Bendamustine in B-Cell Malignancies: The New 46-Year-Old Kid on the Block

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Introduction

On March 20, 2008, bendamustine HCl (Treanda, Cephalon, Inc.) was approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic lymphocytic leukemia (CLL). This approval was based on a randomized, multicenter trial comparing the test drug ($n = 162$) to chlorambucil ($n = 157$) as a first line treatment (1). Overall response rates (ORR) were 68% and 31% for bendamustine and chlorambucil, respectively, and were accompanied with an increased progression-free survival (PFS) with bendamustine.

About 6 months later, on October 31, 2008, bendamustine was approved by the FDA for patients with indolent B-cell non-Hodgkin’s lymphoma (NHL) that progressed during or within 6 months of treatment with rituximab alone or in combination ($n = 100$). This approval was based on a single arm clinical trial with an ORR of 74% with 9.2 months of duration of response.

What is Bendamustine?

Chemically, bendamustine is 4-[5-{bis(2-chloroethyl)amino]-1-methyl-2-bezimidazolyl} butyric acid hydrochloride (Fig. 1). Structurally, it contains three major moieties: first a 2-chloroethylamine alkylating group, second a benzimidazole ring, and finally, a butyric acid side chain. Addition of the butyric acid side chain results in water solubility. Functionally, the 2-chloroethyl group with a substituted amine group represents the N-lost group of the nitrogen mustard family. The nitrogen mustard group, which is responsible for the alkylating action of the molecule, resembles chlorambucil and cyclophosphamide (Fig. 1), the two most commonly used alkylating agents for treatment of CLL and NHL. Bendamustine is chemically related to the alkylating agent chlorambucil with the benzene ring in the chlorambucil molecule replaced by a 1-methyl-benzimidazole nucleus.

Bendamustine: Revival of an Old Drug

Bendamustine originally was synthesized in 1963 at the Institute for Microbiology and Experimental Therapy in Jena in the former East German Democratic Republic (GDR) by Ozegowski and colleagues (2). In subsequent preclinical studies, bendamustine (at that time called IMET3393) displayed encouraging activities in hematopoietic cancers, such as myeloma models. In 1971, bendamustine was introduced into the market as cytostahan by the Volkseigener Betrieb/VEB (people-owned enterprise) Jenapharm. Despite considerable activity in patients with CLL (3), Hodgkin’s disease, mature B-cell lymphomas, multiple myeloma (4), and lung cancer (5), cytostasan did not become a broadly prescribed drug in the GDR (6). After the reunification of Germany in 1989, bendamustine was acquired by Ribosepharm in 1993 and marketed as Ribomustin. Three years later, in 1996, Ribosepharm became an operating unit of Klingen Pharma/Fujisawa Pharmaceutical Co., Ltd. In 2003, Salmedix Inc., a San Diego-based company, entered into a licensing agreement with Fujisawa Pharmaceutical to develop this drug and gave a new name to bendamustine (SDX-105). In 2005, Fujisawa Pharmaceutical merged with Yamanouchi Pharmaceutical Co., Ltd. to form Astellas Pharma, Inc. The German subsidiary (Astellas Deutschland GmbH, Munich) of the Tokyo-based Astellas Pharma Inc. was responsible for development of bendamustine in Europe. In October 2006, Mundipharma International Corp. Ltd. acquired exclusive development and marketing rights for bendamustine from Astellas Deutschland GmbH, Munich, Germany. Salmedix was responsible for introducing bendamustine to the United States and was later (2005) acquired by Cephalon, Inc., who now has the rights to develop bendamustine under the generic name of Treanda. In 2003, Salmedix Inc., a San Diego-based company, acquired exclusive development and marketing rights from Astellas Deutschland GmbH for the development and commercialization of bendamustine hydrochloride in Japan, China, Korea, Taiwan, and Singapore. Cephalon, Mundipharma, and SymBio are actively pursuing clinical trials with bendamustine.

