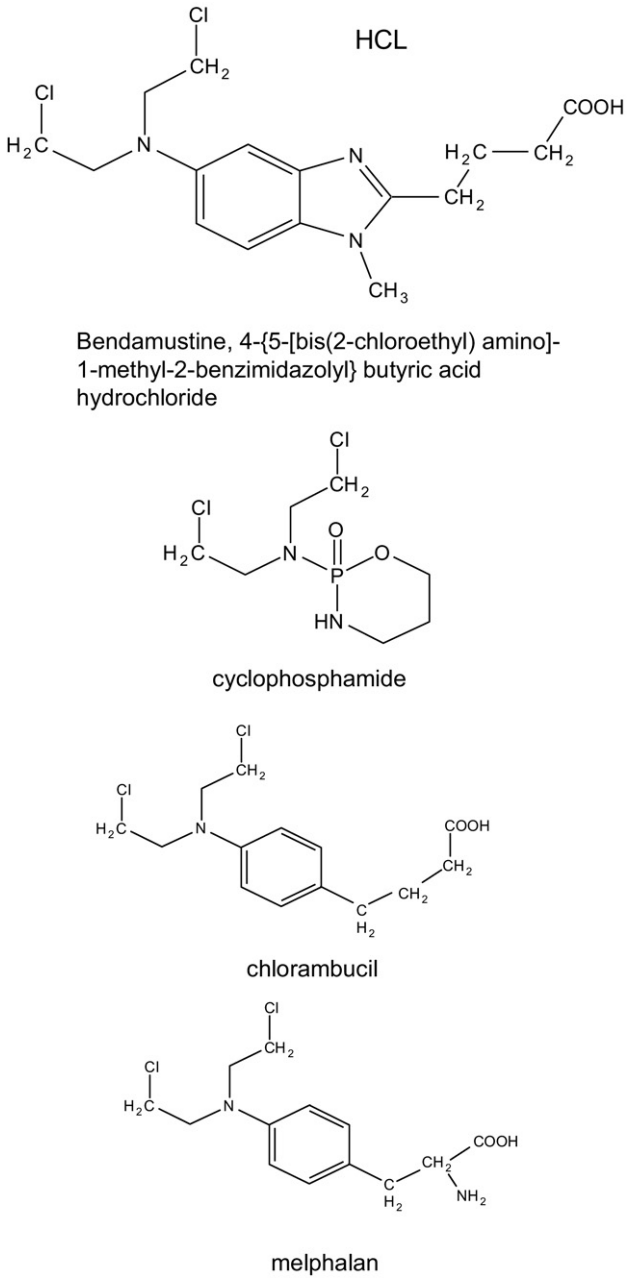

Figure 1. Chemical structure of bendamustine in comparison to cyclophosphamide, chlorambucil, and melphalan. Cl, chlorine; H, hydrogen; N, nitrogen; O, oxygen; P, phosphorus. Reprinted with permission from Leoni LM, et al. Clin Cancer Res. 2008;14:309–317.[3]

as Ribomustin. Then in 2003, Salmedix, Inc, a privately-held oncology drug development company based in San Diego, CA, acquired the rights to market bendamustine in North America under the brand name Treanda, and in 2005, Cephalon merged with Salmedix, thereby obtaining rights to market Treanda in the United States and Canada. Treanda is currently approved in the United States as first-line therapy for CLL and for rituximab-refractory indolent NHL.

STRUCTURE/FUNCTION RELATIONSHIP

Structurally, bendamustine has 3 active moieties: (1) a chloroethylamine alkylating group; (2) a benzimidazole ring; and (3) a butyric acid side chain (Figure 1).[2,3] The chloroethylamine alkylating group is common to many other alkylating agents (eg, cyclophosphamide, chlorambucil, and melphalan), and chlorambucil also has a butyric acid side chain similar to bendamustine. What is different about bendamustine (among the 2-chloroethylamine alkylators) is the benzimidazole ring, which may contribute its unique antitumor activity. Unfortunately, given the rather unusual developmental history of bendamustine, few studies have been conducted to clearly define its mechanism of action (MOA). What is known is that bendamustine, like several other alkylating agents, crosslinks DNA and causes both single-strand and double-strand breaks that are cytotoxic. However, bendamustine appears to cause more extensive and more durable DNA strand breaks than other 2-chloroethylamine alkylators,[4] and this may result from the unique way in which bendamustine interacts with the DNA.

