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

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Bendamustine has also demonstrated significant activity in the treatment of indolent NHL, which is a very heterogeneous disease and the most common hematologic malignancy in the United States. The histology and stage of the disease guide treatment for patients with indolent NHL.

— Susanne Liewer, PharmD, BCOP, page 10
Efficacy of Bendamustine in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

This is the second article in a 4-part series on bendamustine. This article discusses 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. Subsequent articles in this series will discuss the safety of bendamustine and describe ongoing clinical investigations of the agent.

Chronic Lymphocytic Leukemia

CLL, the most common form of leukemia in Europe and North America, is a disorder in which morphologically mature but immunologically less mature lymphocytes accumulate in the blood, bone marrow, and lymphatic tissues. According to the American Cancer Society, an estimated 15,680 new cases of CLL will occur in 2013 (9720 in men and 5960 in women), and 4580 people will die of the disease. However, the clinical course of patients with CLL is heterogeneous, with some patients experiencing rapid disease progression and others living for decades without requiring treatment. The clinical staging systems developed by Rai et al and Binet et al are used to classify patient stage and predict survival (Table 1).

For many years, alkylating agents, especially chlorambucil, were considered the drugs of choice for first-line treatment of CLL. More recently, first-line treatment is frequently conducted with chlorambucil, fludarabine, or fludarabine plus cyclophosphamide, either alone or in combination with rituximab. Studies have shown significantly higher response rates, longer duration of remission, and longer progression-free survival (PFS) rates in patients treated initially with fludarabine than in those treated with chlorambucil. However, the median survival times did not differ among the patients treated with fludarabine and chlorambucil.

Bendamustine in CLL

On March 20, 2008, the FDA approved bendamustine hydrochloride (Treanda), an alkylating agent administered IV, 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 for previously untreated patients with advanced CLL. Because of this, the

### Table 1. Staging Systems for CLL

<table>
<thead>
<tr>
<th>Staging System</th>
<th>Stage</th>
<th>Characteristics</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rai Staging System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rai stage 0</td>
<td>Lymphocytosis</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Rai stage I</td>
<td>Lymphocytosis plus enlarged lymph nodes</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Rai stage II</td>
<td>Lymphocytosis plus an enlarged spleen</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Rai stage III</td>
<td>Lymphocytosis plus anemia (ie, hemoglobin &lt;11 g/dL)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Rai stage IV</td>
<td>Lymphocytosis plus thrombocytopenia (platelet count &lt;100 x 10^9 cells/L)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td><strong>Binet Staging System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binet stage A (corresponds to Rai stages 0, I, and II)</td>
<td>&lt;3 areas of lymphoid tissue enlarged, with no anemia or thrombocytopenia</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Binet stage B (corresponds to Rai stages I and II)</td>
<td>≥3 areas of lymphoid tissue enlarged, with no anemia or thrombocytopenia</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Binet stage C (corresponds to Rai stages III and IV)</td>
<td>Anemia and/or thrombocytopenia present</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
US product label points out that efficacy relative to first-line therapies other than chlorambucil has not been established. 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.

The trial was conducted in 301 patients (153 on bendamustine and 148 on chlorambucil) with Binet stage B or C (Rai stages I-IV) CLL requiring treatment.

Need-to-treat criteria included:
- Hematopoietic insufficiency
- B symptoms (such as weight loss of 10% or more, drenching night sweats, extreme fatigue, or unexplained fever of 100.5°F or higher)
- Rapidly progressive disease
- Risk of complications from bulky lymphadenopathy

Exclusion criteria included:
- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Richter’s syndrome
- Transformation to prolymphocytic leukemia

Patients were randomly assigned to receive either bendamustine 100 mg/m² IV on days 1 and 2 every 28 days or chlorambucil 0.8 mg/kg orally on days 1 and 15 every 28 days (Figure 1). Up to 6 cycles were administered to each patient.

The patient populations in the bendamustine and chlorambucil treatment groups were balanced with regard to baseline characteristics, as shown in Table 2. Ninety percent of patients in both treatment groups had immunophenotypic confirmation of CLL (CD5, CD23, and either CD19, CD20, or both).

