Demographics, treatment patterns, safety, and real-world effectiveness in patients aged 70 years and over with chronic lymphocytic leukemia receiving bendamustine with or without rituximab: a retrospective study

Kathryn S. Kolibaba, James A. Sterchele, Avani D. Joshi, Michael Forsyth, Erin Alwon, Hooman Beygi and Gerard T. Kennealey

Abstract

Objectives: Bendamustine is a unique cytotoxic agent active against various human malignancies, including chronic lymphocytic leukemia (CLL). *In vitro* studies suggest that cytotoxic activity of bendamustine on CLL-derived cells is synergized by rituximab. A retrospective chart review was conducted to characterize treatment-naïve outpatients and those with relapsed disease aged 70 years and over with CLL receiving bendamustine (with or without rituximab) and to evaluate real-world patterns of care, safety, and effectiveness.

Methods: Using McKesson Specialty Care/US Oncology Network iKnowMed databases, 91 outpatients with at least two recorded visits and at least two cycles of bendamustine monotherapy or bendamustine–rituximab combination therapy were identified and included. Mean age at diagnosis and start of first therapy was 70.3 and 77.4 years respectively, and 63.7% of patients were men.

Results: Observed overall response rate was 56.3% in pooled treatment-naïve patients ($n = 9$; complete response (CR) 18.8%; partial response (PR) 37.5%; nodular partial response (nPR) 0%) and 58.7% in pooled patients with relapsed disease ($n = 44$; CR 13.3%; PR 44.0%; nPR 1.3%). Median time to progressive disease has not been reached for the 16 treatment-naïve patients (median follow up 15.1 months), and was 18.4 months for those with relapsed disease ($n = 73$). No unexpected toxicities were observed. Overall rate of blood/bone marrow toxicities (all grades) was 40.7%; grade 3/4 rates were 18.8% in treatment-naïve patients and 25.3% in those with relapsed disease. Most frequent nonhematologic adverse events were fatigue and rash.

Conclusion: In this retrospective chart review of 91 outpatients with CLL aged 70 years and over, bendamustine (with or without rituximab) was an effective therapeutic option with manageable toxicity.

Keywords: bendamustine, chart review, chemoimmunotherapy, chronic lymphocytic leukemia, retrospective, rituximab

Introduction

Chronic lymphocytic leukemia (CLL), the most common adult leukemia in Western countries [Kim *et al.* 2010; Knauf *et al.* 2009], is a progressive hematopoietic disorder characterized by the

expansion of neoplastic lymphocytes in the blood, bone marrow, spleen, and lymph nodes [Wierda *et al.* 2008]. The incidence of CLL is two times higher in men than women, and nearly 70% of patients with CLL are older than age 65 years at

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Correspondence to:

Kathryn S. Kolibaba, MD
Compass Oncology, 120 SE
136th Avenue, Vancouver,
WA 98684, USA
[kathryn.kolibaba@
usoncology.com](mailto:kathryn.kolibaba@usoncology.com)

James A. Sterchele, PharmD
Teva Branded
Pharmaceutical Products
R&D, Inc., Frazer, PA, USA

Avani D. Joshi, B Pharm, PhD
Abbott Laboratories
(formerly of McKesson
Specialty Care, The
Woodlands, TX, USA)

Michael Forsyth, RPh, MBA
US Oncology, The
Woodlands, TX, USA

Erin Alwon, MS
OptumHealth, Inc.
(formerly of McKesson
Specialty Care, The
Woodlands, TX, USA)

Hooman Beygi, PhD
Teva Branded
Pharmaceutical Products
R&D, Inc., Frazer, PA, USA

Gerard T. Kennealey, MD, MA
Formerly of Cephalon,
Inc. (now Teva Branded
Pharmaceutical Products
R&D, Inc.), Frazer, PA,
USA

the time of diagnosis [Gribben, 2010]. Notably, in 2010, CLL was estimated to account for 14,990 new cancer cases and 4390 deaths in the USA [Jemal *et al.* 2010].

Although allogeneic stem-cell transplantation has been shown to provide a durable response in select patients with CLL [Dreger *et al.* 2010; Gribben *et al.* 2005], many patients with CLL are considered poor candidates for allogeneic stem-cell transplantation due to age, comorbidities, and vulnerability to treatment-related toxicities [Hallek, 2009; Gribben *et al.* 2005]; thus, for many patients, the disease remains incurable with a highly variable clinical course [Gribben, 2010; Foon and Hallek, 2010]. Many patients remain asymptomatic for years and face a lengthy disease course [Wierda *et al.* 2008]. At present, patients with CLL are generally managed with a 'watch and wait' strategy until an indication for treatment emerges [Gribben, 2010]. Treatment is recommended for active/progressive disease, which may be indicated by constitutional symptoms attributable to CLL (e.g. fever, night sweats, severe fatigue, or involuntary weight loss) or cytopenias; massive, painful, or progressive adenopathy or splenomegaly; or rapidly progressive lymphocytosis [Cheson *et al.* 1996; Hallek *et al.* 2008].

Choice of initial therapy is based on several factors, including individual patient characteristics, prognostic markers, disease burden, and the rate of disease progression [Foon and Hallek, 2010]. In recent years, a deeper understanding of CLL and the introduction of purine analogues and anti-CD20 monoclonal antibodies as treatment options have switched the focus of management from a palliative approach to one directed at improving progression-free survival (PFS) and overall survival [Gribben, 2010; Foon and Hallek, 2010].

