C
define lymphoid malignancies, which are a
significant burden to patients and to the
healthcare system. In light of the morbidity,
mortality, and quality-of-life challenges
associated with CLL and NHL, there is a
marked need for additional therapeutic
options for patients with these malignancies.

**Chronic Lymphocytic Leukemia**

CLL, a cancer of B-cell lymphocytes, is the
most common type of leukemia in adults. An
estimated 18,960 individuals will be
diagnosed with CLL in 2016, and
approximately 4660 patients will die from this
in the same period. CLL is a disease of the
elderly; the incidence of CLL increases
significantly among individuals aged ≥50 years,
with only a small fraction of people
diagnosed in their 30s and 40s. The majority of
patients with CLL are diagnosed without
symptoms as the result of routine blood
work. As it advances, CLL can cause
severe fatigue, swollen lymph nodes, enlarged
spleen, shortness of breath, and infections.

The clinical course of CLL is heterogeneous—
whereas some patients live for decades with
no treatment, others have disease that is
rapidly aggressive. The 5-year relative
survival rate for patients with CLL (all
stages combined) is approximately 82%.

With the approval of several novel
targeted agents for CLL, the costs associated
with treating this disease have risen
exponentially. Using data from a population
of patients in Olmsted County, MN, researchers
estimated the total out-of-pocket drug
spending costs over 10 years after
diagnosis for a hypothetical cohort of 100
patients with newly diagnosed CLL. The
researchers considered 3 scenarios—(1)
before the approval of ibrutinib and
idelalisib for CLL (historical scenario),
(2) after the approval of these
generically, as salvage therapy (current
scenario), and (3) after the use of
ibrutinib as first-line treatment
for CLL (potential future scenario). The
10-year out-of-pocket costs under the
historical scenario increased to
approximately $325 per patient; the
costs under the current scenario increased
to $8800 per patient; the costs under
the future scenario approached $35,600 per patient.

**Indolent Non-Hodgkin Lymphoma**

Lymphoma begins in certain immune
system cells, and is classified as either
Hodgkin lymphoma or NHL. The
5-year and 10-year survival rates for
patients with NHL are 69% and 59%,
respectively. More than 80,000
new cases of lymphoma were diagnosed in 2015.

NHL is subdivided into 2 broad
categories—indolent and aggressive. Follicular
lymphoma is one of the most
common types of indolent NHL; approximately
20% of patients with NHL have
follicular lymphoma.

Common symptoms of NHL include
lymphadenopathy, chest pain, shortness of
breath, abdominal fullness, and loss of appetite.
Other symptoms of NHL include
itching, night sweats, fatigue, unexplained
weight loss, and intermittent fever.

The economic costs associated with the
progression of follicular NHL among
US-based patients are significant. Using a
retrospective claims database of
patients who were managed in the
outpatient setting between 2006
and 2009, researchers estimated that
patients with relapsed follicular
lymphoma spent an average of more
than $3500 monthly in overall costs.

**New Formulation of Bendamustine Approved**

On December 8, 2015, the US Food and
Drug Administration (FDA) granted
accelerated approval to a
rapid-infusion formulation of bendamustine
hydrochloride (Bendeka; Teva and
Eagle Pharmaceuticals) for the
treatment of 2 hematologic
malignancies—CLL and
indolent NHL that has progressed
during or within 6 months of

treatment with rituximab or a rituximab-containing
regimen. The rapid-infusion
formulation of bendamustine also received
orphan drug designations for
CLL and NHL.

