Bendamustine in Indolent Non-Hodgkin's Lymphoma: A Practice Guide for Patient Management

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Disclosures of potential conflicts of interest may be found at the end of this article.

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ABSTRACT

For patients with advanced indolent non-Hodgkin's lymphoma (NHL) or elderly patients with mantle cell lymphoma (MCL), the recently reported results of the German StIL NHL-1 2003 and the international BRIGHT phase III trials showed that, as first-line treatment, the combination of bendamustine and rituximab is at least as effective as rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone or rituximab/cyclophosphamide/vincristine/prednisone, possibly with a better therapeutic index. Bendamustine is therefore increasingly used in clinical practice. Be-

cause bendamustine has been used for many years in Germany and in Switzerland, our institutions have had extensive experience with bendamustine, both as a single agent and in combination with rituximab. In this comprehensive review, we summarize the most important clinical data from phase II/III trials with bendamustine in patients with indolent NHL and MCL, both in the relapsed/refractory setting and in the first-line setting. In addition, this review provides practical advice on how to optimally manage bendamustine therapy in patients with NHL. *The Oncologist* 2013;18:954–964

Implications for Practice: Based on clinical data from randomized phase III trials, bendamustine, with or without rituximab, has been shown to be an appropriate option for first-line treatment or treatment of relapsed/refractory patients with indolent non-Hodgkin's lymphoma (NHL) or elderly patients with mantle cell lymphoma (MCL). Bendamustine treatment is associated with a better therapeutic index and offers an improved overall quality of life compared to R-CHOP or R-CVP. It is now often used as a chemotherapy backbone for combination with novel drugs including ibrutinib or idelalisib. This article provides a comprehensive summary of the clinical data along with practical advice on how to optimally manage patients with bendamustine therapy, including dose recommendations, antiemetic prophylaxis, prevention of infusion and skin reactions, as well as prophylaxis of opportunistic infections. This information might be helpful for clinicians using bendamustine in their daily practice.

INTRODUCTION

After many years of clinical research, there is still much controversy regarding optimal first-line treatment for patients with indolent, mainly follicular non-Hodgkin's lymphoma (NHL) [1]. Treatment choices are made based on disease activity, age, performance, and comorbidity status as well as on patient preferences and potential side effects of the treatment. Currently, there are several evidence-based treatment options, ranging from watchful waiting to aggressive chemoimmunotherapy [2]. This is reflected in the U.S. National Lymphocare study, which demonstrated that approximately 18% of patients with follicular lymphoma (FL) underwent watchful waiting initially, 14% were treated with rituximab monotherapy, and 52% were treated with chemotherapy plus rituximab for first-line therapy. Among the chemoimmunotherapy regimens, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) or rituximab/cyclophosphamide/vincristine/

prednisone (R-CVP) were used most often [3]. More recently, clinical data from randomized studies as well as provider surveys suggest that bendamustine plus rituximab (BR) is an appropriate option and is currently the most popular and widely used regimen in North America and Europe for first-line treatment of indolent NHL [4]. This observation is based on the recent publication of two large randomized phase III trials comparing R-CHOP (or R-CVP) with BR as part of first-line treatment in patients with indolent NHL and in elderly patients with mantle cell lymphoma (MCL) [5, 6]. These trials showed non-inferiority of BR versus R-CHOP or R-CVP, and one study reported less toxicity and an improved quality of life with BR [7].

Bendamustine is an alkylating agent with multiple unique mechanisms of action [8, 9]. It is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines

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Table 1. Bendamustine plus or minus rituximab or other agents in patients with relapsed/refractory NHL or MCL

Patient population	Studies	Phase	Country	n	ORR	CR/CRu	PFS (months)	Reference
Indolent NHL								
Fit (ECOG 0–2)	BR	II	Germany	63	90%	NR	24	Rummel et al. [24], JCO 2005
	BR	II	Canada	66	92%	55%	32	Robinson et al. [13], JCO 2008
	BR (vs. FR)	III	Germany	219	82%	39%	30	Rummel et al. [16], ASH 2010
Fit (ECOG 0–2)	B mono	II	Canada	100	75%	17%	9	Kahl et al. [12]
	B mono	II	United States	74	77%	34%	8.3	Friedberg et al. [36], JCO 2008
					61%	13%	7.7	
MCL								
Fit (ECOG 0–2)	BR	II	Germany	16	75%	50%	18	Rummel et al. [24], JCO 2005
	BR	II	Canada	12	92%	59%	19	Robinson et al. [13], JCO 2008
	BR (vs. FR)	III	Germany	43	NR	NR	18	Rummel et al. [16], ASH 2010
	BR + bortezomib	II	United States	7	71%	NR	NR	Friedberg et al. [44], Blood 2011
	R-BAC	II	Italy	20	80%	70%	24 (70%)	Visco et al. [19], JCO 2013

Abbreviations: BR, bendamustine + rituximab; CR/CRu, complete response/unconfirmed CR; ECOG, Eastern Cooperative Oncology Group; FR, fludarabine + rituximab; NHL, non-Hodgkin's lymphoma; MCL, mantle cell lymphoma; NR, not reported; ORR, overall response rate; PFS, progression-free survival; R-BAC, rituximab, bendamustine, cytarabine.