**Efficacy Results**

A National Cancer Institute (NCI)-sponsored working group had formulated standardized guidelines in 1996 for criteria related to response to be used in clinical trials in CLL. The efficacy analyses were based on this NCI-sponsored working group’s criteria, as follows:

- **Overall response rate (ORR)** included patients with a best response of complete response (CR), nodular partial response (nPR), and partial response (PR) (ORR = CR + nPR + PR).
- **CR** was defined as peripheral lymphocyte count ≤4.0 x 10⁹/L, neutrophils ≥1.5 x 10⁹/L, platelets >100 x 10⁹/L, hemoglobin >11.0 g/dL without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤1.5 cm, <30% lymphocytes without nodularity in at least a normocellular bone marrow, and absence of B symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.
- **nPR** was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.
- **PR** was defined as ≥50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥50% reduction in lymphadenopathy, or ≥50% reduction in the size of spleen or liver, as well as 1 of the following hematologic improvements: neutrophils ≥1.5 x 10⁹/L or 50% improvement over baseline, platelets >100 x 10⁹/L or 50% improvement over baseline, hemoglobin >11.0 g/dL or
EFFICACY OF BENDAMUSTINE

The efficacy of bendamustine was compared with chlorambucil in a randomized trial for patients with previously untreated B-cell lymphomas. The primary endpoint was overall response rate (ORR), defined as at least a 50% improvement over baseline without transfusions, for a period of at least 56 days.

ORR was higher in patients in the bendamustine treatment group compared with those in the chlorambucil group (Figure 2). In the bendamustine group, an ORR of 59% (90 of 153 patients) was achieved, with 73 of 153 (48%) achieving a PR, 4 of 153 (3%) an nPR, and 13 of 153 (8%) a CR, while in the chlorambucil group an ORR of 26% (38 of 148 patients) was achieved, with 37 of 148 (25%) achieving a PR, 0 patients an nPR, and 1 of 148 (<1%) a CR.1

The median PFS (defined as time from randomization to progression or death from any cause) was 18 months (95% CI, 11.7-23.5) for bendamustine versus 6 months (95% CI, 5.6-8.6) for chlorambucil (hazard ratio 0.27; 95% CI, 0.17-0.43; *P<.0001).1 Survival data were not mature. Kaplan-Meier estimates of PFS comparing the bendamustine and chlorambucil treatment groups are shown in Figure 3.1

B-CELL NON-HODGKIN LYMPHOMA

According to the American Cancer Society, 69,740 new cases of NHL (both B-cell and T-cell) are expected (37,600 in men and 32,140 in women) in 2013, and 19,020 people will die of these diseases.1 The subtypes of NHL are characterized in 2 ways:14

- By the type of cells (B cells, T cells, or natural killer cells) they affect
- By how rapidly or slowly the disease progresses: indolent (slow growing) or aggressive (fast growing)

B-cell lymphomas make up most (about 85%) of NHLs in the United States.15,16 B-cell lymphomas with indolent histologies, and their relative incidences, include14:

- Follicular lymphoma (22% of all NHL)
- Mucosa-associated lymphatic tissue lymphoma (7.5% of all NHL)
- Small cell lymphocytic lymphoma/CLL (7% of all NHL)
- Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia (<2% of all NHL)
- Nodal marginal zone B-cell lymphoma (<2% of all NHL)

Treatment of indolent NHL depends on the histology and stage of the disease. The stages of NHL are listed in Table 3.14 Because indolent NHL is often asymptomatic in early stages, it is generally advanced (stage III or IV) at the time of detection.

Over the past decade, the addition of rituximab, an anti-CD20 monoclonal antibody, to conventional chemotherapy has revolutionized the treatment of B-cell malignancies. Studies have established rituximab as a viable treatment option in patients with relapsed or refractory indolent NHL,17 and treatment guidelines from the National...
Comprehensive Cancer Network now recommend a rituximab-based regimen as initial therapy for patients with B-cell lymphoma. However, patients tend to become refractory to rituximab over time. In addition, patients with indolent B-cell lymphoma who are treated with rituximab-chemotherapy combinations often develop rituximab resistance, so innovative treatments were sought for this rituximab-refractory patient population.