Bendamustine, a bifunctional derivative of mechlorethamine [Tageja and Nagi, 2010], is a unique cytotoxic agent [Cheson and Rummel, 2009] that has demonstrated activity against various human malignancies [Leoni *et al.* 2008], including CLL [Knauf *et al.* 2009], non-Hodgkin's lymphoma [Cheson *et al.* 2010], multiple myeloma [Cheson *et al.* 2010], and solid tumors [Cheson *et al.* 2010]. In 2008, the US Food and Drug Administration (FDA) approved bendamustine for the treatment of CLL [Hallek, 2009] on the basis of data from a phase III trial in treatment-naïve patients in which the overall

response rate (ORR) and PFS were significantly greater with bendamustine than chlorambucil [Knauf *et al.* 2009].

Rituximab is a chimeric monoclonal immunoglobulin G₁ κ antibody to CD20, containing murine light and heavy chain variable region sequences and human constant region sequences [Robak *et al.* 2010b]. Since receiving FDA approval in 1997, rituximab in combination with chemotherapy has become the standard of care for several B-cell malignancies [Robak *et al.* 2010b].

Recent studies in treatment-naïve patients with CLL or those with relapsed disease have shown improved efficacy with the addition of rituximab to purine analogues and cyclophosphamide [Hallek *et al.* 2010; Robak *et al.* 2010a]. *In vitro* studies suggest that the cytotoxic activity of bendamustine on CLL-derived cell lines is synergistically enhanced by the addition of rituximab [Rummel *et al.* 2002]. Furthermore, studies conducted recently by the German Chronic Lymphocytic Leukemia Study Group (GCLLSG) have reported favorable findings with the use of bendamustine combined with rituximab in both treatment-naïve patients with CLL and those with relapsed/refractory disease [Fischer *et al.* 2011, 2012].

The National Comprehensive Cancer Network (NCCN) consensus guidelines include the use of bendamustine combined with rituximab as a suggested treatment regimen in most treatment-naïve patients with CLL and those with relapsed/refractory disease [NCCN, 2012]. In patients without del(17p), the guidelines recommend bendamustine plus rituximab for the following: as first-line therapy in patients aged at least 70 years or younger patients with comorbidities; first-line therapy in patients aged under 70 years or older patients without significant comorbidities; and therapy for relapsed/refractory disease in patients with short duration of response (e.g. <2 years based on clinical judgment) who are aged under 70 years or are older without comorbidities [NCCN, 2012]. The guidelines also include the use of bendamustine, with or without rituximab, as therapy for relapsed/refractory disease in patients with short response who are aged at least 70 years without del(17p) [NCCN, 2012].

This retrospective chart review sought to characterize outpatients aged at least 70 years with CLL

receiving bendamustine (with or without rituximab) and evaluate patterns of care, safety, and real-world effectiveness outside of the controlled environment of clinical trials. The purpose was to examine whether real-world patient populations and results were consistent with results from carefully controlled clinical trials.

Methods

Overview

The current retrospective chart review was designed to provide a descriptive analysis of treatment-naïve outpatients with CLL and those with relapsed disease aged at least 70 years receiving bendamustine (with or without rituximab) and to evaluate patterns of care, safety, and real-world effectiveness outside of the controlled clinical trial environment. The protocol and related documents received US Oncology Network Institutional Review Board approval. Patient confidentiality was maintained according to US Oncology Network policies, and only US Oncology Network staff members were involved in data handling and analysis. Because of these controls and because the potential for patient risk or benefit related to this retrospective study is minimal, waiving informed consent does not adversely affect patients' rights.

Data sources

Demographic, clinical, and treatment data used in the current retrospective chart review were extracted from McKesson Specialty Care/US Oncology Network iKnowMed (iKM) record databases, which include more than 16 million patient records and are used by 900 oncologists. The iKM databases contain information on outpatients under care in the US Oncology Network, including (but not limited to) laboratory results, diagnosis, therapy administration, line of therapy, staging, comorbidities, and performance status. Vital-status data from the Social Security Administration Death Index were supplemented with iKM data to determine mortality.

Patient population and time period

The current retrospective chart review included outpatients with CLL who received bendamustine alone or in combination with rituximab during the period between 1 March 2008 and 31 May 2010, and met prespecified inclusion and exclusion criteria. The chart-review index

date was defined as the date on which the first treatment with the target drugs was initiated. Patients were followed until the end of the data stream or date of death, whichever occurred first.

Patients enrolled in a clinical trial and those being treated for another tumor type during the chart-review time period were excluded from evaluation. Patients were evaluated if they received care at a site that used the complete electronic medical record capabilities of iKM before the start of therapy, had at least two visits recorded, had received at least two cycles of bendamustine monotherapy or combination therapy with bendamustine plus rituximab, were aged at least 70 years, and met the inclusion criteria. The final patient population was divided into four groups based on previous therapy (treatment naïve or relapsed) and therapy received during the chart-review period (bendamustine monotherapy or combination therapy with bendamustine plus rituximab).

Objectives

The design of the retrospective chart review was based on five objectives. The strategy for identifying required data files included a review of each of the objectives to optimize data retrieval, and the minimum number of variables was extracted from data files to accomplish analysis goals. Only data from the chart-review time period were used in the analysis. All results were reported in the aggregate.

The first objective was to provide a descriptive analysis of the patient population with respect to demographics and clinical/treatment characteristics, with a focus on the following variables: age, sex, disease stage, performance status, median lactate dehydrogenase levels, first-line/relapsed therapy, and monotherapy/combination therapy. The Charlson comorbidity index was used to calculate weights for comorbidities, which were identified through programmatic queries of iKM databases for each patient.

The second objective was to determine response rates for all patients by subgroup, with a focus on complete response (CR), partial response (PR), nodular partial response (nPR), stable disease, and progressive disease. Chart reviews were conducted to provide detailed response rate information.

The third objective was to describe patterns of care in terms of median dose, median number of

cycles, previous treatments, relative dose intensity, dose delay, dose reduction, and proportion of patients receiving a granulocyte colony-stimulating factor (GCSF), antiemetics, and antibiotics.

