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ORIGINAL PAPER

Dose reductions in patients with Waldenström macroglobulinaemia treated with ibrutinib

Shayna Sarosiek[1,2] | **Joshua N. Gustine**[1,3] | **Catherine A. Flynn**[1] | **Carly Leventoff**[1] | **Megan Little**[1] | **Timothy White**[1] | **Kirsten Meid**[1] | **Steven P. Treon**[1,2] | **Jorge J. Castillo**[1,2]

[1]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

[2]Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA

Correspondence
Shayna Sarosiek, Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, 450 Brookline Ave, Mayer 223, Boston, MA 02215, USA.
Email: shayna_sarosiek@dfci.harvard.edu

Summary

Waldenström macroglobulinaemia (WM) is characterized by the presence of a *MYD88*^{L265P} mutation. This mutation promotes growth and survival of malignant cells through Bruton tyrosine kinase (BTK) activation. Ibrutinib was the first BTK inhibitor approved for WM. Intolerance to ibrutinib frequently leads to dose reductions, though the impact of reducing ibrutinib dosing has not been systematically studied. We performed a retrospective study to determine the frequency and impact of reducing ibrutinib dosing in WM patients. With a median treatment time of 64 months, 96 (27%) of 353 WM patients required a dose reduction due to adverse events such as musculoskeletal symptoms, cardiac events, dermatologic symptoms, cytopenias, and gastrointestinal symptoms. The median time to initial dose reduction was 9.3 months (range, 0.5–74). Dose reductions were more common in those 65 years of age or older versus under 65 [hazard ratio (HR) 2.46, 95% confidence interval (CI) 1.55–3.90; $p < 0.001$], and in females versus males (HR 2.20, 95% CI 1.41–3.28, $p < 0.001$). Most patients (65%) had improvement or resolution of adverse effects after initial dose reduction. With a median follow-up of three years from dose reduction, hematologic response sustained or deepened in 79% of patients. These data suggest that dose reduction of ibrutinib is a reasonable treatment approach for patients with intolerable side effects.

KEYWORDS
BTK inhibitor, ibrutinib, Waldenström macroglobulinaemia

INTRODUCTION

Waldenström macroglobulinaemia (WM) is an indolent lymphoma characterized by the presence of an IgM paraprotein and bone marrow infiltration by lymphoplasmacytic cells.[1] The most common somatic mutation found in more than 90% of patients with WM is an amino acid substitution (L265P) in *MYD88*.[2,3] This mutation promotes growth and survival of malignant cells in WM via Toll-like receptor signalling involving Bruton tyrosine kinase (BTK) activation. Based on this aberrant signalling, BTK inhibitors have become an important treatment option for WM and other B-cell malignancies. Ibrutinib was the first FDA-approved BTK inhibitor and is used in the treatment of chronic lymphocytic leukaemia (CLL), marginal zone lymphoma, mantle cell lymphoma, and WM. Ibrutinib has shown activity in WM in multiple studies, including an initial phase 1 study designed for treatment of relapsed or refractory B-cell malignancies, in which four participants had WM and three of these patients achieved a haematologic response.[4] In this study, pharmacokinetic data demonstrated rapid absorption and elimination of ibrutinib with peak plasma concentrations of the drug achieved within one to two hours of dosing. There was no evidence of drug accumulation with repeated dosing and no data to suggest a difference in drug metabolism based on age or sex. Ibrutinib was then administered at a dose of 420 mg orally once daily in a single-arm open label pivotal study with 63 symptomatic patients with previously treated WM and showed an overall

response rate of 91% and a major response rate of 73%.[5,6] An additional trial was initiated for patients with symptomatic, treatment-naïve WM and overall response rate was 100% and major response rate was 83%.[7,8] The response activity of ibrutinib in combination with rituximab was also shown to be superior to rituximab alone in a phase 3 randomized study in WM, leading to FDA approval of ibrutinib in combination with rituximab for the treatment of symptomatic WM.[9,10]

Ibrutinib was efficacious and well-tolerated in these clinical trials though treatment-emergent adverse events were reported. The most common adverse effects included neutropenia and thrombocytopenia, in addition to bleeding and bruising, infections, atrial fibrillation and hypertension. Despite these adverse effects, most patients were able to continue therapy without dose adjustments, although in the trial for treatment-naïve disease two patients stopped therapy due to cardiac arrhythmia and drug-induced hepatitis, and two patients had dose reductions related to foot pain and rash. In the trial of patients with relapsed or refractory disease, 16% of patients required dose reductions due to toxicity, as may be expected in a heavily pretreated population.