**Efficacy Results**

Efficacy was assessed by a blinded independent review committee using the modified International Working Group response criteria (IWG-RC) for NHL. Modifications to the IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. The end points were defined as follows:

- **Overall response rate (ORR)**
- **Duration of response**

**Bendamustine in Indolent B-Cell Non-Hodgkin Lymphoma**

On October 31, 2008, the FDA approved bendamustine for the treatment of patients with indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. As the basis for its approval, the FDA used the 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. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received bendamustine IV over 60 to 120 minutes at a dose of 120 mg/m² on days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

Seventy-six percent of patients had advanced-stage disease at enrollment, and the median number of prior chemotherapy regimens was 2 (range, 0-6 regimens). The baseline patient demographics and disease characteristics are shown in Table 4. Ninety-seven percent of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

### Table 4. Baseline Patient Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median age (years)</td>
<td>60</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65</td>
</tr>
<tr>
<td>Disease stage (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8</td>
</tr>
<tr>
<td>II</td>
<td>16</td>
</tr>
<tr>
<td>III</td>
<td>33</td>
</tr>
<tr>
<td>IV</td>
<td>43</td>
</tr>
<tr>
<td>World Health Organization performance status of 0 or 1 (%)</td>
<td>95</td>
</tr>
<tr>
<td>Histology (%)</td>
<td></td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>62</td>
</tr>
<tr>
<td>Diffuse small lymphocytic lymphoma</td>
<td>21</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>16</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>1</td>
</tr>
<tr>
<td>Previous chemotherapy (%)</td>
<td></td>
</tr>
<tr>
<td>0 previous regimen</td>
<td>99</td>
</tr>
<tr>
<td>1 previous regimen</td>
<td>1</td>
</tr>
<tr>
<td>2 previous regimens</td>
<td>41</td>
</tr>
<tr>
<td>3 previous regimens</td>
<td>36</td>
</tr>
<tr>
<td>&gt;3 previous regimens</td>
<td>14</td>
</tr>
<tr>
<td>Previous alkylator therapy (%)</td>
<td>8</td>
</tr>
</tbody>
</table>

CR indicates complete response; CRu, unconfirmed complete response; ORR, overall response rate; PR, partial response.

**Bendamustine Monotherapy**

On October 31, 2008, the FDA approved bendamustine for the treatment of patients with indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. As the basis for its approval, the FDA used the 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. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received bendamustine IV over 60 to 120 minutes at a dose of 120 mg/m² on days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

Seventy-six percent of patients had advanced-stage disease at enrollment, and the median number of prior chemotherapy regimens was 2 (range, 0-6 regimens). The baseline patient demographics and disease characteristics are shown in Table 4. Ninety-seven percent of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. Efficacy was assessed by a blinded independent review committee using the modified International Working Group response criteria (IWG-RC) for NHL. Modifications to the IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm. The end points were defined as follows:

- **Overall response rate (ORR)**
- **Duration of response**

**Efficacy Results**

Efficacy was assessed by a blinded independent review committee using the modified International Working Group response criteria (IWG-RC) for NHL. Modifications to the IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm. The end points were defined as follows:
• ORR was defined as the proportion of patients who achieved as their best response a CR, an unconfirmed CR (CRu), and a partial response (PR)
• Duration of response was defined as the time from the first documentation of response until disease progression, death, or change of therapy

In this population of patients with B-cell NHL who were previously treated with and resistant to rituximab-containing regimens, an ORR of 74% (74 of 100 patients) was achieved with bendamustine monotherapy, with 57 of 100 (57%) achieving a PR, 4 of 100 (4%) a CRu, and 13 of 100 (13%) a CR (Figure 5).1

In addition, single-agent bendamustine provided durable responses that lasted a median of 9.2 months.1

Part 3 in the Series
The next article in this series will discuss the safety data in patients with CLL and NHL reported in the registration studies cited in the bendamustine US product labeling.