This formulation has a low volume and a short
infusion time; it is administered in a
50-mL admixture as an

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**Bendeka (Bendamustine Hydrochloride): Rapid-Infusion Formulation Approved for Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphomas**

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intravenous infusion for 10 minutes on days 1 and 2 of a 21- or 28-day cycle for 6 to 8 cycles.\textsuperscript{10,11}

The original formulation of bendamustine (Treanda; Teva) is administered as an intravenous infusion in a 500-mL admixture for 30 to 60 minutes.\textsuperscript{12} This formulation was first approved by the FDA in March 2008 for the treatment of patients with CLL; it later received an expanded indication in October 2008 for the treatment of indolent B-cell NHL.\textsuperscript{13,14}

**Mechanism of Action**

Bendamustine is a bifunctional derivative of mechlor-ethamine or nitrogen mustard.\textsuperscript{11} Bendamustine is active against quiescent and dividing cells, but its exact mechanism of action remains unknown.\textsuperscript{11}

**Dosage and Administration**

The rapidly infused bendamustine delivers the same amount of the active ingredient as the original formulation of bendamustine, but with a lower admixture volume, which enables this rapidly infused bendamustine to be administered more quickly than the original formulation.\textsuperscript{10}

**CLL.** The recommended dosage of rapid-infusion bendamustine for patients with CLL is 100 mg/m\textsuperscript{2} infused intravenously for 10 minutes on days 1 and 2 of a 28-day cycle for a maximum of 6 cycles.\textsuperscript{11}

**Indolent NHL.** The recommended dosage for patients with indolent NHL is 120 mg/m\textsuperscript{2} infused intravenously for 10 minutes on days 1 and 2 of a 21-day cycle for a maximum of 8 cycles.\textsuperscript{11}

Treatment with rapid-infusion bendamustine should be delayed for grade 4 hematologic toxicity or clinically significant grade 2 or higher nonhematologic toxicity.\textsuperscript{11}

Rapid-infusion bendamustine is provided in a multiple-dose vial containing 100 mg/4 mL (25 mg/mL) of bendamustine. Rapid-infusion bendamustine must be diluted before infusion.\textsuperscript{11}

**Clinical Trials**

The FDA approval of rapid-infusion bendamustine for CLL and indolent NHL was supported by favorable results from an open-label, randomized, crossover, phase 1 clinical trial that was designed to compare the bioequivalence of the rapidly infused bendamustine (delivered intravenously in a 50-mL admixture for 10 minutes) with the original formulation of bendamustine (administered in a 500-mL admixture for 60 minutes), and to assess the safety and tolerability of the rapidly infused bendamustine.\textsuperscript{15}

The study evaluated 81 patients with a histologically confirmed diagnosis of solid tumors and hematologic malignancies for which no curative or standard therapy is appropriate.\textsuperscript{15} The study results showed that rapid-infusion bendamustine was bioequivalent to the original formulation of bendamustine.\textsuperscript{15}

**CLL.** The safety and efficacy of the original formulation of bendamustine hydrochloride for CLL were evaluated in an open-label, randomized, controlled, multicenter clinical trial comparing bendamustine with chlorambucil.\textsuperscript{11,16} This clinical trial enrolled patients with previously untreated CLL (Rai stages I-IV) who required treatment based on hematopoietic insufficiency, B symptoms, rapidly progressive disease, or risk for complications from bulky lymphadenopathy.\textsuperscript{11,16}

A total of 301 patients enrolled in this clinical trial, 153 of whom received bendamustine (100 mg/m\textsuperscript{2} intravenously for 30 minutes on days 1 and 2 of each 28-day cycle) and 148 received chlorambucil (0.8 mg/kg administered orally on days 1 and 15 of each 28-day cycle) for up to 6 cycles.\textsuperscript{11,16} The primary efficacy end points included the objective response rate and progression-free survival.\textsuperscript{11,16}

The objective response rate was significantly higher in patients who received bendamustine compared with patients who received chlorambucil (59% vs 26%, respectively; \(P < .0001\)).\textsuperscript{11,16} The median progression-free survival was 18 months in the bendamustine group compared with 6 months in the chlorambucil group (\(P < .0001\)).\textsuperscript{11,16} The use of bendamustine was associated with a 73% reduction in the risk for disease progression or death from any cause compared with chlorambucil.\textsuperscript{11}

The efficacy of bendamustine relative to first-line therapies other than chlorambucil has not been established in CLL.\textsuperscript{10,11}