Ibrutinib has remarkable efficacy, but dose reductions may be required due to intolerable adverse effects. However, the rate of dose reduction and the outcomes of patients after dose reduction have not been evaluated systematically in WM. We sought to determine the rate of dose reduction, as well as the effect of dose reduction on haematologic response and rate of adverse event resolution, in a large cohort of patients with WM treated with ibrutinib.

METHODS

We performed a retrospective analysis of consecutive patients seen at our centre between May 2012 and October 2020 who received ibrutinib. Of the patients with WM who were seen during this timeframe and treated with ibrutinib, pertinent clinicopathological data were collected, including age at diagnosis, age at ibrutinib initiation, sex, reasons for treatment initiation, and disease characteristics. Response to ibrutinib was assessed using modified response criteria from the 6th International Workshop for WM criteria.[11,12] A decrease of 25%–49%, 50%–89%, and ≥90% in serum IgM levels denoted minor (MR), partial (PR), and very good partial (VGPR) responses. Normalization of serum IgM level, no monoclonal IgM spike, bone marrow clearance and resolution of adenopathy and splenomegaly were required for complete response (CR). The overall response rate included MR or better, and major response rate included PR or better. Progression-free survival (PFS) was defined as the time between ibrutinib initiation and disease progression or death from any cause. Overall survival (OS) was defined as the time between ibrutinib initiation and death from any cause.

Descriptive statistics were used to present baseline patient and disease characteristics. Differences between variables were assessed using the rank sum test for continuous variables and the chi-squared for categorical variables. Variables included in the analysis included age at ibrutinib initiation (≤65 years vs >65 years), sex (male vs female), treatment status (previously untreated vs previously treated), haemoglobin level (≤115 g/L vs >115 g/L), platelet count (≤100 K/μl vs >100 K/μl), serum IgM level (≤4000 mg/dl vs >4000 mg/dl), β2-microglobulin (≤3 mg/L vs >3 mg/L), bone marrow infiltration (≥60% vs <60%), *CXCR4* mutational status (mutated vs wild-type), serum albumin (≥3.5 g/dl vs >3.5 g/dl), and International Prognostic Scoring System (IPSSWM; low vs intermediate vs high) were used to identify factors associated with dose reduction. Time to events were estimated using the Kaplan–Meier method for incomplete observations, and comparisons between survival distributions were assessed using the log-rank test. Cox proportional hazards regression models were fitted to assess variable associated with dose reductions and with PFS. The outcomes of the Cox proportional hazards regression models are reported as hazard ratio (HR) with 95% CI. *P*-values <0.05 were considered statistically significant. Calculations and graphs were obtained using STATA 17 (StataCorp, College Station, TX, USA).

RESULTS

We identified 383 patients with WM who received treatment with ibrutinib. Thirty patients were excluded from evaluation due to ibrutinib initiation above or below the FDA approved dose of 420 mg once daily (n = 27) or prolonged dose reduction due to drug–drug interactions (n = 3) (Figure 1).

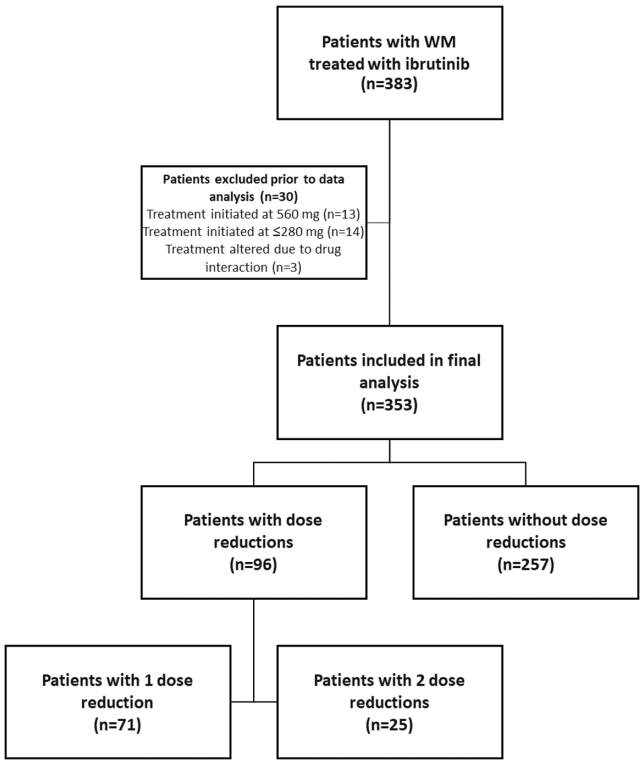

FIGURE 1 Study schematic. WM, Waldenström macroglobulinaemia.