References
The second in a series of 4 articles describes the natural history of chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (NHL). As 2 indolent lymphocytic malignancies, they have a similar natural history of a slowly progressive illness that can have progressive cytopenias and/or lymphadenopathy that eventually may require therapy. The initial therapies that have been used to treat CLL and indolent NHL have mostly included the use of alkylating agents or purine analogs in conjunction with rituximab. Although these agents have a high response rate, side effects can include myelosuppression and infectious complications. This article outlines the information for the use of bendamustine in patients with CLL or indolent NHL.

Bendamustine has been compared with chlorambucil for treatment of CLL that demonstrated a higher overall response rate (ORR) of 59% compared with 26% for chlorambucil. The progression-free survival for those patients in the bendamustine arm was improved over those patients receiving chlorambucil. This information led to the FDA approval of bendamustine for the treatment of CLL. Bendamustine is well tolerated in patients of all age groups.

Indolent NHL is a group of diseases that include mostly follicular lymphoma, in addition to other more rare types such as marginal zone lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma. Standard therapy for this group of lymphomas has typically consisted of the combination of an alkylating agent, purine analog, or an anthracycline with rituximab. Bendamustine has been tested in rituximab-resistant indolent NHL patients as a single agent and found to have a high ORR of 74%, with a duration of response of 9.2 months.

Although we have many treatment options for our patients with CLL and indolent NHL, the patients have multiple episodes of remissions and relapses and will need many treatment options over the years of their disease. With the addition of bendamustine for the treatment of indolent NHL and CLL, 1 additional therapeutic has been identified.

With all of these options for therapy, the toxicity profile of the agents becomes an important comparison. In the next article, toxicities of bendamustine will be discussed in detail.
In 2013, an estimated 15,680 people in the United States will be diagnosed with chronic lymphocytic leukemia (CLL), and 4580 will die of the disease. The mean age at diagnosis is 72 years, and the 5-year survival rate is 82%.1

Patients with indolent disease are able to go long periods with a watch-and-wait approach. The criteria for treatment require some of the following symptoms: rapidly progressing disease, ie, bulky lymphadenopathy and risk of complications from lymphadenopathy; cytopenias; B symptoms, ie, weight loss of greater than 10%, drenching night sweats, extreme fatigue; and other signs of failure to thrive.

Chlorambucil was a first-line choice in the treatment of CLL. Combination chemotherapy – fludarabine, cyclophosphamide, and rituximab (FCR) – showed longer progression-free survival; however, median survival was not improved when compared with chlorambucil. FCR is considered a toxic treatment due to its aggressive side effect profile, and its use became problematic for the elderly and patients with significant comorbidities. Toxicities forced treatment holds, dose reductions, and discontinuation of therapy, thus decreasing efficacy.

Bendamustine was approved for use in CLL in 2008 as a result of a study comparing bendamustine and chlorambucil. In a cohort of 301 patients, 153 patients received single-agent therapy with bendamustine and 148 patients received chlorambucil. The bendamustine dosing was 100 mg/m² on days 1 and 2 of a 28-day cycle, and chlorambucil was dosed at 0.8 mg/kg po on days 1 and 15 every 28 days. Bendamustine as monotherapy showed a higher overall response rate than chlorambucil alone. Median time to progression was 18 months for bendamustine versus 6 months for chlorambucil. The toxicity profile proved to be greater with bendamustine than with chlorambucil, but better than with FCR. The most common side effects were hematologic toxicities, infections, nausea, vomiting, and an increased incidence of tumor lysis syndrome.2

Bendamustine Use in B-Cell Non-Hodgkin Lymphoma

B-cell lymphoma is the most common type of lymphoma. Approximately 69,740 cases of both B- and T-cell lymphoma was diagnosed in 2012.3 Treatment depends on the type and staging of the disease. Even with current treatment regimens, non-Hodgkin lymphoma (NHL) and mantel cell lymphoma remain incurable.2

The addition of rituximab to chemotherapy regimens has increased efficacy of treatment with adjunct chemotherapy. In 2008, bendamustine was approved for second-line treatment in patients who have failed first-line treatment with a rituximab or rituximab-containing regimen or were declared to have rituximab-resistant disease.3 Patients who fail first-line treatment or become resistant tend to have lower response rates to subsequent treatments.2 A single-arm study of 100 patients who relapsed within 6 months of rituximab as monotherapy or combination therapy were treated with bendamustine 120 mg/m² on days 1 and 2 of a 21-day treatment cycle. Sixty-seven percent of patients had advance disease and had received a median of 2 previous treatments. An overall response rate of 74% was seen in patients who received bendamustine in this setting.3

