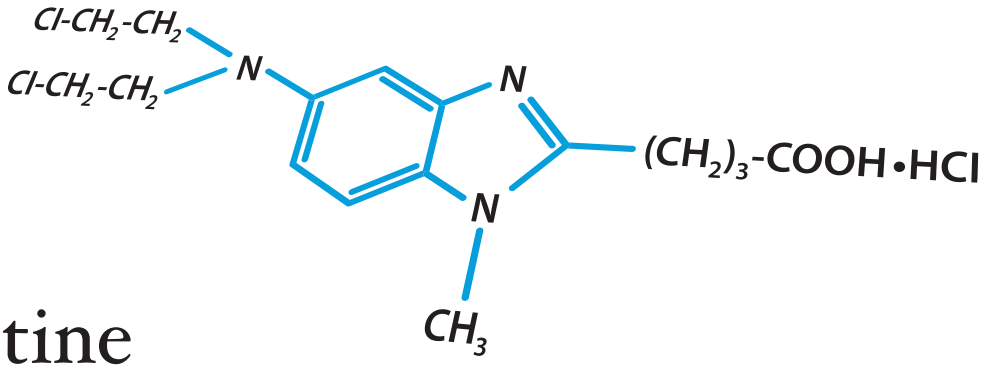

Bendamustine

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The treatment of low-grade lymphoid malignancies has seen major progress in the past decade, with improved response rates and survival in indolent B-cell lymphomas (Hiddemann et al., 2005; Herold et al., 2007) and historic comparisons suggestive of improved survival in chronic lymphocytic leukemia (CLL; Byrd et al., 2005; Keating et al., 2005). Approximately 26,500 new cases of low-grade non-Hodgkin's lymphoma (NHL) and 15,490 new cases of CLL were diagnosed in the United States in 2009 (Jemal et al., 2009).

Despite this recent progress, patients with NHL or CLL are still expected to relapse and require multiple treatment regimens over many years. This reality makes it critical to have extensive, effective therapeutic options available (Cheson & Rummel, 2009). One agent approved for use in patients with NHL or CLL is bendamustine (Treanda).

Class of Agent

Bendamustine is a novel hybrid agent created in the early 1960s in the former German Democratic Republic (GDR), also known as East Germany. Relocation of the nitrogen-mustard group to position 5 on a benzimidazole ring resulted in an agent with a structure similar to that of alkylating agents and purine analogs (Ozegowski & Krebs, 1971; Leoni et al., 2008). The effect of the benzimidazole ring on the clinical activity of bendamustine is unknown. Despite the use of bendamustine in the GDR for over 30 years, the drug underwent few studies considered validated by today's standards (Hartmann & Zimmer, 1972; Cheson & Rummel, 2009). After German reunification, trials were initiated to assess bendamustine's value in a variety of hematologic and solid malignancies (Cheson & Rummel, 2009).

Mechanism of Action

Bendamustine's antitumor effects include DNA damage through double- and single-stranded DNA cross-links and down-regulation of mitotic checkpoint genes that regulate DNA synthesis and cell division (Leoni et al., 2008). The concomitant activity of these pathways may further increase the cytotoxicity of bendamustine through a process called mitotic catastrophe, a form of necrotic cell death that occurs independently of normal apoptosis (Niemeyer et al., 2005). Bendamustine also has been shown to be active in tumors refractory to other chemotherapies, including alkylating agents (Friedberg et al., 2008; Strumberg et al., 1996; Leoni et al., 2008; Leoni et al., 2003).

The image at top is an illustration of the structural formula of bendamustine hydrochloride (source: Cephalon Oncology, 2009).

Table 1. Binet Staging System for chronic lymphocytic leukemia

Stage	Symptom/sign	Risk of progression	Median survival	Prevalence at diagnosis
A	Lymphocytosis, < 3 lymphoid areas enlarged	Low	> 10 years	60%
B	Lymphocytosis, > 3 lymphoid areas enlarged	Intermediate	7 years	30%
C	Lymphocytosis with either of anemia or thrombocytopenia	High	5 years	10%

Note: Based on information from Binet et al., 1981.

Table 2. Knauf et al. CLL endpoint summary

	Bendamustine	Chlorambucil
Number of patients	162	157
Median number of cycles	6	6
Overall response rate	68% (31% CR; 11% nodular PR)	31% (2% CR; 3% nodular PR)
PFS at median follow-up of 35 months	26.1 months	8.3 months
Median duration of response	21.8 months	8.0 months
Deaths	31 (13 CLL-related)	41 (21 CLL-related)

Note: CLL = chronic lymphocytic leukemia; CR = complete response; PR = partial response; PFS = progression-free survival. Based on information from Knauf et al., 2009.

Pivotal Trials Leading to FDA Approval

Today, bendamustine is approved by the U. S. Food and Drug Administration (FDA) for use in indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab (Rituxan) or a rituximab-containing regimen and in CLL, with efficacy established only as first-line therapy when compared with chlorambucil (http://www.treanda.com/). Two pivotal trials led to FDA approval of bendamustine in early 2008.