The baseline characteristics for the 353 patients included in the analysis are shown in Table 1. Anaemia, constitutional symptoms, symptomatic hyperviscosity (or risk of hyperviscosity), extramedullary disease, and neuropathy were the most common reasons for treatment initiation. In all, 323 patients (92%) received ibrutinib as monotherapy and 30 (8%) in combination with rituximab. With a median on-treatment duration of 64 months (95% CI 56–not reached), 96 patients (27%) required dose reductions for intolerance. Of the 115 previously untreated patients, 35 (30%) required a dose reduction and 64 (26%) of the 238 previously treated patients had a dose reduction. Initial dose reduction was from 420 mg to 280 mg in all but three patients in which the dose reduction was to 140 mg (Figure 1). These included nine patients (9%) who also received rituximab, which was similar to the number of patients without dose reduction, 21/257 (8%). The most common reasons for dose reduction included musculoskeletal symptoms (n = 27, 28%) such as myalgias, arthralgias, and muscle cramps; cardiac events, such as arrhythmia, hypertension, and palpitations (n = 17, 18%); nail, skin, or hair changes (n = 16, 17%); cytopenias (n = 16, 17%); and gastrointestinal symptoms, such as diarrhoea, nausea, and reflux (n = 13, 14%) (Table 2). Of the 96 patients that required a dose reduction in ibrutinib, 25 (26%) required a second dose reduction.

TABLE 1 Patients' characteristics

	Dose reduction (n = 96)	Full dose (n = 257)	p-value
Median age at WM diagnosis, years (range)	65 (42–89)	60 (34–91)	p = 0.02
Female sex, n (%)	49 (51)	78 (30)	p < 0.001
Male sex, n (%)	47 (49)	179 (70)	
Characteristics at ibrutinib initiation[a]			
Median age, years (range)	71 (44–96)	66 (40–93)	p = 0.04
Treatment naïve at ibrutinib initiation, n (%)	35 (36)	80 (31)	p = 0.34
Age ≤ 65 years	25 (26)	117 (46)	p = 0.01
Age > 65 years	71 (74)	140 (54)	
Haemoglobin level ≤ 115 g/L	65 (74)	165 (69)	p = 0.43
Haemoglobin level > 115 g/L	23 (26)	73 (31)	
Platelet count ≤100 K/μl	11 (13)	30 (13)	p = 0.99
Platelet count >100 K/μl	74 (87)	201 (87)	
Serum IgM level ≤ 4000 mg/dl	58 (62)	150 (60)	p = 0.66
Serum IgM level > 4000 mg/dl	35 (38)	101 (40)	
β2-microglobulin level ≤3 mg/L	17 (29)	54 (35)	p = 0.41
β2-microglobulin level >3 mg/L	41 (71)	99 (65)	
Bone marrow infiltrate, ≥60%	37 (50)	91 (52)	p = 0.81
Bone marrow infiltrate, <60%	37 (50)	85 (48)	
CXCR4 mutated	20 (32)	75 (42)	p = 0.16
CXCR4 wild-type	43 (68)	103 (58)	
Albumin level <3.5 g/dl	24 (31)	61 (29)	p = 0.81
Albumin level ≥3.5 g/dl	54 (69)	147 (70)	
Low IPSSWM	11 (19)	39 (26)	p = 0.42
Intermediate IPSSWM	18 (31)	49 (33)	
High IPSSWM	29 (50)	61 (41)	

[a]Data missing for the following number of patients: haemoglobin (n = 27), platelet count (n = 37), serum IgM level (n = 9), β-2 microglobulin level (n = 142), bone marrow involvement (n = 103), serum albumin (n = 67), *CXCR4* mutational status (n = 112).

The median time to first dose reduction from initiation of ibrutinib was 9.3 months (range, 0.5–74), and the time to first dose reduction was 7.1 months and 10.5 months in those with treatment-naïve and previously treated disease respectively. The median time to second dose reduction was 21.6 months (range, 2–75). The median follow-up after dose reduction was 35 months (95% CI 30–41). The cumulative incidence rates of dose reduction at one, two, and three years were 18% (95% CI 14–23), 25% (95% CI 20–30), and 28% (95% CI 23–34) respectively (Figure 2A). The three-year dose reduction rate was higher for patients of 65 years of age or older (38%, 95% CI 31–47) than those younger than 65 years of age (14%, 95% CI 8–21; p < 0.001; Figure 2B). The three-year dose reduction rate was higher for women (38%, 95% CI 29–49) than men (23%, 95% CI 17–30; p < 0.001; Figure 2C).