To better understand its unique MOA, Leoni and colleagues profiled the antitumor activity of bendamustine via the National Cancer Institute (NCI) In Vitro Cell Line Screening Project (IVCLSP) and compared the profile of bendamustine with other alkylating agents.[3] These investigators also used gene expression microarrays to characterize genes regulated by bendamustine. This analysis demonstrated that the antitumor activity of bendamustine is distinct from that of other alkylating agents, that bendamustine primarily activates base excision repair pathways rather than mismatch repair pathways, and that bendamustine activates genes involved in DNA-damage stress responses, apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe.[3] These topics will be explored in more detail in a subsequent section.

The pattern and extent of DNA damage induced by bendamustine has important clinical implications. First, compared to other alkylating agents, bendamustine is more potent. At equitoxic concentrations, bendamustine induced more DNA double-strand breaks and more long-lived (ie, unrepaired) strand breaks compared with carmustine or cyclophosphamide,[4] and yet it exhibits low clastogenicity (ie, induction of chromosomal aberrations) in bone marrow hematopoietic cells.[5] Second, the cytotoxic effects of bendamustine are relatively insensitive to O^6-benzylguanine, an inhibitor of O^6-methylguanine DNA-methyltransferase (MGMT) activity, the enzyme responsible for repair of O^6-methylguanine (O^6-MeG).[3] This suggests that bendamustine-induced N^3-alkyladenine and N^7-alkylguanine adducts may be more important than O^6-alkylguanine adducts. Both N^3-adenine and N^7-guanine monoadducts may be repaired by the base excision repair pathway,[6,7]

whereas O^6-alkylguanine adducts, if unrepaired, lead to mismatched base pairing that can only be corrected by DNA mismatch repair pathways. Consequently, O^6-alkylguanine can be highly mutagenic, and N^3-alkyladenine can be highly cytotoxic without being mutagenic.[8] Finally, the pattern of DNA damage induced by bendamustine also suggests possible synergy with poly ADP-ribose polymerase (PARP) inhibitors because PARP is an important enzyme in the base excision repair pathway, but this hypothesis has yet to be tested experimentally. Although these bits of information provide many tantalizing clues, there remain many unanswered questions regarding the specific pattern of DNA damage induced by bendamustine.

The extent to which the benzimidazole ring contributes to the antitumor activity of bendamustine is another unanswered question. The early concept was that the structure of bendamustine might confer a dual antitumor MOA. At least two possible mechanisms could explain how this moiety could enhance the antitumor potential of bendamustine. First, it could directly confer antimetabolite activity, thereby allowing the drug (or its metabolites) to become incorporated into newly synthesized DNA molecules or to inhibit ribonucleotide reductase or other enzymes involved in generation of deoxynucleoside triphosphates (dNTPs). Indeed, the observation that bendamustine is associated with delayed DNA repair is consistent with this hypothesis. Second, the benzimidazole ring could enhance the alkylating activity of bendamustine possibly by facilitating nuclear transport and allowing the drug to reach higher concentrations in the nucleus or by inhibiting DNA repair. Although these are attractive hypotheses, there is currently no direct evidence to suggest that the benzimidazole ring plays any role in the antitumor activity of bendamustine. Therefore, although many have described bendamustine as a "bifunctional" chemotherapy agent, there is little evidence to suggest that it actually has two distinct antitumor MOAs.

CLINICAL PHARMACOLOGY OF BENDAMUSTINE

The clinical pharmacology of bendamustine has not been fully characterized, but a clearer picture of its metabolism is emerging. Bendamustine undergoes extensive first-pass metabolism in the liver by the cytochrome P450 (CYP) system (primarily CYP1A2).[9–11] Hepatic metabolism gives rise to two major phase I metabolites: gamma-hydroxybendamustine and N-demethylbendamustine (Figure 2).[9,10] Hydroxylation of the methylene carbon at the C-4 position of the butyric acid side chain gives rise to gamma-hydroxybendamus-