A phase III multicenter study of bendamustine versus chlorambucil in untreated CLL patients was reported by Knauf et al. (2009). Untreated CLL patients with Binet stage B or C disease up to 75 years of age (Table 1) were randomly assigned in a 1:1 ratio to receive bendamustine (100 mg/m^2 by intravenous infusion over 30 minutes on days 1 and 2) or chlorambucil (0.8 mg/kg orally on days 1 and 15), both on 28-day cycles for up to 6 cycles. Primary endpoints were overall response rate (ORR) and progression-free survival (PFS), with secondary safety endpoints. Efficacy results revealed superiority in the bendamustine group (Table 2), and safety profiles were acceptable in both groups. No differences in overall survival have been seen between the two groups

Table 3. Safety summary of commonly reported adverse events of bendamustine in CLL and NHL

Adverse event	Incidence (grade 3/4) in CLL	Incidence (grade 3/4) in NHL
Hematologic		
Neutropenia	27% (23%)	83% (61%)
Thrombocytopenia	25% (12%)	88% (25%)
Anemia	22% (14%)	94% (10%)
Nonhematologic		
Nausea	19% (1%)	77% (4%)
Vomiting	16% (1%)	40% (2%)
Infection	6% (2%)	69% (21%)
Diarrhea	10% (1%)	42% (5%)

Note: Based on information from Knauf, et al., and Kahl et al., 2009.
CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin's lymphoma

(Knauf et al., 2009). These results led to FDA approval of bendamustine in untreated CLL.

Kahl et al. (2009) reported a multicenter study of single-agent bendamustine in patients with rituximab-refractory, indolent B-cell lymphomas. In this study, 100 patients aged 18 years or older, who had received a median of two prior lymphoma regimens, received bendamustine (120 mg/m^2 by intravenous infusion over 60 minutes on days 1 and 2 of 21-day cycles for 6–8 cycles). Primary endpoints were ORR and duration of response (DOR), with secondary objectives including safety and PFS. Patients completed a median of 6 cycles. The ORR was 75% (14% complete response, 3% unconfirmed complete response, 58% partial response), with a median DOR and median PFS of 9.2 months and 9.3 months, respectively. Six deaths were possibly related to the study. Acceptable hematologic and nonhematologic toxicities were noted. These results let to FDA approval of bendamustine in previously treated indolent B-cell lymphomas. Commonly reported side effects of both pivotal trials are listed in Table 3.

Nursing Implications and the Treatment Armamentarium

Bendamustine adds the option of a well-tolerated, efficacious, "new" agent for use in patients with indolent B-cell NHL and CLL. Common clinical management strategies are listed in Table 4 and are reflective of alkylator therapy in patients with potentially massive tumor burdens (Blummel et al., 2008). Although current FDA indications are based on the two pivotal trials previously described, National Comprehensive Cancer Network (NCCN) guidelines also include bendamustine with or without rituximab in relapsed/refractory CLL, as well as initial therapy for indolent B-cell lymphomas (NCCN, 2010). The advanced prac-

Table 4. Clinical management strategies

Side effect	Intervention
Myelosuppression	• Dose modify or delay for grade 3 or 4 hematologic toxicity • Educate patients to report signs and symptoms of infection • Use growth factors at provider's discretion
Nausea and vomiting	• Consider antiemetic premedication and post-dose on running or as needed basis • Modify diet
Tumor lysis syndrome	• Assess risk for each patient • Institute hydration, allopurinol, and monitoring of serum chemistries as appropriate
Infusion reactions	• Although rare, assess for fever, chills, rash, and back pain, especially during second and third cycles

Note: Based on information from Blummel et al., 2008.

Table 5. Dosage and administration of bendamustine

	Chronic lymphocytic leukemia	Low-grade non-Hodgkin's lymphoma
Dose	100 mg/m^2 IV	120 mg/m^2 IV
Administration	Infuse over 30 minutes	Infuse over 60 minutes
Schedule	Administer on days 1 and 2 of 28-day cycles for up to 6 cycles	Administer on days 1 and 2 of 21-day cycles for up to 8 cycles
Hematologic toxicity dose reduction	For grade 3 or greater toxicity, reduce to 50 mg/m^2 on days 1 and 2 of each cycle If grade 3 or greater toxicity recurs, reduce to 25 mg/m^2 on days 1 and 2 of each cycle Dose re-escalation may be considered	For grade 4 toxicity, reduce to 90 mg/m^2 on days 1 and 2 of each cycle If grade 4 toxicity recurs, reduce to 60 mg/m^2 on days 1 and 2 of each cycle
Nonhematologic toxicity dose reduction	For clinically significant grade 3 or higher toxicity, reduce to 50 mg/m^2 on days 1 and 2 of each cycle Dose re-escalation may be considered	For grade 3 or greater toxicity, reduce to 90 mg/m^2 on days 1 and 2 of each cycle If grade 3 or greater toxicity recurs, reduce to 60 mg/m^2 on days 1 and 2 of each cycle

Note: Based on information from Treanda (bendamustine) prescribing information (Cephalon Oncology, 2009).

titioner plays a critical role in educating not only patients but also oncology nurses about the side effects and administration of this unique agent (Table 5).

Conclusion

Bendamustine is a novel, newly available agent for patients with indolent lymphoid malignancies. It has been shown to be superior to chlorambucil in CLL, an active single agent in relapsed indolent B-cell lymphomas, and, in a recent randomized phase III trial that combined this agent with rituximab, superior to R-CHOP (rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) in relapsed indolent B-cell and mantle cell lymphomas (Rummel et al, 2009). Bendamustine may be the most exciting new agent for these patient populations since rituximab became widely available in the late 1990s. Many studies are currently under way and more are in the pipeline exploring bendamustine in various solid and hematologic malignancies and in combination with both standard therapies and novel investigational agents. Advanced practitioners should be aware of bendamustine and its significant potential to further improve outcomes in patients with indolent B-cell malignancies.

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