Univariate Cox proportional hazards regression models are shown in Table 3. There was a higher risk of dose reduction for patients of 65 years or older than for those younger than 65 at ibrutinib initiation (HR 2.46, 95% CI 1.55–3.90; p < 0.001) and a higher risk in women than men (HR 2.20, 95% CI 1.47–3.28; p < 0.001). In a multivariate Cox regression model including age and sex, both variables were independently associated with dose reductions; the adjusted HR was 2.44 (95% CI 1.54–3.87; p < 0.001) for patients of 65 years or older when compared with patients younger than 65, and 2.19 (95% CI 1.47–3.27; p < 0.001) for women when compared with men. An additional multivariate model including age, sex and an interaction term between age and sex confirmed both variables were independently associated with dose reduction, with a HR of 3.28 (95% CI 1.62–6.63; p = 0.001) for patients of 65 years or older compared with patients younger than 65 and a HR of 3.28 (95% CI 1.47–7.32; p = 0.004) for women compared with men.

Of the 96 patients requiring a dose reduction, 63 patients (65%) had either complete resolution of all their intolerance symptoms (n = 22; 23%) or improvement in at least one of their symptoms (n = 41; 43%) that prompted the initial dose reduction. Conversely, 27 patients (28%) had no change in symptoms. Twenty-four of these patients then had a second dose reduction. Among these, six patients (25%) had improvement or resolution of symptoms after a second dose reduction to 140 mg.

Seventeen patients had a dose reduction due to cardiac symptoms, which included palpitations, arrhythmias, and hypertension. Ten of these patients had atrial fibrillation as the reason for dose reduction. Two patients had a history of previously treated atrial fibrillation and were in sinus

TABLE 2 Reasons for first ibrutinib dose reduction

	Total (*n*)	Dose reduction occurred at <12 months *n* (%)	Dose reduction occurred at ≥12 months *n* (%)	Resolved or improved after dose reduction *n* (%)[a]
Rheumatologic (myalgias, arthralgias, muscle cramping)	28	17 (61)	11 (39)	20 (71)
Cardiac (arrhythmia, hypertension, palpitations)	17	11 (65)	6 (35)	11 (65)
Nail/skin/hair changes	16	10 (63)	6 (38)	9 (56)
Cytopenias	16	12 (75)	4 (25)	9 (56)
Gastrointestinal symptoms (diarrhoea, nausea, reflux)	13	6 (46)	7 (54)	10 (77)
Bleeding/bruising	12	5 (42)	7 (58)	4 (33)
Mucosal symptoms (dry mouth, oral ulcers, lip swelling)	8	7 (88)	1 (13)	6 (75)
Infection	8	5 (63)	3 (38)	7 (88)
Fatigue	8	5 (63)	3 (38)	5 (63)
Ocular (pemphigoid, dry eyes)	2	1 (50)	1 (50)	2 (100)
Liver and renal dysfunction	2	2 (100)		2 (100)
CNS (dizziness, cognitive changes)	2	2 (100)		1 (50)
Edema	2		2 (100)	0 (0)

[a]Changes in bleeding, cytopenias, edema, rheumatologic symptoms, and skin changes in six patients were unknown after dose reduction.

rhythm at the time treatment was started. The remaining eight patients had no prior history of atrial fibrillation. Of those 10 patients, four had persistent atrial fibrillation after dose reduction, five had reduction in the frequency of the atrial fibrillation episodes, and one patient had no recurrence of the arrhythmia. Three patients had hypertension which resolved after dose reduction in two patients but was unchanged in the third patient.

Twelve patients had dose reductions related to bleeding. In most cases ($n = 6$) the bleeding was characterized as bruising, with the other cases related to gastrointestinal, intracerebral, and genitourinary bleeding. Three patients (25%) had improvement in bleeding with one dose reduction and one additional patient (8%) had improvement with a second dose reduction. The remaining eight patients (67%) had no improvement in bleeding with dose reductions.