The fourth objective was to determine time to progressive disease (change in line of therapy, relapse after remission, or death due to any cause was used as a proxy for PFS), relapse after remission, or death from any cause. Patients who did not die, did not have relapsed disease, did not have progressive disease during the observation period, or were lost to follow-up were censored.

The final objective was to determine the incidence of adverse events (AEs) associated with bendamustine monotherapy or combination therapy with bendamustine plus rituximab. Treatment-related AEs were reported and graded according to the Common Terminology Criteria for AEs (version 4). Chart reviews were conducted to provide detailed information on AEs.

Statistical methods

Statistical analyses were performed using Statistical Analysis Software (v. 9.1). Estimates for continuous variables (e.g. age) were reported using mean, standard deviation, and ranges, and those for categorical variables [e.g. gender and Eastern Cooperative Oncology Group (ECOG) status] were reported using frequencies and proportions. Estimates for response rate variables were provided using frequencies and proportions, and 95% confidence intervals (CIs) were reported for each of the estimates. Kaplan–Meier curves were provided for estimates of PFS in the pre-specified patient subgroups; median survival and 95% CIs were also reported.

Results

Patient demographics and characteristics

A total of 465 patients with CLL receiving bendamustine between 1 March 2008 and 31 May 2010 were screened for the retrospective chart review. Of these, 42 patients were excluded because of enrollment in a clinical trial, and 15 patients were excluded because they were being treated for another tumor type during the chart-review period. Only 91 of the remaining 408 patients met all inclusion criteria (i.e. at least two recorded visits, availability of complete electronic medical

Inclusion/exclusion criteria: 'Patients with CLL'	N
CLL patients receiving bendamustine from March 2008 through May 2010	465
Patients enrolled in clinical trials excluded (n=42)	423
Patients treated for another tumor type in the chart-review period excluded (n=15)	408
Only patients with ≥2 visits included	406
Only patients with full electronic medical records included	255
Only patients with ≥2 bendamustine cycles included	185
Only patients aged ≥70 years included	91

Figure 1. Patient inclusion and exclusion results. Eligibility screening based on prespecified inclusion and exclusion criteria. CLL, chronic lymphocytic leukemia.

records, completion of at least two cycles of bendamustine, and age ≥70 years) (Figure 1).

The median age of the 91 patients at the start of first therapy was 75.1 years (range 70.2–89.9), and the median age at diagnosis was 69.6 years (range 55.0–86.9); 63.7% of the patients were men (Table 1). Of those patients with a recorded Rai stage (60/91) and ECOG score (82/91), 40.0% and 23.3% of patients were in Rai stage I and II respectively, and almost 99% of patients had an ECOG score of 0 or 1 at initiation of first therapy. B symptoms were absent in over 75% of patients. The most common comorbidities were rheumatologic disease (n = 14), chronic pulmonary disease (n = 12), and diabetes (n = 9). Baseline laboratory values are presented in Table 2.

Treatment patterns

Sixteen of the 91 patients (17.6%) included in the chart review were treatment naïve, whereas 75 (82.4%) had relapsed disease after prior treatment. All patients received a median of three cycles of treatment, with the exception of treatment-naïve patients receiving bendamustine monotherapy, who received a median of two cycles (Table 3). Of the 16 treatment-naïve patients, 10 received three doses of bendamustine monotherapy once per cycle and 32 doses of monotherapy twice per cycle (median 97.9 mg/m² dose); and six patients received three doses of bendamustine combined with rituximab once per cycle and 25 doses of the combination therapy twice per cycle (median 76.1 mg/m² dose). Of the 75 patients with relapsed disease, 20 received seven doses of bendamustine monotherapy once per cycle and 62 doses of monotherapy twice per cycle (median 98.1 mg/m² dose), and 55 received 29 doses of the combination therapy once per cycle

Table 1. Patient demographics and baseline characteristics.

Variable	All (N = 91)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (n = 10)	Bendamustine + rituximab combination therapy (n = 6)	Bendamustine monotherapy (n = 20)	Bendamustine + rituximab combination therapy (n = 55)
Median age at diagnosis (range), years	69.6 (55.0–86.9)	72.3 (63.5–83.4)	72.9 (67.8–85.3)	68.3 (58.9–79.5)	68.89 (55.0–87.0)
Median age at beginning of first therapy (range), years	75.1 (70.2–89.9)	75.4 (71.1–83.5)	74 (70.8–85.7)	74.7 (70.5–89.2)	75.5 (70.3–89.9)
Gender, n (%)					
Women	33 (36.3)	3 (30.0)	4 (66.7)	7 (35.0)	19 (34.5)
Men	58 (63.7)	7 (70.0)	2 (33.3)	13 (65.0)	36 (65.5)
Mean BMI at treatment baseline (SD)	26.3 (4.4)	27.2 (3.3)	29.2 (5.7)	24.9 (3.7)	26.3 (4.5)
Rai stage at diagnosis, n (%)					
0	7 (7.7)	1 (10.0)	0	4 (20.0)	2 (3.6)
I	24 (26.4)	1 (10.0)	3 (50.0)	8 (40.0)	12 (21.8)
II	14 (15.4)	0	0	2 (10.0)	12 (21.8)
III	7 (7.7)	0	1 (16.7)	1 (5.0)	5 (9.1)
IV	8 (8.8)	0	0	2 (10.0)	6 (10.9)
Unknown	11 (12.1)	0	2 (33.3)	1 (5.0)	8 (14.8)
Missing	20 (22.0)	8 (80.0)	0	2 (10.0)	10 (18.5)
ECOG score at initiation of first therapy, n (%)					
0	42 (46.1)	5 (50.0)	5 (83.4)	8 (40.0)	24 (43.6)
1	39 (42.9)	3 (30.0)	0	12 (60.0)	24 (43.6)
2	1 (1.0)	0	0	0	1 (1.8)
Missing	9 (10.0)	2 (20.0)	1 (16.6)	0	6 (11.0)
B symptoms, n (%)					
Absent	70 (76.9)	8 (80.0)	5 (83.3)	16 (80.0)	41 (74.5)
Present	14 (15.4)	1 (10.0)	1 (16.7)	3 (15.0)	9 (16.4)
Missing	7 (7.7)	1 (10.0)	0	1 (5.0)	5 (9.1)
Most frequent comorbidities, n (%)					
Rheumatologic disease	14 (15.4)	1 (10.0)	1 (16.6)	3 (15.0)	9 (16.4)
Chronic pulmonary disease	12 (13.2)	1 (10.0)	0	2 (10.0)	9 (16.4)
Diabetes	9 (9.9)	1 (10.0)	1 (16.6)	4 (20.0)	3 (5.5)
Prior MI	7 (7.7)	2 (20.0)	1 (16.6)	1 (5.0)	3 (5.5)
Ulcer disease	6 (6.6)	0	0	3 (15.0)	3 (5.5)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; MI, myocardial infarction; SD, standard deviation.