Bendamustine has significant activity in CLL and NHL, with an acceptable toxicity profile. The goal of treatment is to maximize response and minimize toxicities while improving quality of life. Careful monitoring of patients is imperative. Supportive patient care for hematologic toxicity and nausea and vomiting and prophylaxis infection treatment are key to maintaining patient safety goals. Ongoing studies will provide data from the use of bendamustine in combination therapy. Some of the purposed studies combine rituximab, ofatumumab, lenalidomide, and fludarabine.2

References
Bendamustine is an active chemotherapy agent that has been studied for many years in a variety of malignancies; however, it has only been approved for use in the United States since 2008. Structurally, bendamustine shares similarities with both purine analogs and alkylating agents. The addition of the benzimidazole ring contributes to its unique structure and extended spectrum of activity. Bendamustine is currently FDA approved for the treatment of both chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of receiving rituximab or rituximab-containing regimens.

CLL is the most common leukemia diagnosed in Western countries. This disease tends to affect older populations, with a median age at diagnosis of 72 years. Therapy for patients with CLL must be individualized based on multiple factors such as age, overall health, comorbid conditions, and specific cytogenetic abnormalities. Bendamustine is a very active agent in the treatment of CLL and has demonstrated efficacy when used as monotherapy as well as in combination with other agents. The FDA approved its use based on a phase 3 randomized, open-label trial that compared bendamustine with chlorambucil as initial therapy in patients with advanced CLL. The overall response rate (ORR) and median progression-free survival (PFS) achieved were 59% and 18 months in the bendamustine group versus 26% and 6 months in the chlorambucil group, respectively ($P<.0001$). In addition to the efficacy of bendamustine when used as a single agent, it has been successfully combined with rituximab in the treatment of CLL. The German CLL Study Group (GCLLSG) reported the results of a phase 2 trial of bendamustine combined with rituximab in the treatment of previously treated patients with CLL. The ORR was reported as 59%, with 9% of the patients experiencing a complete response (CR). Based on these results, the GCLLSG is currently conducting a phase 3 trial comparing bendamustine and rituximab with the active regimen fludarabine, cyclophosphamide, and rituximab. The results from this study may help to further define the use of bendamustine in this patient population.

Bendamustine has also demonstrated significant activity in the treatment of indolent NHL, which is a very heterogeneous disease and the most common hematologic malignancy in the United States. The histology and stage of the disease guide treatment for patients with indolent NHL. In the past decade the use of the anti-CD20 monoclonal antibody rituximab has had a significant impact on response rates and overall survival. Though rituximab is traditionally incorporated into front-line therapies, new and innovative regimens have been developed for patients who relapse after receiving rituximab-containing regimens. Bendamustine was approved by the FDA for the treatment of patients with indolent NHL in 2008. This approval was based on the results in 100 patients with indolent NHL who had been previously treated with rituximab or rituximab-containing regimens. All patients received bendamustine as monotherapy for up to 8 cycles. The ORR reported was 74%, with a median duration of response of 9.2 months. Bendamustine has also been studied in combination with rituximab. A randomized phase 3 trial compared rituximab plus bendamustine with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as first-line therapy in patients with advanced follicular lymphoma and indolent and mantle cell lymphomas ($n=513$). The ORR was similar in both groups. However, the CR, median PFS, and event-free survival were all significantly higher in the bendamustine plus rituximab arm compared with the R-CHOP arm. In addition, patients who received bendamustine experienced fewer serious adverse events associated with treatment. Encouraging results in patients with relapsed and refractory follicular lymphoma have also been reported with novel combinations such as bendamustine, rituximab, and bortezomib.

Bendamustine has demonstrated significant activity as monotherapy or in combination when used as frontline therapy or for relapsed/refractory disease. With a tolerable toxicity profile, bendamustine provides a versatile and favorable treatment option for patients with CLL or indolent NHL.
Efficacy of Bendamustine

References