Of the patients with gastrointestinal symptoms, eight had diarrhoea, two had abdominal discomfort/pain, three had nausea, and one had reflux. Six patients with diarrhoea (75%) had improvement with dose reduction. Abdominal discomfort/pain and reflux improved in all three patients. Nausea improved in two of three patients (67%).

We next sought to clarify the response outcome following dose reduction by evaluating changes in categorical responses. At the time of dose reduction four patients (4%) had no response, 13 (14%) had a MR, 49 (51%) had a PR, 22 (23%) had a VGPR, and one (1%) had a CR. Seven (7%) had an unknown response status. When excluding the latter, 70 patients (79%) maintained their categorical haematologic response at a stable level ($n = 58$, 65%) or showed an improved categorical response ($n = 12$, 14%) following dose reduction (Figure 3A). *CXCR4* mutations were not associated with disease progression after ibrutinib dose reduction ($p = 0.59$). Among the twelve patients who had an improvement in their haematologic response, five went from PR to VGPR, four from MR to PR, two from MR to VGPR, and one from stable disease to MR. Fourteen patients had no follow-up after dose reduction. Twelve patients (13%) had progression of disease. Of those who progressed, five patients were on 140 mg at the time of disease progression and seven patients were on 280 mg. Progression occurred at a range of one to 84 months after initial dose reduction with a median time to progression of 30 months. At the time of progression, two patients had ibrutinib dosing increased to a full dose of 420 mg; one remained stable at the full dose for nine months before disease progression, and the other remained on full dose ibrutinib for an additional 18 months until the patient transitioned to another therapy due to recurrent side effects from ibrutinib. Two additional patients with progression of disease remain on ibrutinib, as they continue to derive clinical benefit despite increases in serum IgM level.

The median follow-up for the entire cohort was 53 months (95% CI 47–57), without a difference between the patients in whom ibrutinib dose was reduced or not ($p = 0.75$). The median PFS was not yet reached, and the four-year PFS rate was 78% (95% CI 72–83; Figure 3B) respectively. Patients requiring a dose reduction had a better PFS than patients who did not with a four-year PFS rate of 85% (95% CI 74–92) versus

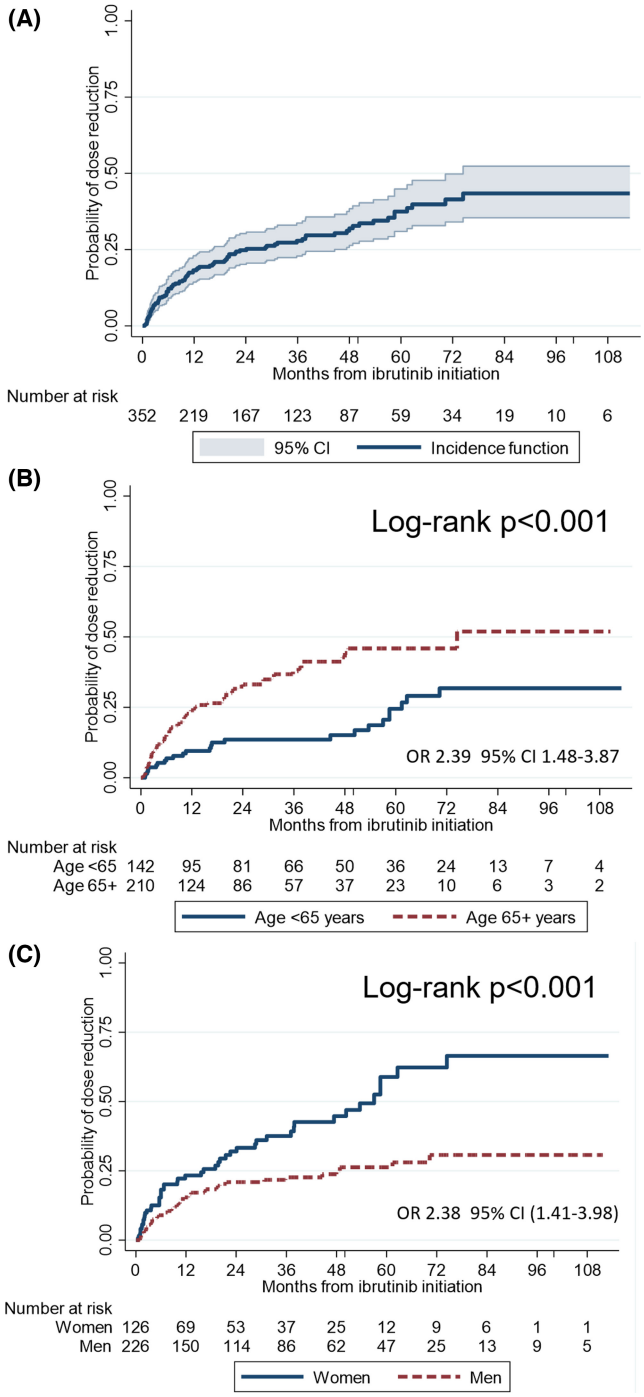

FIGURE 2 Cumulative probability of dose reduction in all patients (A), and according to age (B) and according to sex (C). CI, confidence interval; OR, overall response.