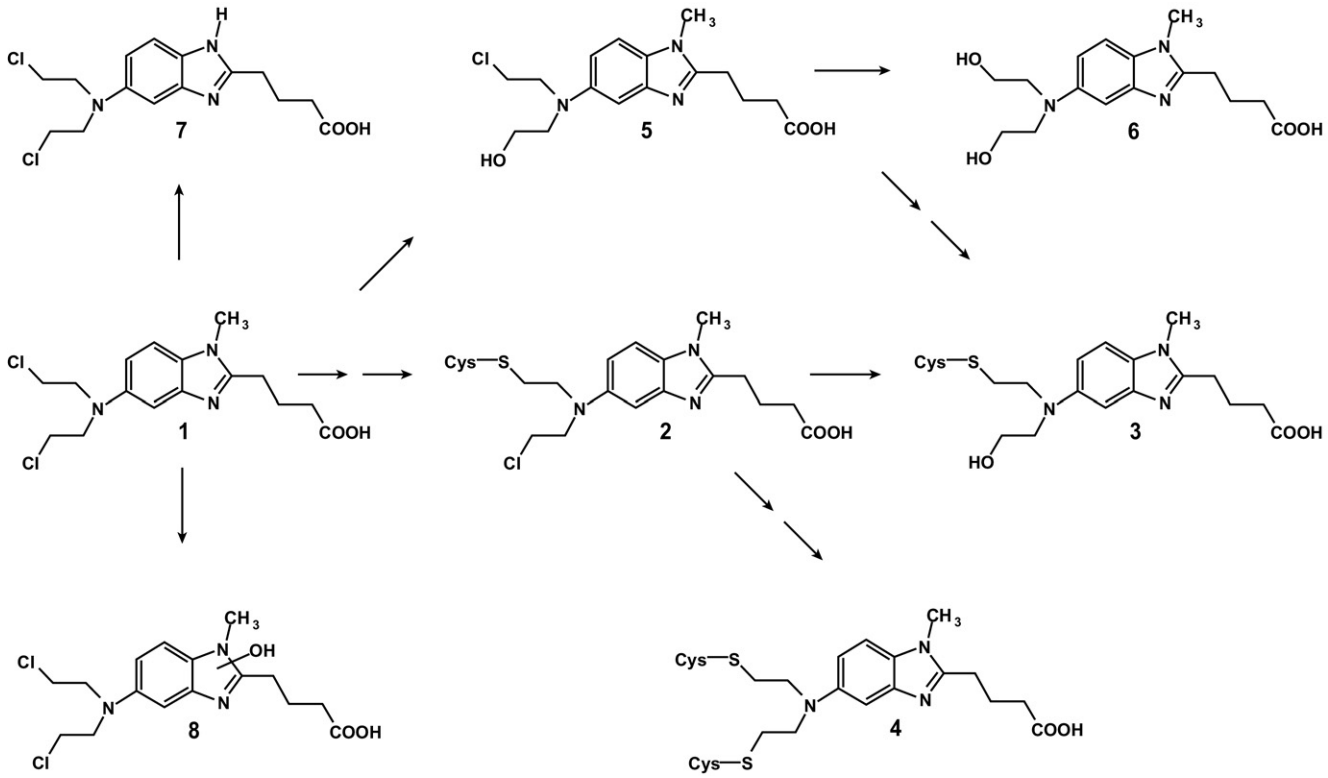

Figure 2. Proposed metabolic pathway for bendamustine. Reprinted with permission from Teichert J, Sohr R, Baumann F, et al. Synthesis and characterization of some new phase II metabolites of the alkylator bendamustine and their identification in human bile, urine, and plasma from patients with cholangiocarcinoma. Drug Metab Dispos. 2005;33:984–92.[10]

Table 1. Doses and Schedules of Bendamustine Used in Single-Agent Studies in Hematologic Malignancies[12,14–24]

Patient Population	Dose, mg/m²	Schedule	Dose per Cycle, mg/m²
NHL, CLL, MM	50–60[15,19]	Days 1–5 every 3 or 4 weeks	250–300
NHL	120[16–18]	Days 1, 2 every 3 weeks	240
CLL	50–60[15]	Days 1, 2 every 4 weeks	100–120
CLL	70[14]	Days 1, 2 every 4 weeks	140
CLL, MM	100[20,21,23]	Days 1, 2 every 4 weeks	200
MM	150[24]	Days 1, 2 every 4 weeks	300