Metabolism and Pharmacokinetics of Bendamustine

Bendamustine undergoes extensive first-pass metabolism (7) primarily in the liver by the action of the cytochrome p450 enzyme complex. Yet, unmetabolized bendamustine accounts for about 45% of the total drug recovered in the urine (7). Hydroxylation of the alkylating group leads to formation of monohydroxy- and dihydroxy-bendamustine, which are virtually inactive. Beta-oxidation of the butyric acid side chain produces γ-hydroxy bendamustine (previously thought to be β-hydroxy), which is an active metabolite (8). Further hydroxylation of this metabolite leads to hydroxy-β-hydroxybendamustine (9). In addition to hydroxylation, the benzimidazole ring can be demethylated to form N-demethylbendamustine (8, 10).

Following intravenous (IV) administration, a high percentage (>95%) of the drug is bound to protein, primarily albumin and only unbound bendamustine is active (11). The extent of binding and formation of metabolites are different among mice, rats, dogs, and humans, and hence extensive pharmacokinetic investigations are required to understand metabolism of the drug in patients.

Peak plasma concentrations of bendamustine are dependent on the dose. For example, concentrations of 0.1 to 30 μg/mL are obtained at 30 to 200 mg/m² dose range of the administered drug. Elimination of bendamustine is rapid, with peak metabolite concentrations found in the urine 1 hour after administration. Elimination is biphasic with a half-life (t₁/₂α) of 6 to 10 minutes, and a terminal elimination half-life (t₁/₂β) of approximately 30 minutes. The central volume of distribution is 8.6 to 11.2 L following IV administration; under steady-state conditions, the volume of distribution is 15.8 to 20.5 L (12). Bendamustine is eliminated primarily by the renal route and therefore should not be given to patients in whom renal function is compromised (glomerular filtration rates <1.8 L/h). Similarly, as primary metabolism occurs in the liver, bendamustine is contraindicated in patients with severe hepatic damage.

Fig. 1. Structures of chlorambucil, cyclophosphamide, and bendamustine. Alkylating agent portion of the structure is shown in red.

Mechanisms of Action of Bendamustine

Bendamustine was originally synthesized with the intention of producing an anticancer agent that contained both alkylating and antimetabolite properties (13). The majority of the published literature suggests that bendamustine acts primarily as an alkylating agent and causes the formation of intrastrand and interstrand cross-links between DNA bases (14–16). This property directly inhibits DNA replication, repair, and transcription. Treatment with bendamustine also leads to disruption of the matrix function of DNA in DNA synthesis. There is some evidence that cross-linkage may also occur between DNA and proteins and among proteins; however, these phenomena are not clearly understood (17).

Is Bendamustine Different from Other Alkylating Agents?

For leukemia and lymphomas, the most commonly used alkylating agents are chlorambucil and cyclophosphamide, whereas for myeloma, melphalan is the choice. When these established alkylating agents were compared with bendamustine in the NCI 60-panel cell lines using COMPARE analyses, melphalan, cyclophosphamide, and chlorambucil showed Pearson correlation coefficient of >0.8 (>65% agreement) with several alkylating agents, whereas bendamustine did not reach that value (16). There was also incomplete cross-resistance between bendamustine and other alkylating agents (15). These are limited data but suggest additional and/or unique mechanisms of action of bendamustine.

When used in equitoxic concentrations, bendamustine induces more DNA double-strand breaks than other commonly
Another study explored the activity of bendamustine given as single dose administration defined 260 mg/m² as the maximum tolerated dose, with cardiovascular dose-limiting toxicities; one each from neutropenic sepsis, diffuse alveolar hemorrhage with grade 3 thrombocytopenia, and pneumonia from a cytomegalovirus infection. These data supported the FDA approval for patients with indolent NHL who are rituximab-refractory and the recommended dose of bendamustine in NHL of 120 mg/m² on days 1 and 2 of a 21-day cycle for up to eight cycles.

**Clinical Activity of Bendamustine**

**Dose-finding studies.** In early studies, the dosing of bendamustine has been largely empiric; but with the more common use of bendamustine in CLL and NHL patients over the last decade, it became obvious that bendamustine displays a rather narrow therapeutic window, and that dosing depends upon the disease to be treated, and the intensity of prior treatments.

Single dose administration defined 260 mg/m² as the maximum tolerated dose, with cardiovascular dose-limiting toxicities (19). Early studies in CLL and NHL patients used bendamustine doses of 100 mg/m² up to 120 mg/m² on two consecutive days every 3 to 4 weeks (20, 21). Because fractionated bendamustine administration generally was better tolerated, bendamustine given on two consecutive days every 3 to 4 weeks has become the most widely used regimen (22).