75% (95% CI 68–81; $p = 0.03$; Figure 3C). The risk of progression or death was lower in patients who required a dose reduction with a HR of 0.52 (95% CI 0.29–0.93; $p = 0.03$). After adjusting for age at ibrutinib initiation and sex, the risk of progression or death was still significantly lower in patients who required a dose reduction (HR 0.50, 95% CI 0.27–0.91; $p = 0.02$). When evaluating ibrutinib dose reduction as a time-varying covariate in a multivariate Cox proportional hazards regression model adjusting for age at ibrutinib initiation and sex, dose reduction was not associated with a better or worse PFS (HR 0.99, 95% CI 0.98–1.00; $p = 0.12$). The median OS was not yet reached, and the four-year OS rate was 88% (95% CI 83–91). There was no difference in OS between patients who required a dose reduction and the ones who did not ($p = 0.56$).

DISCUSSION

In this study, including over 350 patients with WM treated with ibrutinib, we show that 27% of patients required a dose reduction related to adverse effects. This is higher than demonstrated in the initial ibrutinib trials in WM[5,7] and CLL[13,14] but comparable to other recent publications of real-world experiences with ibrutinib in CLL, including a recent report of a 24% rate of dose reduction, and a series reporting 18% dose reductions in patients with WM treated with ibrutinib.[15,16] The potential side effects of ibrutinib are well known and include cytopenias, fatigue, atrial fibrillation, infections, bleeding, and musculoskeletal symptoms. These were among the most common reasons for dose reduction in our study and correlate well with the previously reported reasons for dose reduction in patients treated with ibrutinib for CLL and WM.

One novel finding in this study was the difference in dose reductions between men and women. We report a significant difference between the number of men and women that require dose reduction, with dose reductions in a higher proportion of women than men ($p < 0.001$), although the reason for this is not clear. Prior pharmacokinetic data with ibrutinib in CLL patients has not shown a difference in drug exposure in males compared to females.[17] It is not clear if the difference in dose reductions is related to pharmacokinetic differences between males and females in WM, or potentially related to a difference between sexes in patient reporting of symptoms or provider response to adverse effects. Additionally, a significant difference in age was seen between patients requiring dose reduction and those who were able to tolerate the full dose. Again, the reason for this difference is not well understood but could be related to comorbid conditions, pharmacokinetic changes, differences in patient symptom reporting, or variations in provider response to adverse effects based on age. This difference in age was not noted in previous reports of patients with CLL requiring a dose reduction.[18,19] Larger data sets are needed to explore these newly reported phenomena to determine if these are disease-specific or consistent throughout all populations taking ibrutinib. Furthermore, our statistical analysis suggests both older age and female sex are independently associated with higher odds of ibrutinib dose reduction in patients with WM.

We noted in this study that most patients maintained their haematologic response after ibrutinib dose reduction. Although some data report a decline in outcomes for patients with prolonged interruptions in dosing of ibrutinib,[20] there are prior studies in CLL that have noted that outcomes,

TABLE 3 UnivariateCox proportional hazardss regression models evaluating the risk of ibrutinib dose reductions in patients with Waldenström macroglobulinaemia

