bjh research paper

Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenström macroglobulinaemia

Jorge J. Castillo, Joshua N. Gustine, Kirsten Meid, Toni E. Dubeau, Patricia Severns, Lian Xu, Guang Yang, Zachary R. Hunter and Steven P. Treon

Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Received 26 October 2017; accepted for publication 28 December 2017

Correspondence: Jorge J. Castillo, Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, Mayer 221, Boston, MA 02215, USA.
E-mail: jorgej_castillo@dfci.harvard.edu

Summary

Waldenström macroglobulinaemia (WM) is a rare and incurable lymphoma. Comparative studies evaluating the efficacy of primary therapy in symptomatic WM patients have not been performed. In this study, we compared response and survival outcomes in WM patients who received primary therapy with cyclophosphamide-dexamethasone-rituximab (CDR), bortezomib-dexamethasone-rituximab (BDR) and bendamustine-rituximab (Benda-R), as well as maintenance rituximab following primary therapy. Analyses were adjusted for relevant clinical factors associated with response and survival. Maintenance rituximab was analysed as a time-varying covariate. Our study included 182 patients, of which 57 (31%) received Benda-R, 87 (48%) BDR and 38 (21%) CDR; 116 (64%) received maintenance rituximab. The median time to best response was shorter for Benda-R and BDR than CDR (18, 20 and 30 months, respectively). Benda-R and BDR were associated with better median progression-free survival (PFS) than CDR (5·5, 5·8 and 4·8 years, respectively), and better 10-year overall survival rates (OS; 95%, 96% and 81%, respectively). Maintenance rituximab was associated with higher rates of major response (97% vs. 68%), and better median PFS (6·8 years vs. 2·8 years) and 10-year OS rate (84% vs. 66%) when compared to not receiving maintenance. Benda-R, BDR and maintenance rituximab associate with higher response rates and longer survival in WM patients than CDR and no maintenance, respectively.

Keywords: Waldenström macroglobulinaemia, bendamustine, bortezomib, rituximab, survival.

Waldenström macroglobulinaemia (WM) is characterized by the malignant accumulation of IgM-secreting lymphoplasmacytic cells in the bone marrow or other organs (Swerdlow *et al*, 2016). WM is rare and incurable with current treatment options. However, the survival of WM patients has improved, and in some cases can be measured in decades (Castillo *et al*, 2015). Therefore, the treatment of WM should be personalized, taking into account the patients' symptoms, comorbidities, preferences and genomic profile, among other factors.

Primary therapy for symptomatic WM patients often consists of combination regimens, such as cyclophosphamide, dexamethasone and rituximab (CDR), bortezomib, dexamethasone and rituximab (BDR) and bendamustine and rituximab (Benda-R). Prospective studies, however, are small and, in many cases, without a comparator, as in the case of cyclophosphamide and bortezomib-based regimens (Treon *et al*, 2009; Dimopoulos *et al*, 2013; Kastritis *et al*, 2015). The use of Benda-R is supported by a subset analysis of a randomized study that included approximately 20 WM patients per arm (Rummel *et al*, 2013). In WM patients, the use of maintenance rituximab after rituximab-containing regimens is commonly used based on prospective data from other indolent B cell lymphomas. A previous retrospective study evaluated the role of maintenance rituximab *versus* observation following induction with a rituximab-containing regimen in WM patients a univariate manner (Treon *et al*, 2011).

We therefore performed a retrospective study evaluating and comparing the characteristics, response to therapy,

 doi: 10.1111/bjh.15148

survival and factors associated with response and survival in WM patients who received primary therapy with Benda-R, BDR and CDR at our institution as well as the role of maintenance rituximab following induction with rituximab-containing regimens.