Agency (EMA) for the treatment of patients with rituximab-refractory indolent B-cell NHL [10–13]. In addition, it has recently been approved by Swissmedic for the first-line treatment of patients with FL in Switzerland [14]. Approval by the FDA and EMA for first-line treatment of patients with FL and/or other indolent NHL is currently pending. Bendamustine has been approved by the FDA for the treatment of patients with chronic lymphocytic leukemia (CLL) [10, 11], whereas in the European community, bendamustine has been approved only for those with CLL in whom first-line treatment with fludarabine combinations is not appropriate [11, 15]. Finally, bendamustine is EMA-approved for the first-line treatment of a subgroup of patients (>65 years) with multiple myeloma for whom autologous transplantation is not feasible and who have clinical signs of peripheral neuropathy at diagnosis [11].

In this comprehensive review, we summarize the most important clinical data from phase II/III trials with bendamustine in patients with indolent NHL and MCL, both in the relapsed/refractory setting and in the first-line setting. In addition, this review provides practical advice learned from our long experience with bendamustine about the optimal management of bendamustine therapy in patients with NHL.

Clinical Data: Bendamustine Therapy in Patients With Relapsed or Refractory Indolent Lymphoma or MCL

Although patients with indolent lymphoma usually respond very well to first-line treatment, most eventually experience relapse, and the disease remains largely incurable. Several studies have investigated bendamustine in the relapsed/refractory setting, either as a single agent or in combination with rituximab (Table 1). Response rates of 61% in patients with re-

fractory disease and approximately 75% in those with relapse were reported with single-agent bendamustine, with median progression-free survival (PFS) of 7.7 to 9 months. In combination with rituximab, the overall response rate (ORR) was between 82% and 92% with a median PFS of 23 to 30 months (Table 1). Most of these studies, however, were nonrandomized, uncontrolled phase II trials with fewer than 100 patients enrolled. Currently, only one phase III study comparing BR with fludarabine/rituximab (FR) in patients with indolent NHL and MCL has been presented at an American Society of Hematology meeting [16]. In this particular trial, which included 219 patients with relapsed disease, BR was significantly more efficacious than FR, with higher overall remission, higher complete response/unconfirmed CR (CR/CRu) rates, and higher rates of PFS. In all of these trials, the most important side effects of single-agent bendamustine or the BR combination were grade 3 or 4 neutropenia, neutropenic fever, and infections, which were largely manageable [5, 6, 8, 17, 18].

Of note, both patients with indolent NHL and patients with relapsed/refractory MCL responded very well to bendamustine when given in combination with rituximab or with bortezomib or cytarabine combinations (Table 1). The most promising data were obtained with BR in combination with cytarabine, as recently reported in an Italian phase II study, which reported a 70% CR rate and a 2-year PFS of 70% [19]. Neutropenia and thrombocytopenia were the most often reported toxicities in these patients, mainly resulting from cytarabine, because the dose of bendamustine was rather low, <70 mg/m² in this study [19].

Several additional phase III studies with bendamustine as a chemotherapy basis combined with other agents including

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rituximab, ofatumumab, obinutuzumab (GA101), and idelalisib are currently ongoing in patients with relapsed/refractory indolent NHL and MCL (Table 2) [20]. Finally, early phase I/II trials with BR as a basis plus novel agents such as temsirolimus, lenalidomide, ibrutinib, or idelalisib are ongoing, and some early results have recently been presented [21–23].

Clinical Data: First-Line BR for Patients With Indolent Lymphoma or MCL

The results of two large prospective, randomized phase III noninferiority trials comparing BR with R-CHOP or R-CVP in first-line treatment of patients with advanced indolent NHL or MCL have recently been reported: the German StIL NHL-1 2003 trial and the international BRIGHT trial (Table 3) [5, 6]. These two trials had similar inclusion and exclusion criteria, and patients with grade 3a FL were not included in either trial. The primary objectives and measures, however, were different. PFS was noninferior in the NHL 1–2003 trial, and in the BRIGHT study, the CR rate with BR was noninferior compared with CR for standard R-CHOP or R-CVP treatment. Based on the results of the StIL NHL 1–2003 trial, bendamustine was approved in Switzerland for first-line treatment of patients with FL. FDA and EMA approval for first-line treatment of indolent NHL is pending.

A total of 549 patients were randomly assigned in the StIL study and 447 patients underwent randomization in the BRIGHT study. The median age distributions reflected a “real-life situation,” with the median age of 64 for those in the StIL study and of 60 years for those in the BRIGHT study (Table 3). Both studies met their primary end points, with noninferior PFS rates and CR rates with BR versus R-CHOP/R-CVP.

