Optimal Use of Bendamustine in Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphomas, and Multiple Myeloma: Treatment Recommendations From an International Consensus Panel

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Abstract

Bendamustine is a novel bifunctional alkylating agent with promising activity in lymphoid malignancies and several solid tumors. Unfortunately, the early development of this agent did not provide sufficient information on which to determine an optimal systematic dose and schedule. As a result, administration of the agent has been inconsistent among studies. The use of this drug has been increasing since it has been approved by the US Food and Drug Administration for chronic lymphocytic leukemia and rituximab-refractory indolent B-cell non-Hodgkin lymphoma, and is expected to increase further following anticipated European regulatory approval. Thus, a consensus meeting was convened to develop recommendations for standardizing the administration of the drug based on the available clinical data. Recommendations were developed including dose and schedule for the various clinical indications, as a single agent and in combination therapy, and to provide guidance for supportive measures. This report, representing the conclusions of that meeting, should provide guidance for the clinician until definitive dose-finding studies have been conducted.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, No. 1, 21-27, 2010; DOI: 10.3816/CLML.2010.n.002
Keywords: Alkylating agent, Non-Hodgkin's lymphoma, Phase I trial, Refractory, Relapsed, Rituximab

Introduction

For over 40 years, bendamustine was used in the former German Democratic Republic as monotherapy in the treatment of non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), multiple myeloma (MM), Hodgkin lymphoma (HL), breast cancer, and small-cell lung cancer. Following the German reunification, further studies with bendamustine resulted in its regulatory approval for the treatment of patients with indolent NHL, CLL, and MM, as well as breast cancer and HL. Based on preliminary encouraging data, other study groups initiated additional trials of bendamustine to confirm its efficacy. Randomized data demonstrating the superiority of bendamustine over chlorambucil in CLL led to its Food and Drug Administration (FDA) approval for that indication.[1] Recent US studies confirmed single-agent activity for bendamustine in follicular, low-grade, and transformed NHL,[2,3] leading to its FDA approval in rituximab-refractory indolent B-cell NHL.[4]

Despite the increasing number of studies demonstrating efficacy for this agent, many questions remain unanswered. The mechanism of action is just becoming understood.[5] The optimal dose and schedule, and the appropriate use of supportive measures have varied widely among studies, with no guidance as to its proper administration. Throughout its development, bendamustine has been administered in a variety of doses and schedules that have been primarily

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Submitted: Jul 17, 2009; Revised: Sep 15, 2009; Accepted: Oct 18, 2009

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Table 1 Published Single-Agent Bendamustine Doses and Schedules

Disease	Dose, mg/m^2	Schedule	Dose/Cycle, mg/m^2
Solid Tumor			
	150[6]	Days 1, 2 every 28 days	300
	160[8]	Days 1, 8 every 28 days	320
	180[9]	Days 1, 2 every 21 days	360
	260[10]	Day 1 every 21 days	260
NHL			
	50-60[11]	Days 1-5 every 28 days	250-300
	120[2,3,13]	Days 1, 2 every 21 days	240
CLL			
	50-60[15]	Days 1-5 every 28 days	250-300
	50-60[11]	Days 1, 2 every 28 days	100-120
	70[12]	Days 1, 2 every 28 days	140
	100[1,14,16]	Days 1, 2 every 28 days	200
MM			
	50-60[11]	Days 1-5 every 21 days	250-300
	100[18]	Days 1, 2 every 28 days	200
	150[17]	Days 1, 2 every 28 days	300

Abbreviations: CLL = chronic lymphocytic leukemia; MM = multiple myeloma; NHL = non-Hodgkin lymphoma

developed empirically and with no clear drug development strategy (Table 1).[2,6-18] As bendamustine becomes more widely used, it is important for clinicians to have information on how to administer the drug with safety and effectiveness. In November 2008, an international group of investigators with extensive experience using this agent met to develop recommendations for treating patients with bendamustine. This report represents the consensus of that meeting.

