

Bendamustine in chronic lymphocytic leukemia

Recent studies have shed light on the potential value of an old—and largely overlooked—therapy

What's new, what's important

Bendamustine (Treanda), a novel hybrid compound that combines the properties of an alkylating agent with those of a purine analog, currently has orphan drug status in the US for the treatment of chronic lymphocytic leukemia (CLL). A decision by the US Food and Drug Administration regarding approval for its use in CLL is expected by March 20, 2008.

In clinical trials, bendamustine was found to be effective in patients who failed to respond to alkylating agents and rituximab (Rituxan), with a response rate of 60% and 70%, respectively. Bendamustine also has demonstrated activity in patients refractory to fludarabine therapy. The maximum tolerated dose of bendamustine in patients with CLL ranges from 70 to 100 mg/m², given intravenously on days 1 and 2 every 3–4 weeks. The side-effect profile of the drug, which includes myelosuppression and infection, is manageable.

Studies are ongoing to define the exact role of bendamustine in the management of CLL, as well as relapsed, indolent non-Hodgkin's lymphoma. But it is a very promising drug with an excellent side-effect profile and is highly active, even in patients whose disease fails to respond to current standard treatment options.

— Jame Abraham, MD
Section Editor

Bendamustine (Treanda) is a purine analog/alkylator hybrid. The agent has been commercially available in Germany for many years and has been used in the treatment of a number of nonhematologic and hematologic malignancies, including chronic lymphocytic leukemia (CLL). A number of early-phase studies showing activity of bendamustine in CLL have been followed by a recently reported phase III trial demonstrating the superiority of bendamustine over chlorambucil (Leukeran) in treatment-naïve patients with CLL.

First-line therapy

In a phase III trial reported by Knauf and coworkers at the 49th Annual Meeting of the American Society of Hematology,¹ 305 patients with untreated CLL were randomized to receive open-label bendamustine, 100 mg/m² IV on days 1 and 2, or chlorambucil, 0.8 mg/kg orally on days 1 and 15, every 28 days for up

to 6 cycles. The primary endpoints were overall remission rate (ORR) and progression-free survival (PFS); remission was defined as complete response (CR), nodular partial response, or partial response (PR) confirmed after 8 weeks. At the time of reporting (December 9, 2007), safety results were available for 298 of the 305 patients who received the study drug (156 bendamustine patients and 149 chlorambucil patients), and 264 patients (139 bendamustine patients and 125 chlorambucil patients) were included in the efficacy analysis.

For both randomized groups, median age was 64 years, 70% of patients had Binet stage B disease, and 30% had stage C disease. Patients received a median of 6 cycles of treatment, and median follow-up was 18.5 months. The ORR was 68% in the bendamustine group versus 39% in the chlorambucil group ($P < 0.0001$), with a CR occurring in 30% versus 2% of patients, respectively. Remission rates were 70% versus 47% among patients

with Binet stage B disease and 61% versus 22% among those with stage C disease. Median PFS was 21.7 months in the bendamustine group compared with 9.3 months in the chlorambucil group ($P < 0.0001$). The median duration of remission was 18.9 months versus 6.1 months ($P < 0.0001$); however, no difference in overall survival between the two groups of patients was observed.

Toxicities of bendamustine were manageable and were not associated with impairment of quality of life. Grade 3/4 hematologic toxicities included neutropenia in 43% of bendamustine patients versus 24% of chlorambucil patients. Grade 3/4 infection occurred in 5.8% versus 3.5%, respectively. On the basis of these findings, the investigators concluded that bendamustine should be considered for first-line treatment of CLL.

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Second-line therapy

In early-phase studies, bendamustine has also shown good activity in patients with treatment-refractory CLL. In a phase I/II study reported by the German CLL Study Group,² response was achieved in 9 of 16 patients (2 with a CR, 5 with a PR, and 2 with stable disease) who had received a median of three prior regimens. Major grade 3/4 toxicities were leukopenia (eight patients) and infection (seven patients). Due to frequent dose-limiting toxicity at the starting dose of 100 mg/m² on days 1 and 2 every 3 or 4 weeks, the study dose was reduced to as low as 70 mg/m² in some patients. Responses were observed in seven patients receiving doses ≤ 80 mg/m². The maximum tolerated dose was defined as 70 mg/m², and it was recommended that the optimal dose in refractory CLL be considered as 70 mg/m² on days 1 and 2 every 4 weeks. The median duration of response was 42.7 months, with five patients remaining in remission after 53.2 months' fol-

low-up. The median overall survival for all patients was 45.6 months.