In the StIL NHL1–2003 trial, the PFS rate in all evaluable patients was better in patients treated with BR (69.5 months) than for those treated with R-CHOP (31.2 months) [5]. This was also the case for patients with FL, MCL, and Waldenström's macroglobulinemia. Exploratory subgroup analyses of PFS revealed that all groups (patients <60 years old vs. >60 years old, groups of patients with normal vs. elevated lactate dehydrogenase levels, and those with favorable vs. unfavorable Follicular Lymphoma International Prognostic Index scores) demonstrated a benefit of BR compared with R-CHOP treatment, although results did not reach statistical significance in all subgroups. Of note, none of the subgroups analyzed has shown a detrimental effect of BR treatment compared with R-CHOP treatment. Finally, overall toxicity with BR was less pronounced compared with that of R-CHOP treatment, with no grade 3 or 4 alopecia, less neutropenia, and fewer episodes of paresthesia, stomatitis, and infection [5]. In contrast, skin toxicity/drug hypersensitivity was more

pronounced in BR-treated patients. The overall survival between those treated with BR and those who received R-CHOP was not different at a median follow-up of 45 months [5].

In the BRIGHT study, the ORR with BR was 94%, with a 31% CR rate. This was noninferior to R-CHOP/R-CVP treatment, which had an ORR of 84% and a CR rate of 25%. CR rate for those with indolent NHL, primarily those with FL, was numerically but not statistically higher for those treated with BR (27%) compared with patients treated with R-CHOP/R-CVP (23%). In contrast, for those with MCL, the CR rate was significantly higher with BR compared with R-CHOP/R-CVP (Table 3) [6]. At a follow-up of 2 years, the preliminary median PFS was not different between patients treated with BR and those treated with R-CHOP/R-CVP.

The adverse events in the BRIGHT study were somewhat different from those observed in the StIL NHL 1–2003 trial. Patients in the BRIGHT study had a higher incidence of nausea and vomiting, pyrexia, drug hypersensitivity, and rash with BR, whereas R-CHOP treatment was associated with a higher incidence of paresthesia, peripheral neuropathy, alopecia, and febrile neutropenia and mucositis [6]. The quality of life analysis revealed that in all patients, global health score and overall quality of life scores were significantly improved from baseline to final visit with BR versus R-CHOP/R-CVP [7].

When comparing the results of the StIL trial with those of the BRIGHT trial, it should be mentioned that maintenance rituximab was given to some patients in the BRIGHT trial, whereas no rituximab maintenance was given to any patient in the StIL trial. This might explain the narrow PFS curves at 2-year follow-up in the BRIGHT study. Moreover, in 86 participating centers in the BRIGHT trial, the number of patients treated per center was rather low, suggesting less broad experience with the experimental BR arm compared with long-term experience with the standard R-CHOP/R-CVP arm. Finally, antiemetic prophylaxis and best supportive care treatment between the two arms were different. Those in the R-CHOP arm received more aprepitant and granulocyte colony-stimulating factor than the BR-treated patients, which might explain some of the distinct adverse event profiles of BR compared with R-CHOP/R-CVP.

In addition to studies of bendamustine in the relapsed/refractory setting, there are several ongoing phase III trials with bendamustine in the first-line treatment of patients with indolent NHL, including a comparison of rituximab plus any chemotherapy (including bendamustine) versus a chemotherapy-free regimen with rituximab plus lenalidomide (Table 4).

Because bendamustine has been used for many years in Germany and Switzerland, our institutions have extensive experience with this drug as a single agent or in combination with rituximab. Based on this long experience, we will provide some practical suggestions about the optimal management of bendamustine therapy in patients with indolent NHL or elderly patients with MCL.

Bendamustine Dose and Treatment Schedule

The recommended dose of bendamustine varies depending on the disease entity. The doses and schedules approved by authorities, the ones used in published clinical trials, and those that we commonly use in clinical practice are summarized in Table 5.

For first-line treatment of patients with FL, other indolent NHL (e.g., small lymphocytic lymphoma, marginal zone lym-

Table 2. Phase III trials with bendamustine in patients with relapsed/refractory NHL or MCL