**Indolent NHL.** Because of the early experience from the 1970s, in which high remission rates with single-agent bendamustine in front-line treatment of CLL and multiple myeloma were reported (5) and its particular toxicity toward B lymphocytes (23), mature B-cell malignancies became a major focus in the clinical development of bendamustine. A more recent German study in relapsed or refractory patients with indolent NHL reported an ORR of 73%, a complete remission rate of 11%, and a median remission duration of 16 months, using bendamustine at 120 mg/m² on days 1 and 2 every 3 weeks (21). Another study explored the activity of bendamustine given as 5-day cycles of daily 60 mg/m² in pretreated patients with indolent NHL with similar ORR, but the median duration of response was 39 months for NHL and 17 months for multiple myeloma patients (Table 1; ref. 24). In high-grade NHL, bendamustine was found to be active in relapsed and/or refractory patients with an ORR of 44% (25).

A recent U.S. study in rituximab-refractory patients with indolent NHL explored bendamustine, given at 120 mg/m² on days 1 and 2 of a 21-day cycle for 6 to 12 cycles (26). Here, the authors reported an ORR of 77% with 15% complete remissions, 19% unconfirmed complete remissions, and 43% partial remissions. Comparable data were presented from another study in rituximab-refractory NHL patients (27), confirming that bendamustine displays significant activity in this patient population. In this pivotal single arm, bendamustine was administered at 120 mg/m² on days 1 and 2 of a 21-day treatment cycle for up to eight cycles. The ORR was 74% and median duration of remission was 9.2 months. Complete remissions were reported in 13%, unconfirmed complete remissions in 4%, and partial remissions in 57% (Table 1). The most frequently reported nonhematologic adverse reactions were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and pyrexia (34%). Grade 3 or 4 adverse reactions were reported in 71%, the most frequently reported nonhematologic grade 3 or 4 adverse reactions were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia, and dehydration (each reported in 5% of patients). Grade 3 or 4 hematologic laboratory abnormalities were lymphocytopenia (94%), neutropenia (60%), leukopenia (56%), thrombocytopenia (25%), and anemia (11%). Three patients died of myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with grade 3 thrombocytopenia, and pneumonia from a cytomegalovirus infection. These data supported the FDA approval for patients with indolent NHL who are rituximab-refractory and the recommended dose of bendamustine in NHL of 120 mg/m² on days 1 and 2 of a 21-day cycle for up to eight cycles.

**Bendamustine combinations in indolent NHL.** Over the last decade, combinations of chemotherapy with rituximab (R) such as R-CHOP (cyclophosphamide, adriamycin, vincristine, prednisone), R-CVP (cyclophosphamide, vincristine, and prednisone), and R-fludarabine have become the most commonly used treatment approaches in newly diagnosed and relapsed patients with indolent NHL (28, 29). At relapse, there is no standardized treatment approach, and the therapeutic options range from low-intensity treatments, such as single agent rituximab, over radio-immunotherapy, chemotherapy with or without monoclonal antibodies, to more intensive approaches, such as high-dose chemotherapy with autologous or allogeneic stem cell transplantation. Because of the major impact of rituximab (30), bendamustine combinations with rituximab and/or chemotherapy have been explored or are being investigated.