and 172 doses of the combination therapy twice per cycle (median 82.0 mg/m² dose). Nearly two-thirds of patients with relapsed disease had previously received rituximab alone or in combination therapy, and more than one-third of these patients

had received combination therapy with cyclophosphamide (Figure 2).

Nearly 40% of patients experienced no cycle delay, and nearly 20% of patients experienced a

Table 2. Baseline laboratory values.

Variable	All (N = 91)	Bendamustine monotherapy (n = 10)	Bendamustine + rituximab combination therapy (n = 6)	Bendamustine monotherapy (n = 20)	Bendamustine + rituximab combination therapy (n = 55)
Hemoglobin (mg/dl)					
Mean (SD)	11.5 (1.7)	12.3 (2.2)	11.7 (1.4)	11.1 (1.5)	11.5 (1.6)
Median (range)	11.4 (7.5–16.3)	11.8 (9.8–16.3)	12.5 (9.2–13.0)	11.1 (8.3–15.2)	11.7 (7.5–14.2)
Hematocrit (%)					
Mean (SD)	34.5 (4.9)	37.3 (7.1)	34.6 (4.3)	33.3 (4.4)	34.5 (4.7)
Median (range)	34.5 (22.9–48.8)	36.4 (28.3–48.8)	35.9 (27.7–38.4)	33.2 (24.9–46.4)	35.1 (22.9–42.4)
Missing	1	0	0	0	1
Creatinine (mg/dl)					
Mean (SD)	1.2 (0.4)	1.2 (0.3)	1.2 (0.28)	1.1 (0.3)	1.2 (0.4)
Median (range)	1.1 (0.5–2.7)	1.08 (0.87–1.8)	1.1 (0.87–1.6)	1.04 (0.58–2.0)	1.1 (0.67–2.7)
Missing	1	0	1	0	0
Lactate dehydrogenase (U/liter)					
Mean (SD)	247.6 (108.9)	301.3 (146.3)	299 (126.8)	199.1 (78.9)	254.8 (107)
Median (range)	232.5 (95–636)	295 (109–577)	286 (189–435)	184 (95–354)	242.5 (110–636)
Missing	13	2	2	0	9
White blood cell count ($\times 10^3/\mu\text{l}$)					
Mean (SD)	61.8 (74.4)	144.2 (121.4)	40.2 (37.0)	63.6 (58.9)	49.3 (63.1)
Median (range)	39 (2.5–395)	98.5 (37.8–395)	26.1 (8.0–90.5)	40.6 (5.0–191)	20 (2.5–266.5)
Missing	9	1	0	4	4
Neutrophils ($\times 10^3/\mu\text{l}$)					
Mean (SD)	6.4 (10.2)	13.1 (19.8)	5.9 (3.7)	6.4 (10.7)	5.4 (7.9)
Median (range)	3.5 (0.5–62.0)	6.3 (3.8–62.0)	4.8 (3.0–13.1)	3.3 (0.9–44.1)	3.0 (0.5–44.5)
Missing	16	2	0	5	9
Lymphocytes ($\times 10^3/\mu\text{l}$)					
Mean (SD)	49.2 (59.8)	97.0 (82.2)	33.9 (30.0)	55.2 (52.4)	40.6 (57.4)
Median (range)	32.3 (0.7–276.4)	56.9 (29.3–276.5)	34.2 (3.8–66.9)	36.0 (2.8–163.4)	13.9 (0.7–206.4)
Missing	17	2	1	5	9
Platelets ($\times 10^3/\mu\text{l}$)					
Mean (SD)	139.8 (66.7)	127.3 (43.2)	163.6 (71.9)	118.3 (67.1)	146.5 (67.9)
Median (range)	126.5 (16.0–351)	134 (70.0–179.0)	143.5 (74.0–262.0)	106 (16.0–281.0)	132.5 (47.0–351.0)
Missing	7	3	0	1	3

SD, standard deviation.

maximum cycle delay of more than 15 days. During the chart-review period, 100% of patients received an antiemetic, 67% a GCSF, and 9.9% an oral or intravenous antibiotic (Table 3).