NCT number	Title	Recruitment	Conditions	Start date	Outcome measures	URL
NCT00139841	Safety and Efficacy of Treanda (Bendamustine HCl) in Patients With Indolent Non-Hodgkin's Lymphoma (NHL) Who Are Refractory to Rituximab	Completed	NHL	Oct 2005	<p>ORR (CR + CRu + PR) and DR of bendamustine in patients refractory to rituximab therapy</p> <p>Assess safety profile of bendamustine in patient population with NHL</p> <p>Assess PFS duration reported by Visco et al. [19], JCO 2013</p> <p>Estimate basic pharmacokinetic parameters</p> <p>Assess effects of plasma concentrations of drug</p>	http://clinicaltrials.gov/show/NCT00139841
NCT01596621	Bendamustine in the Treatment of Chinese Patients With Indolent Non-Hodgkin Lymphoma Refractory to Rituximab Treatment	Recruiting	NHL	June 2012	<p>ORR</p> <p>DR for patients who achieved PR or better</p> <p>PFS for all patients</p> <p>Pharmacokinetic parameters</p> <p>Safety parameters</p>	http://clinicaltrials.gov/show/NCT01596621
NCT01059630	A Study to Investigate the Efficacy and Safety of Bendamustine Compared With Bendamustine + RO5072759 (GA101) in Patients With Rituximab-Refractory, Indolent Non-Hodgkin's Lymphoma (GADOLIN)	Recruiting	NHL	Apr 2010	<p>PFS</p> <p>OS</p> <p>CR</p> <p>OR (CR or PR)</p> <p>Best response</p>	http://ClinicalTrials.gov/show/NCT01059630
NCT01500083	Bendamustine Hydrochloride (HCl) in Indolent Non-Hodgkin's Lymphoma That Has Progressed During or Following Treatment With a Rituximab Regimen or Previously Untreated Chronic Lymphocytic Leukemia (BENDACT)	Completed	Indolent NHL and CLL	Mar 2012	<p>Number of adverse events in patients in Canada with indolent NHL that has progressed during or following treatment with a rituximab regimen</p> <p>Number of adverse events in patients in Canada with previously untreated CLL</p>	http://ClinicalTrials.gov/show/NCT01500083
NCT01732926	A Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Indolent Non-Hodgkin Lymphomas	Recruiting	Indolent NHL	Dec 2012	<p>PFS</p> <p>Tumor control</p> <p>Overall well-being</p> <p>Safety profile</p>	http://clinicaltrials.gov/show/NCT01732926
NCT01289223	A Trial to Investigate the Efficacy of Bendamustine in Patients With Indolent Non-Hodgkin's Lymphoma (NHL) Refractory to Rituximab (ROBIN)	Recruiting	Indolent B-cell NHL	Feb 11	<p>PFS</p> <p>ORR</p>	http://ClinicalTrials.gov/show/NCT01289223
NCT01570049	Safety and Efficacy Study of Bendamustine to Treat Non-Hodgkin Lymphoma	Recruiting	NHL by clinical course	Apr 10	<p>ORR (CR + PR) of bendamustine hydrochloride in patients refractory to rituximab therapy</p> <p>Safety profile</p> <p>PFS</p> <p>OS</p>	http://ClinicalTrials.gov/show/NCT01570049
NCT01077518	Ofatumumab and Bendamustine Combination Therapy Compared With Bendamustine Monotherapy in Indolent B-cell Non-Hodgkin's Lymphoma (NHL) Unresponsive to Rituximab or a Rituximab-Containing Regimen (COMPLEMENT A+B)	Recruiting	FL	Aug 10	<p>PFS following ofatumumab and bendamustine combination therapy</p> <p>Clinical benefit, changes in patient-reported outcome measures, and pharmacokinetics following ofatumumab and bendamustine combination therapy</p> <p>ORR, OS, time to DR, and DR following ofatumumab and bendamustine combination therapy</p> <p>Safety and tolerability of ofatumumab and bendamustine combination therapy</p>	http://ClinicalTrials.gov/show/NCT01077518
NCT01232556	A Study Of Inotuzumab Ozogamicin Plus Rituximab For Relapsed/Refractory Aggressive Non-Hodgkin Lymphoma Patients Who Are Not Candidates For Intensive High-Dose Chemotherapy	Recruiting	NHL	Apr 11	<p>OS</p> <p>Safety and tolerability: incidence of adverse events by treatment arm</p> <p>Efficacy: ORR, PFS, DR</p> <p>Patient-reported health-related quality of life</p>	http://ClinicalTrials.gov/show/NCT01232556
NCT01456351	Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab (StL NHL 2–2003 study)	Completed	NHL and MCL	Sep 03	<p>EFS</p> <p>Remission rates</p>	http://ClinicalTrials.gov/show/NCT01456351

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; CRu, unconfirmed CR; DR, duration of response; EFS, event-free survival; FL, follicular lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; OR, overall response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QTCF, QT interval as corrected by the Fridericia method.

Table 3. First-line phase III studies comparing BR with R-CHOP/R-CVP in patients with indolent NHL or MCL [5, 6]

	NHL 1–2003	NHL 1–2003	BRIGHT	BRIGHT
	BR	R-CHOP	BR	R-CHOP/R-CVP
<i>N</i>	261	253	224	223
Median age, years (range)	64 (34–83)	63 (31–82)	60 (28–84)	58 (25–86)
Subentities:				
Indolent NHL	82%	81%	83%	83%
MCL	18%	19%	16%	17%
CR rate:				
All patients	40%	30%	31%	25%
Patients with indolent NHL/MCL	NR	NR	24%/48%*	23%/30%*
PFS (months)	69.5	31.2	NR	NR
OS at 5 years	80.1%	77.8%	NR	NR

*Patients treated with BR versus patients treated with R-CHOP only ($n = 82$ BR; $n = 81$ R-CHOP).

Abbreviations: BR, bendamustine/rituximab; CR, complete response; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; NR, not reported; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-CVP, rituximab/cyclophosphamide/vincristine/prednisone.