In patients with relapsed indolent B-cell NHL or mantle cell lymphoma (MCL) without documented resistance to prior rituximab, rituximab 375 mg/m² on day 1 and bendamustine 90 mg/m² on days 2 and 3 of each 28-day cycle for four to six cycles was given. The authors reported an ORR of 92% with 41% complete remissions, 14% unconfirmed complete remissions, and 38% partial remissions. Median duration of response was 21 months and median PFS was 23 months (31). Similar results were obtained with bendamustine at 90 mg/m² on days 1 and 2 combined with 375 mg/m² rituximab on day 1 for a maximum of four cycles every 4 weeks in patients with relapsed indolent B-cell NHL or MCL (32). Here, the ORR was 90% with a complete remission rate of 60%. The median time of PFS was 24 months. In conclusion, the combination of bendamustine and rituximab is a highly active regimen in relapsed and/or refractory lymphomas. A German cooperative group randomized trial compared R-CHOP with the combination of rituximab and bendamustine in patients with newly diagnosed, previously untreated indolent and mantle cell lymphoma (33). The investigators reported similar response rates in both arms, but lower rates of toxicities for the combination of rituximab and bendamustine, such as alopecia (0% with B-R versus 89% CHOP-R), numbers of infectious complications (25% in the B-R group versus 37% in CHOP-R group). Hematotoxicity also was less common for the combination of rituximab and bendamustine (33).
Chronic lymphocytic leukemia. The early trials were conducted in pretreated CLL patients, and several phase II studies indicated that bendamustine induces high response rates in pretreated or refractory patients that ranged between 65 and 93%, along with a favorable safety profile. Main toxicities were hematologic, whereas nonhematologic side effects generally were mild and rather uncommon. In these studies (Table 1), 100 mg/m² on days 1 and 2 every 3 weeks (34, 35) or 5-day cycles of daily 60 mg/m² (or 50 mg/m² in patients >70 years old) every 4 to 6 weeks were given (20, 24, 36).

The recently reported pivotal European phase III multicenter trial compared the efficacy and tolerability of bendamustine (100 mg/m² on days 1 and 2 every 4 weeks) with that of chlorambucil (0.8 mg/kg on days 1 and 14 every 4 weeks) in previously untreated CLL patients. In a total of 319 patients, the authors showed that bendamustine induced significantly higher response rates and longer PFS than chlorambucil in first-line therapy of CLL (1). The ORR was 68% in bendamustine-treated and 31% in chlorambucil-treated patients. The complete remission rate with bendamustine, compared with chlorambucil, was 31% versus 2%. Bendamustine induced significantly longer PFS (21.6 versus 8.3 months) and remission durations (21.8 versus 8.0 months). Grade 3 and 4 adverse events (40% versus 19%), and severe infections events (8% versus 3%) were more common with bendamustine (1). These results were basis for the FDA approval of bendamustine in CLL and for the recommended dose of 100 mg/m² intravenously on days 1 and 2 of a 28-day cycle for up to six cycles.³

The German CLL study group (GCLLSG) investigated the combination of bendamustine 70 mg/m² on days 1 and 2 in combination with rituximab at 375 mg in the first cycle (and at 500 mg/m² in subsequent cycles) in relapsed CLL patients (37). In 62 evaluable patients, they noticed an ORR 77.4% with CR in 14.5% and PR in 62.9%. Given these encouraging results, the GCLLSG is now conducting a phase III trial to compare immuno-chemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) to the combination of bendamustine and rituximab (BR) in previously untreated CLL patients.

Bendamustine in other indications. Bendamustine displays significant activity in other B-cell malignancies, such as multiple myeloma, aggressive B-cell lymphomas, and certain solid tumors, such as breast cancer and small-cell lung cancer (reviewed in ref. 22). Trials of bendamustine as single agent or in combinations are ongoing in myeloma and acute myelogenous leukemia.

Clinical conclusions. Current data indicate that bendamustine as a single agent or in combination with rituximab (BR), is an effective salvage strategy for patients with CLL and indolent B-cell NHL. The role of bendamustine in front-line treatment of these diseases however needs to be better defined. In CLL, the recent data from Knauf and colleagues (1) could create a trend toward replacing chlorambucil and other drugs used in front-line treatment of CLL with bendamustine, which is not justified at this point. First, because of chlorambucil’s notoriously low response rates, it has increasingly been replaced by fludarabine (F), fludarabine plus cyclophosphamide (FC), or the combination of FCR. Trials comparing bendamustine or BR with these regimens are ongoing or in planning, but data are not yet available. Compared with single-agent bendamustine, the fludarabine-based FC (38–40) or FCR (41, 42) regimens display higher remission rates and longer remission durations, and therefore we will have to wait for the clinical results of bendamustine containing regimes.