**Indolent NHL.** The safety and efficacy of the original formulation of bendamustine hydrochloride for indolent NHL were evaluated in a single-arm study of 100 patients (median age, 60 years) with indolent NHL that progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.\textsuperscript{11,17}

Patients with indolent NHL received intravenous bendamustine at a dose of 120 mg/m\textsuperscript{2} on days 1 and 2 of each 21-day treatment cycle for a maximum of 8 cycles.\textsuperscript{11}

The major tumor subtypes included follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%).\textsuperscript{11} Overall, 99% of patients received previous chemotherapy, 91% of patients received previous alkylator therapy, and 97% experienced disease relapse within 6 months of either the first dose (monotherapy) or the last dose (maintenance regimen or combination therapy) of rituximab.\textsuperscript{11}

In this study, the objective response rate associated with bendamustine was 74%, including 13% complete responses, 4% unconfirmed complete responses, and 57% partial responses.\textsuperscript{11} The median duration of re-
The safety of rapid-infusion bendamustine is supported by clinical trials using the original formulation of bendamustine (intravenously administered as a 500-mL admixture for 30-60 minutes), as well as by an open-label study in “end-of-life” patients with cancer who received the rapidly infused bendamustine (intravenously administered as a 50-mL admixture for 10 minutes). The 8-week, open-label, crossover study of rapid-infusion bendamustine enrolled 81 patients with solid tumors and hematologic malignancies, excluding CLL, for which no curative or standard therapy is appropriate. These patients ranged in age from 40 to 82 years. Rapid-infusion bendamustine or the original formulation of bendamustine was administered on days 1 and 2 of every 28-day cycle for 2 consecutive cycles.

Adverse reactions (any grade) that occurred in >5% of patients during the administration of rapid-infusion bendamustine and within 1 hour after the administration of rapid-infusion bendamustine included nausea (8.2%) and fatigue (5.5%). Adverse reactions (any grade) that occurred in >5% of patients within 24 hours of receiving rapid-infusion bendamustine were nausea (10.9%) and fatigue (8.2%). Overall, 4 patients who received rapid-infusion bendamustine withdrew from the study because of adverse reactions, including pyrexia (1.2%), nausea (1.2%), vomiting (1.2%), pneumonia (1.2%), and fatigue (1.2%).

No clinically significant differences in the adverse event profile were noted between patients receiving the original formulation of bendamustine (administered for 30-60 minutes) and the rapid-infusion bendamustine (administered for 10 minutes).

The safety data for the original formulation of bendamustine reflect drug exposure in 329 patients who participated in an actively controlled clinical trial for the treatment of patients with CLL (N = 153), and 2 single-arm studies for the treatment of patients with indolent NHL (N = 176). In the randomized clinical study comparing bendamustine and chlorambucil in patients with CLL, nonhematologic adverse reaction (any grade) that occurred in >15% of patients in the bendamustine group included pyrexia (24%), nausea (20%), and vomiting (16%). The most frequent adverse reactions leading to study withdrawal among patients receiving bendamustine were hypersensitivity (2%) and pyrexia (1%).

In the single-arm clinical study of bendamustine in patients with indolent NHL, the most common nonhematologic adverse reactions included nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and pyrexia (34%). The most common severe (grade 3 or 4) nonhematologic adverse reactions were fatigue (11%), febrile neutropenia (6%), pneumonia (5%), hypokalemia (5%), and dehydration (5%).

In these studies, hematologic abnormalities (eg, lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia) were observed in the majority of patients receiving bendamustine. Febrile neutropenia was documented in 6% of patients with indolent NHL who received bendamustine.

Contraindications

Rapid-infusion bendamustine is contraindicated in patients with a history of hypersensitivity reactions to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

Drug Interactions

No drug interaction studies have been conducted with bendamustine. Inhibitors of cytochrome (CY) P1A2 may increase the plasma concentrations of bendamustine and decrease the plasma concentrations of the drug’s active metabolites. Conversely, inducers of CY P1A2 may decrease the plasma concentrations of bendamustine and increase the plasma concentrations of its active metabolites.