Table 4. First-line phase III studies with bendamustine

NCT number	Title	Recruitment	Conditions	Start date	Outcome measures	URL
NCT00877006	Study of Bendamustine Hydrochloride and Rituximab (BR) Compared With R-CVP or R-CHOP in the First-Line Treatment of Patients With Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL) - Referred to as the BRIGHT Study	Active, not recruiting	NHL MCL	Apr 09	Compare CR rate at end of treatment with BR with CR rate after R-CVP or R-CHOP in patients with advanced indolent NHL or MCL Compare safety and tolerability of BR and R-CVP, or R-CHOP ORR (CR + PR) PFS Quality of life, as determined by the EORTC QLQ-C30 Median DR	http://ClinicalTrials.gov/show/NCT00877006
NCT01073163	Study to Assess the Effect of Treatment With Bendamustine in Combination With Rituximab on QT Interval in Patients With Advanced Indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL)	Completed	NHL MCL	Feb 10	Assess the QTCF at the end of the cycle 1 bendamustine infusion QTCF at the 1-hour postinfusion time point (Cmax) CR rate ORR Safety and tolerability of BR administration	http://ClinicalTrials.gov/show/NCT01073163
NCT01724021	A Study of Patient Preference With Subcutaneous Versus Intravenous MabThera/Rituxan (Rituximab) in Patients With CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2 or 3a (PrefMab study)	Recruiting	B-cell lymphoma NHL	Dec 2012	Proportion of patients indicating an overall preference via PPQ for either SC or IV administration of rituxan Safety: Incidence of adverse events Administration time SC vs. IV Patient-assessed satisfaction of SC vs. IV administration using the CTSQ/RASQ CR rate including CRu 4–8 weeks after last dose of induction treatment EFS, DFS, PFS, OS Immunogenicity: Anti-rituximab and anti-human rHuPH20 antibodies, associated rituximab concentration level	http://ClinicalTrials.gov/show/NCT01724021

(continued)

Table 4. (Continued)

NCT number	Title	Recruitment	Conditions	Start date	Outcome measures	URL
NCT00877214	Significance of Duration of Maintenance Therapy With Rituximab in Non-Hodgkin Lymphomas (MAINTAIN) (NHL 7-2008)	Recruiting	FL Immunocytomas Marginal zone lymphomas MCL NHL	Apr 09	PFS Remission rate and DR EFS, PFS, DFS, OS	http://ClinicalTrials.gov/show/NCT00877214
NCT01332968	A Study of Obinutuzumab (RO5072759) Plus Chemotherapy in Comparison With MabThera/Rituxan (Rituximab) Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin's Lymphoma (GALLIUM)	Recruiting	NHL	Jul 11	PFS in patients with FL by investigator assessment according to the Revised Response Criteria for Malignant Lymphoma PFS in the overall study population assessed by investigators PFS as assessed by independent review committee OR, CR assessed by investigator OR, CR assessed by independent review OS, EFS, DFS, DR, time to next antilymphoma treatment Safety: Incidence of adverse events Patient-reported outcomes (assessed by Functional Assessment of Cancer Therapy for Lymphoma scale and EuroQol EQ-5D questionnaire) Medical resource utilization (hospitalizations, subsequent drug therapies, medical and surgical procedures)	http://ClinicalTrials.gov/show/NCT01332968
NCT01650701	A Phase 3 Open Label Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed by Rituximab in Subjects With Previously Untreated Follicular Lymphoma (RELEVANCE study)	Recruiting	Follicular Lymphoma Rituximab - Lenalidomide Rituximab - CHOP Rituximab - CVP Rituximab - Bendamustine	Jul 12	Primary Outcome Measures: CR/CRu rate at 120 weeks, PFS Secondary Outcome Measures: Adverse events, TTF, EFS, Time to next anti-lymphoma treatment (TTNLT), Time to next chemotherapy treatment, OS Health-related quality of life	http://ClinicalTrials.gov/show/NCT01650701

Abbreviations: BR, bendamustine/rituximab; CR, complete response; CRu, unconfirmed CR; CTSQ, Cancer Therapy Satisfaction Questionnaire; DFS, disease-free survival; DR, duration of response; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FL, follicular lymphoma; IV, intravenous; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PPQ, Patient Preference Questionnaire; PR, partial response; QLQ-C30, 30-item Core Quality of Life Questionnaire; QTCF, QT interval as corrected by the Fridericia method; RASQ, Rituximab Administration Satisfaction Questionnaire; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; R-CVP, rituximab/cyclophosphamide/vincristine/prednisone SC, subcutaneous.

phoma, Waldenström's macroglobulinemia), or patients with MCL (each in combination with rituximab), bendamustine is recommended at a dose of 90 mg/m² given on days 1 and 2 of a 28-day cycle for six cycles combined with rituximab. This regimen is based on the findings of a previous phase II study in patients with relapsed indolent NHL [24]. When this regimen was used as first-line therapy, approximately 30% of patients required treatment delays and approximately 20% required dose reductions in subsequent cycles because of prolonged hematological toxicities. In such cases, reducing the dose of bendamustine to 70 mg/m² on days 1 and 2 is recommended. It should be mentioned, however, that dose delays or dose reductions were much less common in the StiL NHL-1 2003 study, in which full doses of treatment were given in 96% of all bendamustine cycles [5].