CLL = chronic lymphocytic leukemia; MM = multiple myeloma; NHL = non-Hodgkin lymphoma.
Data from Cheson BD, et al. Clin Lymphoma Myeloma Leuk. 2010;10:21–7.[12]

tine, which exhibits antitumor activity approximately equivalent to that of the unmetabolized drug. This is the major circulating metabolite. In contrast, N-demethylation of the benzimidazole ring reduces cytotoxic activity by 5-fold to 10-fold.[9] Early studies suggested that a major metabolite was formed via hydroxylation of the beta carbon in the butyric acid side chain, similar to that seen with chlorambucil.[11] This chemical modification enhances the cytotoxic activity of chlorambucil. However, subsequent studies have failed to confirm the formation of beta-hydroxybendamustine,[9,10] and this may explain, in part, the reduced systemic toxicity of bendamustine compared to other alkylating agents. Two products of chemical hydrolysis of the chloroethylamine alkylating group, namely, monohydroxy and dihydroxy bendamustine, have also been detected, and these metabolites have little or no cytotoxic activity. Additional phase II metabolites have recently been identified as cysteine S-conjugates, and these are predominantly excreted in the bile.[10] It is estimated that approximately 20% to 30% of the administered dose of bendamustine is eliminated by urinary excretion, and the unmetabolized drug accounts for nearly half of the total drug recovered in urine. Approximately 40% appears to be eliminated via biliary excretion.[10] Thus a major route of bendamustine metabolism in humans appears to involve conjugation with glutathione.

To date, limited phase I and pharmacokinetic (PK) data are available for bendamustine, and much work remains to be done to establish the optimal dosing regimen and the maximum tolerated dose (MTD) for the various schedules that have been used in clinical practice.[12] When determining the best dose and schedule of bendamustine, it is important to consider whether it is being used as initial therapy or in the relapsed/refractory setting and whether it is being used as single-agent therapy or in combination with other drugs. Rituximab tends to increase the hematologic toxicity of chemotherapy.[13]

Early studies used a variety of empiric dosing regimens, and there was no clear drug development strategy. Dosing regimens reported in the more recent literature are shown in Table 1.[12,14–24] Most studies have administered bendamustine on days 1 and 2 of an every 3-week or 4-week cycle with daily doses ranging from 50 to 150 mg/m². Bendamustine has also been administered for 5 consecutive days every 3 or 4 weeks. These dosing schedules deliver 100 mg/m² to 300 mg/m² per cycle. Phase I, single-agent, dose-escalation studies conducted in patients with hematologic malignancies over the past 10 years have evaluated several different dosing schedules in an effort to better define the MTD and the PK profile of bendamustine (Table 2).[14,21,22,25,26] Until fairly recently, the only reported phase I studies were in patients with MM or CLL. Knop et al[21] reported a study in 31 patients with MM that had progressed after high-dose chemotherapy and established a MTD of 100 mg/m² (days 1 and 2 every 4 weeks). The major dose-limiting toxicity (DLT) was febrile neutropenia. Two phase I/II studies have also been conducted in patients with relapsed or refractory CLL. The first of these was conducted by the German CLL Study Group in 16 patients who had received a median of three prior regimens.[14] Nearly all had received prior treatment with chlorambucil, and eight had also received fludarabine. The starting dose was 100 mg/m² (days 1 and 2 every 3–4 weeks), but the dose had to be de-escalated and the MTD was determined to be 70 mg/m² with DLT consisting primarily of grade 3/4 leukopenia and infection. The second study enrolled 15 patients who had been extensively pretreated but were fludarabine-naïve. These patients tolerated doses up to 110 mg/m² (days 1 and 2 every 3 weeks), and the recommended phase II dose was set at 100 mg/m².[22] The primary DLT was hematologic with the exception of bilirubinemia.