Warnings and Precautions

Myelosuppression. Bendamustine can cause severe myelosuppression, with hematologic nadirs typically occurring in the third week of therapy. Patients should monitor their complete blood counts. Dose delays and/or dose reductions are appropriate if bone marrow recovery has not occurred by the first day of the next scheduled cycle.

Infections. Infection, including pneumonia, sepsis, and septic shock, and death have occurred with bendamustine. Patients should seek medical attention immediately if the symptoms or signs of infection are noted.

Anaphylaxis and infusion reactions. Symptoms of infusion reactions associated with bendamustine therapy include fever, chills, pruritus, and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in second and subsequent therapy cycles. The discontinuation of rapid-infusion bendamustine may be warranted for grade 3 infusion reactions. Bendamustine therapy should be discontinued for grade 4 infusion reactions.

Tumor lysis syndrome. Tumor lysis syndrome, including one resulting in acute renal failure and death, has occurred in clinical trials and in postmarketing reports for bendamustine. The onset of tumor lysis syn-
drome is typically within the first treatment cycle.\textsuperscript{11} Preventive measures include hydration and close monitoring of blood chemistry, including potassium and uric acid levels.\textsuperscript{11}

**Skin reactions.** Skin reactions, including rash, toxic skin reactions, and bullous exanthema, have occurred with bendamustine therapy.\textsuperscript{11} Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes.\textsuperscript{11} Rapid-infusion bendamustine should be withheld or discontinued for severe or progressive skin reactions.\textsuperscript{11}

**Other malignancies.** Premalignant and malignant diseases have developed in patients receiving bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma.\textsuperscript{11}

**Extravasation.** Extravasations of bendamustine resulting in hospitalizations from erythema, marked swelling, and pain have been reported in postmarketing reports. Venous access should be ensured before starting the infusion with bendamustine, and the infusion site should be monitored for redness, swelling, pain, infection, and necrosis during and after the administration of rapid-infusion bendamustine.\textsuperscript{11}

**Use in Specific Populations**

**Pregnancy.** Bendamustine can cause fetal harm when administered to a pregnant woman. Women should avoid becoming pregnant while receiving bendamustine, and for 3 months after therapy has stopped. Men receiving bendamustine should use reliable contraception for the same period of time.\textsuperscript{11}

**Nursing mothers.** It is not known whether bendamustine is excreted in human milk.\textsuperscript{11} The decision to discontinue breast-feeding or to discontinue bendamustine should be based on the importance of the drug to the mother.\textsuperscript{11}

**Pediatric use.** The effectiveness of bendamustine in pediatric patients has not been established.\textsuperscript{11}

**Geriatric use.** There were no clinically significant differences in the rate or nature of adverse reactions between older patients (aged ≥65 years) and younger patients in the CLL and NHL studies.\textsuperscript{11}

**Renal impairment.** No formal studies of the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. Rapid-infusion bendamustine should be used with caution in patients with mild liver impairment, and should not be used in patients with severe renal impairment.\textsuperscript{11}

**Hepatic impairment.** No formal studies of the impact of liver impairment on the pharmacokinetics of bendamustine have been conducted. Rapid-infusion bendamustine should be used with caution in patients with mild liver impairment, and should not be used in patients with moderate or severe liver impairment.\textsuperscript{11}

**Sex.** No clinically significant differences in the rates of adverse reactions or efficacy were observed between men and women in the CLL or NHL studies.\textsuperscript{11}

**Conclusion**

Rapid-infusion bendamustine offers healthcare professionals and patients with CLL and indolent NHL a more convenient alternative to the original formulation of bendamustine, which is delivered in a 500-mL admixture for 30 to 60 minutes. Data from a bioequivalence study demonstrated that rapid-infusion bendamustine can be administered in 10 minutes in a low-volume, 50-mL admixture. The incidence and nature of adverse reactions for rapidly infused bendamustine, including infusion-related and general adverse reactions, were comparable to the original formulation of bendamustine.\textsuperscript{11}

**References**

11. Bendeka (bendamustine hydrochloride) injection [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA; December 2015.