For patients with indolent NHL who are considered to be rituximab refractory, bendamustine is approved as a single agent at a dose of 120 mg/m² on days 1 and 2 every 3 weeks for a maximum of eight cycles. However, because dose delays were observed in 60% of heavily pretreated patients due to neutropenia and/or thrombocytopenia, an international advisory board recommended treating patients with rituximab-refractory lymphoma at 4-week intervals as well [25]. Despite these data and recommendations, the important toxicity of this single agent regimen, and the fact that nowadays almost all treatments with bendamustine associate rituximab, this intensive (3-week) schedule is rarely used in clinical practice, except for the indication of multiple myeloma, a disease which is not in the scope of this review. In heavily pretreated patients with indolent NHL, MCL, or CLL, individual dose reductions

Table 5. Dosing of bendamustine

Indication	Approved dosing	Dosing published in clinical trials	What we do in clinical practice
First-line treatment of indolent (follicular) NHL	FDA: Not yet approved	Combination with rituximab (375 mg/m ² , day 1); 90 mg/m ² , days 1 and 2 every 28 days [5, 6]	Combination with rituximab (375 mg/m ² , day 1); 90 mg/m ² , days 1 and 2 every 28 days
	EMA: Not yet approved	In case of bone marrow suppression or previous grade 3 or greater hematotoxicity, reduce dose to 70 mg/m ² , days 1 and 2	In case of bone marrow suppression or previous grade 3 or greater hematotoxicity, reduce dose to 70 mg/m ² , days 1 and 2
	Swissmedic: 90 mg/m ² , days 1 and 2 every 28 days in combination with rituximab (375 mg/m ² , day 1)	Administer 6 cycles	Administer 6 cycles
	In case of bone marrow suppression, reduce dose to 70 mg/m ² days 1 and 2		
Relapsed/rituximab-refractory indolent NHL	FDA and EMA:		
	Single agent: 120 mg/m ² , days 1 and 2 every 21 days up to 8 cycles	Single agent: 120 mg/m ² , days 1 and 2 every 28 days [12, 36]	Single agent: 90 mg/m ² , days 1 and 2 every 28 days
	For grade 4 hematotoxicity or grade 3 or greater non-hematotoxicity, reduce dose to 90 mg/m ² , days 1 and 2. If toxicity persists, reduce dose further to 60 mg/m ²	In patients with relapse who are not rituximab refractory:	
		Combination with rituximab (375 mg/m ² , day 1); 90 mg/m ² , days 1 and 2 every 28 days [13, 24]	In case of severe bone marrow suppression or previous grade 3 or greater hematotoxicity, reduce dose to 60–70 mg/m ² , days 1 and 2
	In case of CTC grade 3 toxicity, reduce dose by 50% and in CTC grade 4 toxicity, discontinue therapy	In case of bone marrow suppression or previous grade 3 or greater hematotoxicity, reduce dose from 120 mg/m ² to 90 mg/m ² and from 90 mg/m ² to 70 mg/m ² , days 1 and 2	
	Swissmedic: 120 mg/m ² , days 1 and 2, every 21 days	Maximum 6–8 cycles	
CLL			
	FDA: Single agent: 100 mg/m ² , days 1 and 2 every 28 days up to 6 cycles	Single agent (fludarabine-naïve patients): 100 mg/m ² , days 1 and 2 every 28 days [15]	
	For grade 3 or greater hematotoxicity or clinically significant grade 3 or greater nonhematotoxicity, reduce dose to 50 mg/m ² , days 1 and 2		
	If toxicity persists, reduce dose further to 25 mg/m ² *	First-line combination with rituximab (375 mg/m ² , day 0 for cycle 1, then 500 mg/m ² , day 1); 90 mg/m ² , days 1 and 2 every 28 days [45]	First-line combination with rituximab (375 mg/m ² , day 1 for cycle 1, then 500 mg/m ² , day 1): 90 mg/m ² , days 1 and 2 every 28 days
	EMA: Single agent: 100 mg/m ² , days 1 and 2 every 28 days	For relapsed/refractory disease in combination with rituximab (375 mg/m ² , day 0 for cycle 1, then 500 mg/m ² , day 1): 70 mg/m ² , days 1 and 2 every 28 days [46]	
	In case of CTC grade 3 toxicity, reduce dose by 50% and in CTC grade 4 toxicity, discontinue therapy	In case of bone marrow suppression or previous grade 3 or greater hematotoxicity, reduce dose from 90–100 mg/m ² to 70 mg/m ² and from 70 mg/m ² to 50 mg/m ² , days 1 and 2	For relapsed/refractory disease in combination with rituximab or in case of myelosuppression or second-line after fludarabine (375 mg/m ² , day 0 for cycle 1, then 500 mg/m ² , day 1): 70 mg/m ² , days 1 and 2 every 28 days
CLL	Swissmedic: 100 mg/m ² , days 1 and 2 every 28 days	Maximum 6 cycles	
	In case of bone marrow suppression, reduce dose to 70 mg/m ² , days 1 and 2		

Abbreviations: CLL, chronic lymphocytic leukemia; CTC, common toxicity criteria; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; NHL, non-Hodgkin's lymphoma.

might be appropriate; however, single doses below 50 mg/m² are considered subtherapeutic and are not recommended.

Dose Recommendations for Elderly Patients

Pharmacokinetic studies included patients up to 84 years of age and could not demonstrate an effect of age on the phar-

macokinetics of bendamustine [26]. Therefore, there is no evidence that dose adjustments are necessary in the elderly. Similarly, in the StiL NHL-1 2003 study, elderly patients did not require dose reductions significantly more often than younger subjects.