Recently, a small phase I safety and PK study in nine Japanese patients with relapsed/refractory indolent NHL or mantle cell lymphoma (MCL) evaluated two

Table 2. Single-Agent, Phase I and Pharmacokinetic Studies of Bendamustine in Patients With Hematologic Malignancies[14,21,22,25,26]

Patient Population	n	Dose, mg/m², and Schedule	Dose/Cycle, mg/m²	Half-life, min	Dose-Limiting Toxicity
MM[21]	31	100, days 1, 2 every 4 weeks	200	—	Febrile neutropenia
Relapsed or refractory CLL[14]	16	70, days 1, 2 every 3–4 weeks	140	—	Hyperuricemia, pneumonia, infection, anemia, liver enzymes, thrombocytopenia
Previously treated CLL[22]	15	100, days 1, 2 every 3 weeks	200	—	Bilirubinemia, diarrhea, anemia, thrombocytopenia
NHL, MCL[25]	9	120, days 1, 2 every 3 weeks	240	29	None
NHL[26] population PK		120, days 1, 2 every 3 weeks	240	40	NA

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; MM = multiple myeloma; NA = not applicable; NHL = non-Hodgkin lymphoma.

doses (90 mg/m² or 120 mg/m² on days 1 and 2 of every 3-week cycle).[25] Grade 3 and 4 neutropenia and leukopenia occurred in 33% of patients, but the MTD was not reached; thus, the authors recommended 120 mg/m² for phase II testing. Bendamustine was rapidly eliminated, with a mean elimination half-life of 29 minutes in this group of patients without major organ dysfunction. This is consistent with data from a recent population PK analysis of patients with indolent NHL that demonstrated an intermediate terminal half-life of approximately 40 minutes.[26] Bendamustine plasma concentrations declined in a triphasic manner with a rapid distribution phase, an intermediate phase, and a terminal decline. The authors concluded that the intermediate half-life was the most pharmacologically relevant and accounted for 99% of exposure. Notably, there was no evidence of accumulation, and the PK profile was not influenced by mild or moderate renal impairment or mild liver dysfunction. However, safety data in patients with mild-to-moderate renal or hepatic impairment are limited. Therefore, it is recommended that bendamustine be used with caution in these patients. Bendamustine has not been tested and, therefore, should not be used in patients with creatinine clearance less than 40 mL/min or with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.5 times or total bilirubin more than 3 times the upper limit of normal. Taken together, these studies indicate that hematologic toxicity is the major DLT (primarily leukopenia), and patients with extensively pretreated, relapsed or refractory CLL have a lower MTD than patients with relapsed/refractory NHL.

Given the limited phase I data from single-agent studies and continued uncertainty with regard to the optimum dosing regimen in different patient populations or when combining bendamustine with other agents, and particularly rituximab, an international group of investigators with extensive experience using bendamustine met in 2008 to develop recommendations based on the available data.[12] The recommendations of this consensus panel for bendamustine dosing in various clinical settings are shown in Table 3.[12] Bendamustine should be administered on days 1 and 2 of a 4-week cycle at doses ranging from 70 mg/m² to 120 mg/m². A dose of 70 mg/m² is recommended for patients with relapsed/refractory CLL who have been previously treated with fludarabine or when combining bendamustine with rituximab, but doses up to 100 mg/m² are recommended when using bendamustine as initial, single-agent therapy or in patients with fludarabine-naïve relapsed CLL. A dose of 120 mg/m² is recommended for patients with relapsed/refractory NHL who are treated with single-agent bendamustine, with a reduction to 90 mg/m² when used in combination with rituximab.

The approved dosing regimen for single-agent bendamustine in previously untreated CLL is 100 mg/m² (days 1 and 2 every 4 weeks) based on a randomized comparison with chlorambucil (0.8 mg/kg).[20] Although bendamustine resulted in a higher incidence of grade 3/4 neutropenia compared to chlorambucil (23% *v* 11%), there was no substantial difference in the rate of infections between the two arms. When combining bendamustine with rituximab as initial therapy for CLL, it is prudent to reduce the dose to 90 mg/m² to mini-

Table 3. International Consensus Panel Recommendations for Bendamustine Dosing[12]

Clinical Setting	Recommended Dose, mg/m², Days 1, 2[a]
CLL	
Initial therapy, single agent	100
Initial therapy, with rituximab	90
Relapsed/refractory, single agent (fludarabine naïve)	70 (100)
Relapsed/refractory, with rituximab	70[b]
Follicular, low-grade NHL	
Initial therapy, single agent	120
Initial therapy, with rituximab	90
Relapsed/refractory, with rituximab	90
Aggressive B-cell NHL	
Relapsed/refractory, single agent	120
Relapsed/refractory, with rituximab	90

CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma.
Adapted with permission from Cheson BD, et al. Clin Lymphoma Myeloma Leuk. 2010;10:21–7.[12] Permission conveyed through Copyright Clearance Center, Inc.
[a]Every 4 weeks except for aggressive B-cell NHL, which is every 3 weeks.
[b]Escalation to 90 mg/m² if 70 mg/m² is well tolerated.

mize the potential for increased hematologic toxicity. In the relapsed/refractory setting, the recommended starting dose in patients previously treated with fludarabine or when bendamustine is combined with rituximab is 70 mg/m². In a recent study conducted by the German CLL Study Group, bendamustine plus rituximab (BR) resulted in a 77% response rate in heavily pretreated patients.[27] Thus, the lower dose does not appear to compromise efficacy, and the dose can be escalated to 90 mg/m² if the lower dose is well tolerated.

Bendamustine was approved by the US Food and Drug Administration (FDA) for relapsed or refractory low-grade follicular lymphoma (FL) at a dose of 120 mg/m² (days 1 and 2 every 3 weeks). A pooled analysis of the registration trials showed that 34% of patients developed grade 3 or 4 neutropenia, and 18% had an opportunistic infection.[28] Overall, 25% of patients required dose reductions for either grade 4 hematologic toxicity or grade 3 nonhematologic toxicity, and 60% of patients had at least 1 dose delay. A similar safety profile has been reported in other studies in this setting.[16,18] Therefore, the consensus panel recommended a 4-week cycle to minimize dose reductions and delays. When used in combination with rituximab for relapsed/refractory NHL, reducing the dose to 90 mg/m² maintains grade 3/4 hematologic toxicity at an acceptable level.[29,30] When bendamustine (90 mg/m² days 1 and 2 every 4 weeks) plus rituximab was compared with CHOP-R as initial therapy for FL or MCL in a randomized phase III trial, the BR regimen was associated with less hematologic toxicity and fewer infections compared with CHOP-R.[31]

LACK OF CROSS RESISTANCE

Based on the work of Leoni and colleagues, bendamustine exhibits a unique National Cancer Institute (NCI) COMPARE profile that distinguishes it from other alkylating agents such as cyclophosphamide, melphalan, and chlorambucil, all of which have a strong correlation with one another.[3] Moreover, preclinical studies have shown that bendamustine is only partially cross-resistant with other alkylating agents and is fully active against human ovarian and breast cell lines resistant to cisplatin and doxorubicin.[4] A low level of cross-resistance with cisplatin suggested that bendamustine does not undergo significant cytosolic detoxification by either cellular glutathione or by glutathione-S-transferase, and sensitivity to bendamustine was independent of P-glycoprotein overexpression.[4] Moreover, bendamustine is active against primary NHL cells that are refractory to cyclophosphamide and doxorubicin.[3,32] Using the differential staining cytotoxicity (DiSC) assay to test a panel of 20 selected primary NHL specimens with varying levels of drug resistance, most of those that were resistant to either cyclophosphamide, doxorubicin, or etoposide were sensitive to bendamustine.[32] Taken together, these studies suggest that the antitumor activity of bendamustine is not influenced by cytosolic detoxification or multidrug resistance mechanisms.

In the clinical setting, bendamustine has also demonstrated single-agent activity in relapsed or refractory high-grade NHL (44% response rate in 18 evaluable patients) and in heavily pretreated CLL (66% response rate among 21 evaluable patients).[33,34] These findings have clear implications with respect to the precise cytotoxic MOA of bendamustine, its antitumor activity

in the relapsed/refractory setting, its potential for additive or synergistic antitumor activity when combined with other cytotoxic agents, and the potential mechanisms of resistance to bendamustine. Studies are ongoing to clarify mechanisms of resistance. Although the precise MOA of bendamustine has not yet been fully elucidated, studies investigating the DNA repair pathways and cell death mechanisms involved are beginning to bring greater clarity to this question.

STATEMENT OF CONFLICT OF INTEREST

L.M. Leoni discloses the following potential conflict of interest: Consulting fees: Cephalon, Inc.

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