Variables	O/E	HR (95% CI)	*p*-value
Male sex, *n* (%)	47/65	Ref.	
Female sex, *n* (%)	49/31	2.20 (1.47–3.28)	<0.001
Age ≤ 65 years	25/44	Ref.	
Age > 65 years	71/52	2.46 (1.55–3.90)	<0.001
Haemoglobin level > 115 g/L	23/27	Ref.	
Haemoglobin level ≤ 115 g/L	65/61	1.25 (0.78–2.01)	0.35
Platelet count >100 K/μl	74/76	Ref.	
Platelet count ≤100 K/μl	11/9	1.25 (0.66–2.35)	0.50
Serum IgM level ≤ 4000 mg/dl	58/55	Ref.	
Serum IgM level > 4000 mg/dl	35/38	0.86 (0.57–1.31)	0.49
β2-microglobulin level >3 mg/L	41/38	Ref.	
β2-microglobulin level ≤3 mg/L	17/20	1.25 (0.71–2.21)	0.43
Bone marrow infiltrate, <60%	37/41	Ref.	
Bone marrow infiltrate, ≥60%	37/33	0.82 (0.52–1.29)	0.39
CXCR4 wild type	43/39	Ref.	
CXCR4 mutated	20/24	0.75 (0.44–1.28)	0.29
Albumin level ≥3.5 g/dl	24/21	Ref.	
Albumin level <3.5 g/dl	54/58	1.25 (0.77–2.04)	0.36
Low IPSSWM	11/16	Ref.	
Intermediate IPSSWM	18/20	1.31 (0.62–2.77)	0.48
High IPSSWM	29/22	1.92 (0.95–3.85)	0.07
Previously untreated	35/29	Ref.	
Previously treated	61/67	0.77 (0.50–1.17)	0.22

Abbreviations: CI, confidence interval; HR, hazard ratio; IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinemia; O/E, observed/expected.

including PS, OS and response rates were similar in patients with CLL who are treated with a reduced dose of ibrutinib or with full dose.[18,19] Our study supports this conclusion as most patients either maintained their haematologic response or had a deepening of haematologic response after dose reduction.

Although haematologic response was maintained in most patients with a dose reduction, there were many patients who did not achieve resolution or improvement in adverse effects after dose reduction. This was especially true with bleeding, which improved in less than 50% of patients and in atrial fibrillation which remained unchanged in 40% of patients and resolved in only 10%. This suggests that, in addition to considering an ibrutinib dose reduction, providers could also consider changing to a more selective BTK inhibitor, such as acalabrutinib or zanubrutinib. Two recently completed randomized trials performed in patients with CLL and WM demonstrated decreased rates of adverse effects with zanubrutinib compared with ibrutinib and lower rates of treatment discontinuation related to adverse effects.[21,22] The same was also demonstrated in a randomized trial comparing acalabrutinib and ibrutinib which showed non-inferior PFS with fewer cardiovascular side effects.[23] Additionally, recent data suggest that patients initiated on treatment with acalabrutinib or ibrutinib who develop intolerance to treatment could be switched to zanubrutinib with low risk of adverse-event recurrence.[24]

Of interest, it was noted in this study that patients necessitating dose reductions because of adverse events might have a reduced risk of progression or death. The aetiology of the improved outcomes in those patients requiring dose reduction is not well understood but may be related to altered drug metabolism resulting in higher drug concentrations, higher sensitivity to BTK inhibition, decrease in life-threatening drug-related adverse effects, or a higher proportion of *CXCR4* mutations in patients that did not have dose reductions, the latter of which may have led to a higher threshold for providers to recommend ibrutinib dose reduction due to concern about risk of disease progression. Additional studies are needed to confirm this finding and elucidate the underlying cause for this difference in outcomes.

This study is not without limitations however, as it is a retrospective design including only patients with WM treated at a single centre. Dose reductions were dependent on the practices of the individual providers and the preferences of each patient. Factors that may affect risk of adverse effects, such as patient weight, liver function, and comorbidities have not been explored in this study, although they are areas of ongoing