Also, we know that response rates in CLL do not necessary translate into improved PFS, remission durations, or overall survival, a theme that was reinforced by a recent phase III study comparing chlorambucil with fludarabine as a front-line treatment for CLL patients older than 65 years. The authors observed no differences in PFS, and a shorter overall survival in fludarabine-treated patients (46 versus 64 months in the chlorambucil arm). Therefore, they concluded that in elderly CLL patients first-line therapy with fludarabine does not result in a major clinical benefit (43), although trial-inherent issues, such as fludarabine dose reductions and lack of salvage treatment after fludarabine failure explain, at least in part, the low efficacy of fludarabine in this trial. A U.S. intergroup trial comparing chlorambucil with fludarabine for initial treatment in CLL concluded that fludarabine induces higher response rates and longer remission durations and PFS, but the overall survival for both treatments were the same (44). In contrast, younger CLL patients (<70 years old) have an apparent clinical benefit from a regimen that induces high rates of remissions, such as FCR (42). In the indolent NHLs, the situation is similar: a longer follow-up of the front-line trial (33) and subset analysis may

Table 1. Clinical trials of single agent bendamustine in NHL and CLL

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose mg/m² (days administered)</th>
<th>No.</th>
<th>Percentage ORR</th>
<th>Percentage CR</th>
<th>RD, mo</th>
<th>Reference</th>
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<tr>
<td>Rel/ref NHL</td>
<td>120 (d 1, 2)</td>
<td>52</td>
<td>73</td>
<td>11</td>
<td>16</td>
<td>21</td>
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<tr>
<td>Rel/ref NHL</td>
<td>60 (5-d)</td>
<td>77</td>
<td>82</td>
<td>15</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>Rel/ref NHL</td>
<td>120 (d 1, 2)</td>
<td>18</td>
<td>44</td>
<td>17</td>
<td>4.5</td>
<td>23</td>
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<tr>
<td>Ritux ref NHL</td>
<td>120 (d 1, 2)</td>
<td>76</td>
<td>77</td>
<td>15</td>
<td>6.7</td>
<td>24</td>
</tr>
<tr>
<td>Ritux ref NHL</td>
<td>120 (d 1, 2)</td>
<td>40</td>
<td>74</td>
<td>13</td>
<td>9.2</td>
<td>25</td>
</tr>
<tr>
<td>Rel/ref CLL</td>
<td>100 &amp; up, (d 1, 2)</td>
<td>15</td>
<td>60</td>
<td>27</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Rel/ref CLL</td>
<td>100 (d 1, 2)</td>
<td>21</td>
<td>66</td>
<td>29</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Rel/ref CLL</td>
<td>50-60 (5-d)</td>
<td>20</td>
<td>75</td>
<td>30</td>
<td>-</td>
<td>34</td>
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<tr>
<td>Rel/ref CLL</td>
<td>70-100 (d 1, 2)</td>
<td>16</td>
<td>56</td>
<td>13</td>
<td>46</td>
<td>35</td>
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<tr>
<td>Untreated CLL</td>
<td>100 (d 1, 2)</td>
<td>162</td>
<td>68</td>
<td>31</td>
<td>22</td>
<td>1</td>
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</table>

Abbreviations: Rel, relapsed; ref, refractory; CR, complete remission; RD, response duration; ORR, overall response rate; d, days.

Bendamustine in B-cell Malignancies
help to better define the pros and cons of bendamustine-based therapy, such as BR in the front-line setting when compared with the established regimen.

**Overall Conclusions**

Collectively, the clinical studies highlight that we first need better definitions of patient subsets that are likely to benefit from bendamustine or bendamustine combinations (BR), and second, that we need to better define the clinical endpoints that are our goal in treating patients with CLL and indolent NHLs, such as remission rates, survival, and quality of life. Third, side-by-side comparisons of bendamustine with commonly used front-line regimens, such as the FCR regimen in younger CLL patients (ongoing GCLLSG trial) will help us to better understand and compare the activity of bendamustine to other active agents. Furthermore, once the front-line bendamustine data in CLL (1) and indolent NHLs (33) become more mature, we will be updated on how bendamustine impacts overall survival. Finally, metabolism, pharmacokinetics, and detailed mechanistic studies of bendamustine are needed for its optimal dose and schedule and combination with other agents. Collectively, these issues will allow us to better define the most appropriate use of bendamustine in CLL and other indolent B-cell malignancies.

**Disclosure of Potential Conflicts of Interest**

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**References**


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