Safety

No unexpected toxicities were observed. The overall rate (all grades) of blood/bone marrow AEs was 40.7% (Table 4). Grade 3/4 blood/bone marrow AEs occurred in 18.8% and 25.3% respectively of treatment-naïve patients and those with relapsed disease. Other grade 3/4 AEs included upper respiratory infection and

abdominal pain in patients with relapsed disease, as well as rash and sepsis in both patient groups. The most commonly occurring nonhematologic AEs ($\geq 5\%$, any grade) were fatigue (33.0%), weight loss (11.0%), infection (9.9%), gastrointestinal events (8.8%), fever (8.8%), pulmonary disease (6.6%), and rash (5.5%). All were grade 0–2, except for two cases each of grade 3/4 sepsis (one in the monotherapy group and the other in the combination therapy group) and rash (both in the monotherapy group) and one case each of grade 3/4 abdominal pain and upper respiratory infection (both in the combination therapy group).

Table 3. Treatment patterns.

Variable	All (N = 91)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (n = 10)	Bendamustine + rituximab combination therapy (n = 6)	Bendamustine monotherapy (n = 20)	Bendamustine + rituximab combination therapy (n = 55)
Median dose (range), mg/m ²	89.6 (21.8–119.4)	97.9 (72.6–101.9)	76.1 (60.4–100.2)	98.1 (40.2–117.7)	82.0 (21.8–119.4)
Median number of cycles administered (range)	3 (1–11)	2 (2–6)	3 (1–7)	3 (1–11)	3 (1–8)
Median number of cycles planned (range)	6 (2–14)	6 (2–6)	6 (6–8)	6 (2–14)	6 (2–10)
Median number of previous treatments (range)	2 (0–5)	0 (0–0)	0 (0–0)	2 (1–5)	2 (0–5)
Relative dose intensity (%)					
Mean (SD)	44.0 (12.2)	47.4 (8.6)	38.6 (12.2)	40.6 (13.9)	45.1 (12.0)
Median (range)	45.0 (5.4–100.0)	45.6 (38.5–68.4)	43.1 (15–48.3)	44.4 (5.4–61.2)	46.0 (18.1–100.0)
25th–75th percentile	38.1–50.3	41.4–50.5	36.5–45.5	32.8–49.8	37.8–50.5
Relative dose intensity cut points, n (%)					
≤30%	8 (8.8)	0	1 (16.7)	3 (15.0)	4 (7.3)
31–50%	59 (64.8)	6 (60.0)	5 (83.3)	13 (65.0)	35 (63.6)
≥51%	24 (26.4)	4 (40.0)	0	4 (20.0)	16 (29.1)
Reasons for discontinuation, n (%)					
No response to treatment	3 (3.3)	0	0	1 (5.0)	2 (3.6)
Patient refused due to toxicity	1 (1.1)	0	1 (16.7)	0	0
Toxicity, medically required	10 (11.0)	2 (20.0)	0	2 (10.0)	6 (11.0)
Patient-specific reason	4 (4.4)	0	1 (16.7)	1 (5.0)	2 (3.6)
Progression/relapse	2 (2.2)	0	0	0	2 (3.6)
Treatment completed as scheduled	19 (20.9)	1 (10.0)	1 (16.7)	4 (20.0)	13 (23.6)
Other	7 (7.7)	0	0	2 (10.0)	5 (9.1)
Unknown	42 (46.1)	7 (70.0)	3 (50.0)	10 (50.0)	22 (40.0)
Patients who did not discontinue*	3 (3.3)	0	0	0	3 (5.5)
Maximum cycle delay, n patients (%)					
None	36 (39.5)	6 (60.0)	3 (50.0)	6 (30.0)	21 (38.2)
1–5 days	5 (5.5)	0	1 (16.7)	1 (5.0)	3 (5.5)
5–10 days	16 (17.6)	2 (20.0)	0	4 (20.0)	10 (18.1)
10–15 days	16 (17.6)	1 (10.0)	0	6 (30.0)	9 (16.4)
>15 days	18 (19.8)	1 (10.0)	2 (33.3)	3 (15.0)	12 (21.8)
Maximum cycle delay, n doses (%)					
1–5 days	7 (8.9)	0	1 (14.3)	1 (5.0)	5 (10.6)
5–10 days	23 (29.1)	1 (20.0)	0	8 (40.0)	14 (29.8)
10–15 days	24 (30.4)	3 (60.0)	1 (14.3)	8 (40.0)	12 (25.5)
>15 days	25 (31.6)	1 (20.0)	5 (71.4)	3 (15.0)	16 (34.1)

(Continued)

Table 3. (Continued)

Variable	All (N = 91)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (n = 10)	Bendamustine + rituximab combination therapy (n = 6)	Bendamustine monotherapy (n = 20)	Bendamustine + rituximab combination therapy (n = 55)
Total	79	5	7	20	47
Doses with no delay	545	62	47	111	325
Number of cycles with dose reduction, n patients (%)					
1	26 (47.3)	6 (85.7)	0	6 (66.7)	14 (40.0)
2	14 (25.5)	1 (14.3)	2 (50.0)	1 (11.1)	10 (28.6)
3	6 (10.9)	0	0	1 (11.1)	5 (14.3)
4	6 (10.9)	0	2 (50.0)	0	4 (11.4)
5	3 (5.4)	0	0	1 (11.1)	2 (5.7)
Total	55 (60.4)	7 (70.0)	4 (100)	9 (45.0)	35 (63.6)
Dosing					
1 per cycle	42	3	3	7	29
2 per cycle	291	32	25	62	172
3 per cycle	0	0	0	0	0
Patients receiving a granulocyte colony-stimulating factor, n (%)	61 (67.0)	2 (20.0)	4 (66.7)	12 (60.0)	43 (78.2)
Patients receiving an IV/PO antiemetic, n (%)	91 (100)	10 (100)	6 (100)	20 (100)	55 (100)
Patients receiving an IV/PO antibiotic during treatment [§] , n (%)	9 (9.9)	1 (10.0)	1 (16.7)	2 (10.0)	5 (9.1)
Patients receiving an IV/PO anti-infective for prophylaxis prior to bendamustine administration, n (%)					
Yes	13 (14.3)	0	0	3 (15.0)	10 (18.2)
No	64 (70.3)	5 (50.0)	6 (100)	17 (85.0)	36 (65.5)
Missing	14 (15.4)	5 (50.0)	0	0	9 (16.4)

IV, intravenous; PO, oral; SD, standard deviation.