Dose Recommendations for Patients With Renal Insufficiency

Because bendamustine is mainly cleared by the liver, no dose adjustment is required if the creatinine clearance is >10 mL/minute; however, data in those with severe renal impairment or in patients with chronic renal failure undergoing hemodialysis are limited to the results of a pharmacokinetic study performed in patients with multiple myeloma [27]. We have anecdotal cases of patients undergoing hemodialysis at our institutions whose dose of bendamustine was not adjusted and in whom no unexpected myelotoxicity and/or nonhematological toxicities were recorded (unpublished observation). However, close monitoring of full blood counts and clinical chemistry is recommended for these patients. Because bendamustine has a mild diuretic effect, it should not be given to patients with pre-existing hypokalemia. Potassium supplementation should be considered if levels are less than <3.5 mmol/L.

To prevent tumor lysis syndrome, allopurinol therapy should be stopped because it increases the risk for and severity of bendamustine-induced skin toxicity [28]. Tumor lysis prophylaxis should therefore include maintaining adequate circulating volume and monitoring potassium and uric acid levels. In patients whose uric acid levels are elevated prior to the first treatment with bendamustine (and rituximab), we recommend adding rasburicase early in the treatment and maintaining adequate volume intake by infusing normal saline at the same time chemotherapy is administered.

Bendamustine in Patients With Liver Function Impairment

Although bendamustine is mainly cleared by the liver, no dose adjustment is necessary for patients with mild to moderate hepatic impairment (serum bilirubin 1.5 – 3.0 mg/dL), based on pharmacokinetic data. However, no data are available in patients with severe hepatic impairment; therefore, severe liver impairment and jaundice with bilirubin levels >3 mg/dL, not related to the underlying disease, remains the only clinically relevant contraindication [29].

Other Contraindications to Bendamustine Use

Relative contraindications to bendamustine therapy include prior hypersensitivity reactions to bendamustine despite steroid premedication and severe bone marrow suppression with low blood counts (absolute neutrophil count and/or platelet values $<1,500/\mu\text{L}$ or $50,000$ – $75,000/\mu\text{L}$, respectively). Prior infection resulting from neutropenia is not an absolute contraindication to bendamustine therapy but may require dose delays and/or reductions (Table 5) with or without granulocyte colony-stimulating factor support and closer monitoring of the patient.

Recommendations for Patients with Cardiac Comorbidities

There are no contraindications to bendamustine therapy and no special requirements for patients with cardiac comorbidities. During treatment with bendamustine, the concentration of potassium in the blood should be closely monitored, and supplemental potassium should be given if necessary.

Treatment of Patients With Autoimmune Hemolytic Anemia

Unlike fludarabine, bendamustine does not appear to induce or worsen pre-existing autoimmune hemolytic anemia or im-

mune thrombocytopenia and may even reverse these complications. In the randomized trial of bendamustine versus chlorambucil in patients with CLL, which did not exclude patients with positive direct antiglobulin tests, autoimmune hemolytic anemia developed in 1% of patients in both study arms [15]. Therefore, the use of bendamustine is not contraindicated for patients who have a positive direct antiglobulin test or who have active hemolysis, [25] although an anecdotal case of hemolysis resulting from bendamustine therapy has been described [30].

Antiemetic Prophylaxis

Bendamustine is moderately emetogenic, and treatment guidelines recommend antiemetic prophylaxis with a 5-HT₃ antagonist. Although in most clinical trials no additional steroid (pre)medication was systematically recommended, we usually advise giving a single dose of 8 mg dexamethasone as a short intravenous infusion (in combination with a 5-HT₃ antagonist) 30 minutes before each bendamustine infusion. In addition to improving the antiemetic effect, the steroid will prevent infusion-related and skin reactions. In very rare cases where patients have nausea and vomiting despite this combination, consider administering additional aprepitant to prevent delayed nausea.

In the recently reported phase III BRIGHT study comparing BR with R-CHOP or R-CVP [6], the authors reported a higher incidence of nausea and vomiting in the BR arm (63%/29%, respectively) compared with the R-CHOP arm (58%/13%, respectively). This finding is in contrast to the German StiL trial experience and might be related to the different standard antiemetic prophylaxis given in the StiL trial.

Prevention of Infusion Reactions, Anaphylaxis, Skin Reactions, and Phlebitis

Infusion reactions include fever, chills, itching, rash, and anaphylactoid-like reactions [31]. All of these symptoms have been associated with the administration of rituximab, a drug that is almost always administered with bendamustine. Other less frequent infusion and allergic skin reactions have been reported in bendamustine trials, including bullous exanthema, toxic epidermal necrolysis, and Stevens-Johnson syndrome. The latter two, however, have been reported only when bendamustine was administered in combination with rituximab and/or allopurinol. One possibility to prevent or reduce adverse skin reactions, drug hypersensitivity, or infusion-related symptoms is premedication with corticosteroids. Using this approach, we only rarely see any grade of nausea/vomiting, skin reactions, and/or delayed infusion-related symptoms. In Germany, the regular administration of steroids and the omission of allopurinol are common clinical practice, so that drug discontinuation is extremely rare.

If skin reactions occur despite dexamethasone prophylaxis, close monitoring of the patient is required and additional high-dose steroids and antihistamines should be given. In these patients, bendamustine may eventually need to be withheld or discontinued.