Background

Pharmacokinetics

Limited pharmacokinetic data are available to direct the dose and schedule of bendamustine. Rasschaert et al administered the drug once every 3 weeks and found a t_{max} of 35 minutes with a mean elimination half-life of 49.1 min, volume of distribution of 18.31 m^{-2} and a clearance of 265 mL min^{-1} m^{-2}, with no evidence for dose dependency. The amount detected in the urine was highly variable.[9] The pharmacokinetics of bendamustine administered days 1 and 2 every 3 weeks produced virtually identical results, suggesting a lack of schedule dependency.[9] Owen et al[19] conducted a population pharmacokinetic analysis of bendamustine in patients with indolent NHL treated with 120 mg/m^2 day 1 and 2 every 3 weeks. Plasma concentrations declined in a triphasic manner, with a rapid distribution phase, an intermediate phase, and a terminal decline. They determined the intermediate $t_{1/2}$ of 40 minutes to be the most pharmacologically relevant because the initial phases accounted for 99% of the bendamustine area under the curve (AUC). C_{max} was 6 µg/mL. Accumulation was not expected, thus, single-dose pharmacokinetics reflected multidosing schedules. Of interest was that neither mild-to-moderate renal nor mild liver impairment altered pharmacokinetics.

Table 2 Single-Agent Bendamustine Phase I Trials

Recommended Dose, mg/m^2	Dose/Cycle, mg/m^2	Dose-Limiting Toxicity
Solid Tumor		
60 every week × 8[8]	240	Fatigue, dry mouth, fever
160, days 1, 2 every 3 weeks[6]	320	Thrombocytopenia
140, days 1, 8 every 4 weeks[9]	320	Fatigue, dry mouth, diarrhea, cardiac arrhythmia
260, day 1 every 3 weeks[10]	260	Fatigue, cardiac
MM		
100, days 1, 2 every 4 weeks[18]	200	Febrile neutropenia
CLL		
100, days 1, 2 every 3-4 weeks[16]	200	Bilirubinemia, diarrhea, anemia, thrombocytopenia
70, days 1, 2 every 4 weeks[12]	140	Hyperuricemia, pneumonia, leukopenia, infection, anemia, liver enzymes, thrombocytopenia

Abbreviations: CLL = chronic lymphocytic leukemia; MM = multiple myeloma; NHL = non-Hodgkin lymphoma

Phase I Studies in Solid Tumors

Schöffski et al[8] conducted a phase I trial with intravenous bendamustine in patients with solid tumors starting at 80 mg/m^2 weekly (Table 2). Two patients experienced dose-limiting toxicity at the starting dose (fever, mouth dryness, fatigue) and 60 mg/m^2 was determined to be the phase II dose. Schöffski et al[7] identified a maximum tolerated dose (MTD) of 160 mg/m^2 on days 1 and 8 of an every-4-week schedule. Rasschaert et al[10] conducted a phase I trial with an initial dose of bendamustine of 160 mg/m^2 once every 3 weeks, and escalated by increments of 20 mg/m^2. At 280 mg/m^2, grade 4 thrombocytopenia, grade 3 fatigue, and grade 2 cardiotoxicity were encountered; the latter two were considered dose-limiting. These investigators recommended 260 mg/m^2 administered every 3 weeks for subsequent trials. In another phase I study from the same investigators, the starting dose of bendamustine was 120 mg/m^2 days 1 and 2 every 3 weeks and the dose escalated by 20 mg/m^2. The MTD was 180 mg/m^2 and thrombocytopenia was dose limiting.[9]

Phase I Studies in Hematologic Malignancies

Few single-agent phase I studies have been conducted in CLL and myeloma, and none in NHL (Table 2).[12,16,18] It appears that myelosuppression appears less in patients with solid tumors versus those with myeloma, with CLL patients tolerating the lowest doses.

Dose and Schedule Considerations

Factors determining the dose and schedule of bendamustine must take into account whether the drug is being used as initial therapy or in the relapsed/refractory setting, whether it is being delivered as a single agent or in combination with other drugs (primarily rituximab, and the other drugs in those combinations) and a number of patient and disease characteristics.