*These patients did not have stop dates for their first bendamustine regimen, and had approximately 3 months of follow up.

§Patients receiving intravenous antibiotics in a hospital (out of US Oncology Network) were not captured.

Figure 2. Prior therapy in patients receiving current bendamustine monotherapy and current combination therapy with bendamustine plus rituximab.

Real-world effectiveness

Among all 91 patients, the ORR was 58.2% (95% CI 47.4–68.5), with CR, PR, and nPR rates of 14.3%, 42.9%, and 1.1% respectively. Fourteen patients (15.4%) had stable disease, and 19 (20.9%) had progressive disease. Data were missing for five patients (5.5%) (Table 5).

The observed ORR for the pooled treatment-naïve patients was 56.3% ($n = 9$; CR 18.8%; PR 37.5%; and nPR 0%); 6.3% had progressive disease. Among all treatment-naïve patients ($n = 16$), the ORR was 50.0% for those receiving bendamustine monotherapy (95% CI 18.7–81.3) and 66.7% for those receiving combination therapy with bendamustine plus rituximab (95% CI 22.3–95.6); the rate of progressive disease was 10.0% and 0% respectively (Table 5).

Table 4. Adverse events*.

Toxicity category	All (N = 91)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (n = 10)		Bendamustine + rituximab combination therapy (n = 6)	
		All grades (n)	Grade 3/4 (n)	All grades (n)	Grade 3/4 (n)
Total AEs (all grades)					
Weight loss Pulmonary	10	1 (grade 0)	0	2 (grade 0)	0
	6	0	0	0	1
	URI (1)				URI (1)§
	Dyspnea (2)				Dyspnea (2)
	Pleural effusion (1)				Pleural effusion (1)
	Worsened pulmonary function (1)				Worsened pulmonary function (1)
Cardiac	Other (1)			Other (1)	
	1	0	0	1	0
	Mild CHF			Mild CHF	
	37	5	2	13	17
Blood/bone marrow	Hematologic (1)	Thrombocytopenia (1)§	Thrombocytopenia (1)§	Thrombocytopenia (3)	Thrombocytopenia (2)
	Thrombocytopenia (4)	Cytopenia (3)	Cytopenia (1)§	Anemia (2)	Anemia (1)
	Cytopenia (13)	Anemia (1)	Hematologic (1)§	Neutropenia (4)	Neutropenia (6)
	Anemia (4)			Pancytopenia (2)	Myelosuppression (1)§
	Neutropenia (10)			Hemolysis (1)§	Hemolysis (1)§
	Pancytopenia (2)				
	Myelosuppression (1)				
	Hemolysis (2)				
	5	2	1	1	2
	Rash (5)	Rash (2)	Rash (1)§	Rash (1)§	Rash (2)
Fever (no infection)	8	2	0	1	0
Gastrointestinal	8	0	0	2	5
	Nausea/vomiting (4)			Nausea/vomiting (2)	Nausea/vomiting (1)
	Constipation (1)				Constipation (1)
	Abdominal pain (1)				Mucositis (1)
	Mucositis (1)				Diarrhea (1)

(Continued)

Table 4. (Continued)

Toxicity category	All (N = 91)	Treatment naïve				Relapsed or ≥second line			
		Bendamustine monotherapy (n = 10)				Bendamustine + rituximab combination therapy (n = 6)			
		Bendamustine monotherapy (n = 10)		Bendamustine + rituximab combination therapy (n = 6)		Bendamustine monotherapy (n = 20)		Bendamustine + rituximab combination therapy (n = 55)	
		All grades (n)	Grade 3/4 (n)	All grades (n)	Grade 3/4 (n)	All grades (n)	Grade 3/4 (n)	All grades (n)	Grade 3/4 (n)
Total AEs (all grades)									
Neurologic	Diarrhea (1)	0	0	0	0	0	0	0	0
	Blood pressure	0	0	0	0	0	0	0	0
Hypertension (4)									
	Hemorrhage	0	0	0	0	0	0	1	0
Infection	9	1	1	0	0	2	0	6	1
	Herpes zoster (2)	<i>Klebsiella</i>	<i>Klebsiella</i> sepsis (1)	Other (2)	Other (2)	Herpes zoster (2)	Cryptococcal sepsis (1)	Pneumonia (1)	Cryptococcal sepsis (1)
General	34	3	0	1	0	9	0	21	0
	Fatigue (30)	Fatigue (3)		Fatigue (1)		Fatigue (6)		Fatigue (20)	
Weakness (3)						Weakness (2)		Weakness (1)	
	Anorexia (1)					Anorexia (1)			
AE, adverse event; CHF, congestive heart failure; URI, upper respiratory infection. *Frequency is counted by type of events; each patient may have had multiple events. ‡Adverse event(s) led to dose reduction/delay or discontinuation of bendamustine.									

Table 5. Response rates.