In another phase I/II study in 15 pretreated, but fludarabine-naïve, patients (11 with up to three prior treatments, 4 with more than three),³ response was observed in 8 patients (4 with a CR, 2 with a PR, and 2 with no change) at initial doses of 100, 110, or 120 mg/m² of bendamustine on days 1 and 2. The study dosing interval was increased from every 3 weeks to a mean of every 29 days to allow marrow recovery, and several patients needed their doses to be reduced during treatment. The maximum tolerated dose was defined as 110 mg/m². The median duration of response in patients with a CR was 22+ months. Grade 3/4 laboratory abnormalities included an increase in serum bilirubin level (the most common grade 3/4 event, observed in six patients) and decreases in hemoglobin value, white blood cell count, and platelet count.

Bendamustine is also being evaluated in combination with rituximab

(Rituxan)⁴ and mitoxantrone⁵ in advanced/refractory CLL.

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From the Oncologist's Perspective

Bendamustine: a potential new option for patients with refractory hematologic malignancies

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Last August, 2007, the US Food and Drug Administration (FDA) granted orphan drug status to bendamustine (Treanda) for the treatment of chronic lymphocytic leukemia (CLL).

The drug is currently awaiting approval for CLL in March and for follicular lymphoma in the spring of 2008.

CLL is the most common hematologic malignancy in the Western hemisphere, with an estimated 15,340

new cases diagnosed in the US alone in 2007.¹ The clinical course is usually indolent, with a significant proportion of patients managed by a “watch-and-wait” approach before eventually requiring therapy for progressive dis-

ease or the development of symptoms or recurrent infections.

Bendamustine was invented more than 40 years ago in East Germany, but it was never sufficiently studied in cancer patients until the 1990s. The compound consists of a nitrogen mustard group, which gives it the properties of an alkylating agent, and a purine-like benzimidazole group, which has a structure similar to a purine analog, although nucleoside activity has not been established. *In vitro*, bendamustine is non-cross-resistant with alkylating agents.² In clinical trials, bendamustine has demonstrated impressive activity, providing responses in more than 70% of CLL patients resistant to rituximab and about 60% of those who were refractory to alkylating agents. Patients who had failed to respond to prior fludarabine-based therapy also responded to bendamustine.

Two studies presented at the recent 49th Annual Meeting of the American Society of Hematology (ASH) focused interest on the use of bendamustine in CLL. Knauf and colleagues³ reported an international phase III study in which patients with CLL were randomized to receive either bendamustine or chlorambucil (Leukeran) for their initial treatment. The overall response rate (ORR) was significantly higher with bendamustine (68%) than with chlorambucil (39%), with a complete remission (CR) occurring in 30% versus 2%, respectively, of treated patients. The median progression-free survival was 21.7 months with bendamustine and 9.3 months with chlorambucil. Both the toxicity and infection rates associated with bendamustine were low and manageable.

The second study, reported by the German CLL Study Group,⁴ summarized results with bendamustine in combination with rituximab (Rituxan) in patients with relapsed CLL. Only 23 of the 81 patients enrolled were available for evaluation. The ORR was 65%, with a CR rate of 13%. However, no molecular remissions were observed thus far. It is important to note that responses were observed in the majority of patients with genomic aberrations, except those with a 17p deletion. As expected, high rates of myelosuppression and infection were noted.

The standard initial therapy for CLL is fludarabine-based treatment combined with rituximab. However, alemtuzumab (Campath) is also approved for the initial treatment of CLL. The CAM307 trial included 297 treatment-naïve, symptomatic CLL patients who were assigned randomly to treatment with alemtuzumab or chlorambucil.⁵ The ORR, CR, and response duration were significantly better for alemtuzumab than for chlorambucil. Alemtuzumab also demonstrated higher response rates in poor genomic-risk patients with 11q and 17p deletions. Unfortunately, alemtuzumab induces significant myelosuppression and immunosuppression. It also is less effective in patients with bulky lymphadenopathy. Because of these concerns, clinical use of alemtuzumab in CLL patients has been modest.

For those patients who fail to respond to or relapse on fludarabine-based therapy, the approved treatment is alemtuzumab. Consequently, if bendamustine is approved by the FDA, it will become the next sec-

ond-line therapy for CLL. However, bendamustine likely will not be accepted as front-line therapy until it is compared with a fludarabine-based regimen in treatment-naïve patients. Nevertheless, bendamustine looks promising in terms of response rate, a manageable side-effect profile, and applicability in many different diseases, such as lymphoma, multiple myeloma, Hodgkin's lymphoma, and even solid tumors. Clinical trials are exploring its role in combination with such agents as bortezomib (Velcade) and lenalidomide (Revlimid) in relapsed/refractory lymphoma and CLL. Whether such combinations will become our future front-line therapy in CLL remains to be seen. We believe, however, that this drug will be a great addition to treatment options for patients who are suffering from different lymphoid malignancies and will hopefully be commercially available in the near future.

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