Bendamustine is classified as a vein irritant. It does not cause tissue necrosis but, nevertheless, phlebitis may occur in the case of bendamustine extravasation or if bendamustine is infused at a high concentration with a low pH. To circumvent this, larger infusion volumes (500 mL) and/or the use of an implanted port system might be appropriate.

Prophylactic Antibiotics

Generally, no prophylactic anti-infective medication is given or recommended, although cases of severe opportunistic infections, including cytomegalovirus and hepatitis B virus reactivation, were reported [32–34]. In a phase I study in patients with solid tumors, the effect of bendamustine on specific lymphocyte subsets was investigated [35]. Weekly administration of bendamustine induced moderate leukopenia and profound lymphocytopenia, with the predominant effect being B-cell cytotoxicity. NK- and T-cells were less affected. The CD4/8 ratio remained unchanged. However, monitoring of peripheral blood lymphocyte subsets by immunophenotyping was not reported in previous phase II or prospective randomized clinical phase III trials with bendamustine in hematological malignancies. In the StIL NHL-1 2003 study, CD4 helper T-cell numbers were monitored only at the discretion of the various investigators and therefore were not reported for all patients. However, because bendamustine causes grade 3 to 4 lymphocytopenia in 74% of patients, we recommend bimonthly monitoring of CD4 T-helper cells and the initiation of *Pneumocystis jirovecii* pneumonia prophylaxis for patients with counts of $<200/\mu\text{L}$. Within the ongoing StIL NHL 7–2008 trial, prospective analyses of lymphocyte subsets will be performed at all centers.

In clinical trials with single-agent bendamustine in rituximab-refractory indolent NHL [12, 36], patients with prior purine analog exposure had an increased risk for severe neutropenia, bacterial infections, and herpes zoster reactivation. There were no cases of herpes zoster reactivation in patients receiving prophylactic antiviral therapy, but reactivation did occur in 11% of those not receiving prophylactic therapy [29, 37]. Therefore, in patients with recurring infections or those receiving concurrent immunosuppressive therapy for other illnesses, additional antimicrobial prophylaxis may be worth considering [25].

Because patients with prior hepatitis B virus infection were excluded in clinical trials, there are no data available on the management of such patients. However, for patients in urgent need of bendamustine (and rituximab) treatment, hepatitis B virus prophylaxis may be appropriate, based on accepted guidelines for patients treated with rituximab.

Bendamustine With Other Medications

No in vivo interaction studies have been performed on bendamustine. A few cases of Stevens-Johnson syndrome and toxic epidermal necrolysis were reported in patients receiving bendamustine in combination with allopurinol or in combination with allopurinol and rituximab [28, 38].

The combination of bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression, with the risk for secondary lymphoma and opportunistic infections. In these patients, antibacterial or antiviral prophylaxis might be necessary.

Bendamustine metabolism involves the cytochrome P450 (CYP) 1A2 isoenzyme, and therefore, there is a potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine. Preclinical data suggest that bendamustine is unlikely to inhibit metabolism through human CYP isoenzymes CYP1A4, 2C9/10, 2D6, 2E1, or 3A4/5, or induce metabolism of substrates of cytochrome P450 enzymes [39].

Retreatment With Bendamustine

Data supporting the safety and efficacy of retreatment with bendamustine are currently limited. However, in Germany, a

large number of patients with indolent NHL, MCL, and CLL received retreatment with bendamustine, either as a single agent or in combination with rituximab. In a retrospective analysis, retreatment was considered feasible in patients with relapsed or refractory CLL or in patients with indolent NHL, resulting in high response rates and some long-lasting remissions [40]. Unfortunately, no prospective clinical trials studying retreatment with bendamustine have yet been published. An international consensus panel concluded that until additional safety data become available, only four cycles of bendamustine should be given for relapsed disease in patients previously treated with bendamustine [25].

Harvesting Peripheral Blood Stem/Progenitor Cells After Treatment With Bendamustine

The effect of bendamustine therapy on stem cell collection has not been carefully determined. However, successful autologous stem cell collection and transplantation have been performed following treatment with bendamustine in a small number of patients within the StIL NHL 1–2003 study [41] and also in some patients with MCL being treated with rituximab, bendamustine, and cytarabine [19].

CONCLUSION

In summary, as demonstrated in a number of clinical trials, bendamustine treatment is generally very well tolerated and highly effective when given as a single agent or in combination with rituximab. Dose modifications or precautions are required only in a small subgroup of patients undergoing first-line treatment, but some dose modifications may be necessary in heavily pretreated patients. Based on practical considerations, when used in combination with rituximab, we recommend administering bendamustine at the dose of 90 mg/m² on days 1 and 2 for first-line treatment of patients with NHL, MCL, and CLL, as well as for those with relapsed NHL. A dose of 70 mg/m² on days 1 and 2 is recommended in patients with myelosuppression or in patients with relapsed CLL.

Bendamustine plus rituximab has been shown to be an appropriate chemo-immunotherapy basis and this is further explored in several trials, including the NHL 7–2008 trial in indolent NHL [42]. Finally, bendamustine is currently being tested in combination with both old (cytarabine, bortezomib) and new (the BTK-inhibitor ibrutinib or the PI3K-delta inhibitor idelalisib) drugs [19, 21–23, 43], making it a very attractive and promising combination partner for the future.

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