Variable, <i>n</i> (%)	All (<i>N</i> = 91)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (<i>n</i> = 10)	Bendamustine + rituximab combination therapy (<i>n</i> = 6)	Bendamustine monotherapy (<i>n</i> = 20)	Bendamustine + rituximab combination therapy (<i>n</i> = 55)
Overall response rate* [95% CI]	53 [58.2] [47.4–68.5]	5 [50.0] [18.7–81.3]	4 [66.7] [22.3–95.6]	9 [45.0] [23.0–68.4]	35 [63.6] [49.5–76.2]
Complete response [95% CI]	13 [14.3] [7.8–23.2]	1 [10.0] [0.25–44.5]	2 [33.3] [4.3–77.7]	4 [20.0] [5.7–43.6]	6 [10.9] [4.1–22.2]
Partial response [95% CI]	39 [42.9] [32.5–53.6]	4 [40.0] [12.1–73.7]	2 [33.3] [4.3–77.7]	5 [25.0] [8.6–49.1]	28 [50.9] [37.0–64.6]
Nodular partial response	1 (1.1)	0	0	0	1 (1.8)
Stable disease	14 [15.4]	2 [20.0]	2 [33.3]	5 [25.0]	5 (9.1)
Progressive disease	19 [20.9]	1 [10.0]	0	5 [25.0]	13 [23.6]
Missing	5 (5.5)	2 [20.0]	0	1 (5.0)	2 (3.6)

CI, confidence interval.
*Overall response rate = complete response + partial response + nodular partial response.

Table 6. Time to progressive disease.

Variable	All (<i>N</i> = 89)	Treatment naïve		Relapsed or ≥second line	
		Bendamustine monotherapy (<i>n</i> = 10)	Bendamustine + rituximab combination therapy (<i>n</i> = 6)	Bendamustine monotherapy (<i>n</i> = 19)	Bendamustine + rituximab combination therapy (<i>n</i> = 54)
Time to progressive disease, months					
Median [95% CI]	19.1 (14.9–21.3)	26 (20.3–NA)	–	21.6 (19.1–24.3)	14.5 (12.9–18.8)
Mean [SE]*	19 (1.23)	20.3 (3.5)	–	22.8 (2.0)	14.8 (1.1)
Patients with event, <i>n</i>	57	4	0	16	37
Patients censored, <i>n</i>	32	6	6	3	17
Median length of follow up, months	17.8	17.7	15.1	24.5	16.8
CI, confidence interval; NA, not available; SE, standard error. *Mean and SE were provided because median time to next treatment was not reached for some strata. Mean and SE may be underestimated because the largest observation was censored, and the estimation was restricted to the largest event.					

The observed ORR for the pooled patients with relapsed disease was 58.7% (*n* = 44; CR 13.3%; PR 44.0%; and nPR 1.3%); 24.0% had progressive disease. Among all patients with relapsed disease (*n* = 75), the ORR was 45.0% for those receiving bendamustine monotherapy (95% CI 23.0–68.4) and 63.6% for those receiving combination therapy with bendamustine plus rituximab (95% CI 49.5–76.2); the rate of progressive disease was 25.0% and 23.6% respectively (Table 5).

Among 89 patients for whom data were available, median time to progressive disease was 19.1

months (95% CI 14.9–21.3), with a median length of follow up of 17.8 months (Table 6). Progression was reported in 57 patients, and 32 patients were censored.

Median time to progressive disease had not been reached for 16 treatment-naïve patients (median follow up 15.1 months). Among 73 patients with relapsed disease, median time to progression was 18.4 months (95% CI 12.9–21.6), 21.6 months (95% CI 19.1–24.3) for those receiving bendamustine monotherapy, and 14.5 months (95% CI 12.9–18.8) for those receiving combination therapy with bendamustine plus rituximab.

Figure 3. Estimates of time to progressive disease. (a) Kaplan–Meier estimates of time to progressive disease by individual patient groups. (b) Kaplan–Meier estimates of time to progressive disease by pooled treatment-naïve and relapsed patient groups.

Kaplan–Meier estimates for disease progression over time in individual and pooled groups are shown in Figure 3.

Discussion

CLL is predominantly a disease of older people, with a median age at diagnosis of 72 years [Gribben, 2010]. Given the advanced age of affected individuals, management must often be tailored to accommodate specific patient characteristics, such as physical fitness, comorbidities, and degree of tolerability for treatment [Hallek, 2009]. A comprehensive understanding of the rapidly changing CLL therapeutic landscape is therefore especially critical for the optimal management of older patients with CLL [Hallek, 2009].

Rituximab as a combination therapy has been investigated in numerous clinical trials [Hallek,

2009]. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) has been shown to improve PFS and overall survival in treatment-naïve patients with CLL [Hallek *et al.* 2010] and to prolong PFS in patients with relapsed/refractory CLL [Robak *et al.* 2010a]. In the open-label, multicenter, randomized, phase III REACH (Rituximab in the Study of Relapsed CLL) study of patients with relapsed/refractory CD20-positive CLL, PFS was 30.6 months for 276 patients who received FCR *versus* 20.6 months for 276 patients who received fludarabine and cyclophosphamide [hazard ratio (HR) 0.65; 95% CI 0.51–0.82; $p < 0.001$] [Robak *et al.* 2010a]. In a GCLLSG study of treatment-naïve patients with CD20-positive CLL, 65% of 408 patients who received FCR were free of progression at 3 years after randomization, compared with 45% of 409 patients who received fludarabine and cyclophosphamide (HR 0.56; 95% CI 0.46–0.69; $p < 0.0001$); the overall survival rate was 87% *versus* 83% respectively (HR 0.67; 95% CI 0.48–0.92; $p = 0.012$) [Hallek *et al.* 2010].

Although FCR is currently considered to be the most active first-line therapeutic regimen in CLL [Tam *et al.* 2008], the regimen is associated with considerable toxicity, which may be especially problematic in older patients with CLL who may also have numerous comorbidities [Hallek, 2009]. Indeed, data suggest that older patients with CLL have less tolerance for FCR chemoimmunotherapy and experience more infectious complications than younger patients [Badoux *et al.* 2011].