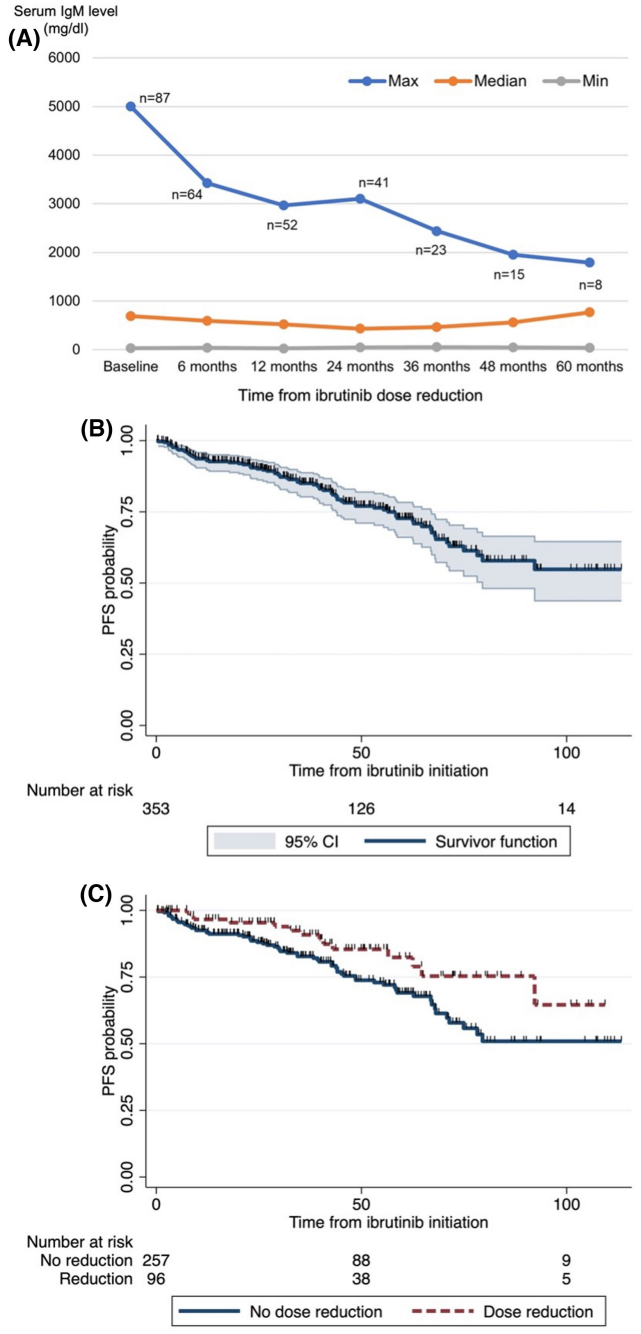

FIGURE 3 Trends in serum IgM levels after ibrutinib dose reduction (A), progression-free survival (PFS) after ibrutinib initiation (B), and progression-free survival in patients with or without a dose reduction (C). CI, confidence interval.

research. Additionally, second-generation BTK inhibitors were not available during the treatment period of this cohort, so this may have led to an underestimate of the proportion of patients in whom dose reduction or treatment change may have occurred earlier if the current repertoire of treatments were available sooner. Despite these limitations, this is the largest report of ibrutinib dose tolerance in WM to date and we believe it provides important insights on patterns of ibrutinib use.

In conclusion, approximately 25% of WM patients in this series on ibrutinib required a dose reduction due to intolerable medication side effects. More dose reductions occurred in women and in patients over 65 years old. In most patients, adverse effects improved or resolved with dose reduction. Importantly, haematologic response remained stable or improved in most patients despite dose reduction. A strategy of dose reduction should be considered for patients with adverse effects of ibrutinib, although switching to a different BTK inhibitor may be preferred in some cases. Dose reductions could also potentially be advisable with other BTK inhibitors, although additional studies that include an adequate representation of both females and older patients are needed to confirm these findings and explore utilization of newer therapies in WM.

AUTHOR CONTRIBUTIONS

Shayna Sarosiek and Jorge J. Castillo designed the study. Shayna Sarosiek, Joshua N. Gustine, Catherine A Flynn and Jorge J. Castillo collected the data. Shayna Sarosiek, Catherine A Flynn, Steven P. Treon and Jorge J. Castillo provided clinical care to patients. Joshua N. Gustine, Carly Leventoff, Megan Little, Timothy White and Kirsten Meid provided regulatory support. Shayna Sarosiek and Jorge J. Castillo performed the analysis. Shayna Sarosiek drafted the initial manuscript. All the authors reviewed, edited, and approved the final manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST

Shayna Sarosiek: Research and/or consulting funding from Acrotech Biopharma, ADC Therapeutics, and BeiGene. Steven P. Treon: Research support and/or consulting from Abbvie/Pharmacyclics, Beigene, BMS, Eli Lilly, X4 Pharmaceuticals. Intellectual property assigned to Dana-Farber Cancer Institute for *MYD88*-, *CXCR4*-related patents. Jorge J. Castillo: Research and/or consulting funding from Abbvie, AstraZeneca, Beigene, Casma Therapeutics, Cellectar, Janssen, Pharmacyclics, Roche, and TG Therapeutics.

DATA AVAILABILITY STATEMENT

Please contact the corresponding author to discuss sharing of these data.

ORCID

Shayna Sarosiek https://orcid.org/0000-0002-0075-6735
Steven P. Treon https://orcid.org/0000-0001-6393-6154
Jorge J. Castillo https://orcid.org/0000-0001-9490-7532

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