The results of the current retrospective chart review suggest that bendamustine (with or without rituximab) was an effective therapeutic strategy in CLL in 91 patients with a mean age of 77.4 years at the start of first therapy. The ORRs were 58.7% among patients with relapsed disease and 56.3% among treatment-naïve patients. Median time to progressive disease was 18.4 months for the 73 patients with relapsed disease and had not yet been reached for 16 treatment-naïve patients at a median follow up of 15.1 months.

Bendamustine monotherapy has shown clinical efficacy in several phase I/II trials in patients with advanced relapsed/refractory CLL [Kath *et al.* 2001; Aivado *et al.* 2002; Bergmann *et al.* 2005; Lissitchkov *et al.* 2006]. Additionally, bendamustine was found to be more effective than chlorambucil in a prospective, randomized, phase III trial in 319 patients with advanced

treatment-naïve CLL who had a mean age of about 63 years and a median of six treatment cycles in both arms [Knauf *et al.* 2009]. The ORR and median PFS were 68% and 21.6 months respectively for 162 patients who received bendamustine, compared with 31% and 8.3 months in 157 patients who received chlorambucil ($p < 0.0001$ for both measures) [Knauf *et al.* 2009]. Although the population in this study was too small to draw definitive conclusions, the observed ORR in treatment-naïve patients receiving bendamustine monotherapy was 50%, with a median PFS of 26 months (95% CI 20.3 to not reached).

Two multicenter phase II studies of bendamustine plus rituximab in treatment-naïve patients with CLL and those with relapsed disease were conducted by the GCLLSG [Fischer *et al.* 2011, 2012]. The first study investigated the safety and effectiveness of bendamustine (70 mg/m² on days 1 and 2) combined with rituximab (375 mg/m² on day 0 of the first cycle and 500 mg/m² on day 1 of all subsequent cycles) in 78 patients with relapsed or refractory CLL [Fischer *et al.* 2011]. The median age was 66.5 years; 37% of the study population was aged 70 years or over. The ORR in the intent-to-treat population ($n = 46$) was 59.0% (95% CI 47.3–70.0), with CR, PR, and nPR rates of 9.0%, 47.4%, and 2.6% respectively. Median PFS at 24 months was 14.7 months.

In the second GCLLSG study, 117 treatment-naïve patients with advanced CLL (median age 64 years; 26% ≥ 70 years) received bendamustine (90 mg/m² on days 1 and 2) combined with rituximab (375 mg/m² on day 0 of the first cycle and 500 mg/m² on day 1 of all subsequent cycles). The ORR, CR, and PR rates were 88.0%, 23.1%, and 64.9% respectively [Fischer *et al.* 2012]. Follow up was 36 months. Median event-free survival was 33.9 months and 106 (91%) patients were still alive at a median follow up of 27 months.

Bendamustine treatment was well tolerated in both of the GCLLSG studies [Fischer *et al.* 2011, 2012]. Given these promising results, GCLLSG has initiated a phase III trial investigating the safety and efficacy of FCR *versus* bendamustine combined with rituximab in treatment-naïve patients with CLL [Clinicaltrials.gov identifier: NCT00769522].

In this study, the median ORR among patients with relapsed disease treated with combination bendamustine and rituximab was 63.6%, and

PFS was 14.5 months, but again, the small size of the cohort precludes drawing a definitive conclusion. Of note in relation to the GCLLSG study in treatment-naïve patients [Fischer *et al.* 2012], the median ORR was 66.7% for the six treatment-naïve patients who received the combination therapy but PFS was not reached.

In the GCLLSG study, grade 3/4 hematologic toxicities ranged from 17% for anemia to 28% for thrombocytopenia in patients with relapsed disease receiving combination therapy [Fischer *et al.* 2011]. For the present chart review, the overall rate of grade 3/4 hematologic toxicities among patients with relapsed disease receiving combination therapy was 24%; cytopenia and neutropenia were the most common, occurring in less than 10% of the study cohort.

Real-world safety and tolerability studies of bendamustine with or without rituximab in patients aged 70 years and over are sparse. A recent review of 20 frail patients (median age 72 years) with aggressive B-cell non-Hodgkin's lymphoma and a median international prognostic index score of 3 showed a low incidence of grade 3/4 AEs [Horn *et al.* 2012]. In a total of 68 treatment cycles, grade 3/4 hematologic toxicities occurred in five cycles (leukopenia and anemia in two cycles each and thrombocytopenia in one), grade 3 infection occurred in two cycles, and grade 4 thromboembolism and grade 3 nausea/emesis occurred in one cycle each.

As for patients with CLL, no special findings regarding toxicities were reported for patients aged at least 70 years in the GCLLSG studies [Fischer *et al.* 2011, 2012].

Potential limitations of the current chart review are acknowledged. In addition to its retrospective nature, the chart review is limited in its ability to identify and stratify risk, as iKM databases do not capture *IgHV* mutation status, Rai stage at the time of treatment initiation, or cytogenetics. Furthermore, iKM data are collected with an intent-to-treat approach (i.e. the data are collected for clinical practice not research purposes), which may impede the standardization of collection methods and instruments, as well as the reporting practices of physicians. It should also be noted that not all community oncology practices are included in iKM datasets and that not all US Oncology Network clinics use full iKM electronic medical records. Finally, inaccurate or inadequate

codes in iKM databases could potentially have introduced bias into the results. Despite these potential limitations, it is important to note that the reported outcomes reflect a median of only three cycles of therapy.

Conclusion

Among all 91 patients analyzed in this retrospective chart review, the ORR was 58.2%, with CR, PR, and nPR rates of 14.3%, 42.9%, and 1.1% respectively. Among all 89 patients for whom data were available, median time to progressive disease was 19.1 months, and the median length of follow up was 17.8 months. No unexpected toxicities were observed, and treatment was generally well tolerated. These findings suggest that bendamustine (with or without rituximab) may be an effective therapeutic strategy with manageable toxicity in older patients with CLL.

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