Patients and methods

We searched our database for WM patients who received primary therapy with Benda-R, BDR or CDR between January 2005 and December 2016. All patients met diagnostic criteria for WM and criteria for treatment initiation based on the recommendations made by the 2nd International Workshop for WM (IWWM) (Kyle *et al*, 2003; Owen *et al*, 2003). Pertinent clinical data were collected, including age, sex, date of WM diagnosis, time from WM diagnosis to treatment initiation, baseline laboratory data [i.e. haemoglobin, platelet count, serum beta-2-microglobulin (B2M) level, serum IgM level and bone marrow involvement], extramedullary disease, baseline International Prognostic Scoring System for WM (IPSSWM) (Morel *et al*, 2009), *MYD88* and *CXCR4* mutational status, treatment, best response and time from initiation of therapy to progression and death or last follow-up. The presence of *MYD88* and *CXCR4* mutations were determined by allele-specific polymerase chain reaction (AS-PCR) and Sanger sequencing methods, as previously described (Xu *et al*, 2013, 2016).

Benda-R was administered as bendamustine 70–90 mg/m^2 intravenously (IV) on days 1 and 2 plus rituximab 375 mg/m^2 IV on day 2 after bendamustine for 4–6 cycles, given every 28 days. BDR was administered as bortezomib 1·6 mg/m^2 IV or subcutaneously plus dexamethasone 20 mg IV or orally on days 1, 4, 8 and 11 or 1, 8, 15 and 22, every 3 and 4 weeks, respectively, plus rituximab 375 mg/m^2 IV on day 11 or 22, respectively, for four cycles. CDR was administered as cyclophosphamide 1000 mg/m^2 IV plus dexamethasone 20 mg IV plus rituximab 375 mg/m^2 IV on day 1, for six cycles. Rituximab was not administered for cycles 1 and 2 of induction therapy in patients with serum IgM level >40 g/l to minimize the risk of an IgM flare. Following induction therapy, maintenance rituximab was administered as rituximab 375 mg/m^2 IV every 2–3 months for up to 2 years. Standard pre-medications were provided prior to rituximab administration. Patients who received BDR received zoster prophylaxis.

Patients' characteristics are presented using descriptive statistics. Continuous variables were categorized to facilitate analysis, and comparisons were made using the Chi-square and Fischer exact test. Response was assessed based on criteria from the 6th IWWM (Owen *et al*, 2013). Univariate and multivariate logistic regression models were fitted to evaluate the association between clinical variables and response. The outcome of interest was odds ratio (OR) with 95% confidence interval (CI) of achieving a response. Progression-free survival (PFS) was estimated as the time from treatment initiation to progression or death from any cause. Overall survival (OS) was estimated as the time from treatment initiation to death from any cause. Time to events was estimated using the Kaplan–Meier method for incomplete observations. The Cox proportional-hazard regression method was used to fit univariate and multivariate models for PFS and OS. The outcome of interest was the hazard ratio (HR) with 95% confidence interval (CI) of progression and death from any cause (for PFS) or death from any cause (for OS). *MYD88* and *CXCR4* mutations were not included in the regression models for response, PFS and OS because these were available is less than 50% of the patients ($n = 58$). Maintenance rituximab was considered a time-varying covariate in the multivariate regression survival models. In the univariate regression analyses, prognostic factors were considered significant if P-values <0·1. Otherwise, P-values <0·05 were considered statistically significant. All calculations and graphs were obtained using STATA (StataCorp, College Station, TX, USA).

Results

Patients and therapy

One hundred and eighty-two patients with WM met the inclusion criteria, of whom 57 (31%) received frontline therapy with Benda-R, 87 (48%) received BDR and 38 (21%) received CDR. The median time from WM diagnosis to initiation of therapy for patients who received Benda-R, BDR and CDR was 9 months (95% CI 4–17 months), 6 months (95% CI 3–9 months) and 3 months (95% CI 1–12 months), respectively (log-rank $P = 0·63$). The median number of cycles of induction administered for Benda-R was 4 (range 3–6), for BDR was 4 (range 2–6) and for CDR was 6 (range 4–8). Patients treated with Benda-R and CDR were more likely to be older than 65 years, patients treated with Benda-R were more likely to have β2-microglobulin (B2M) >3 mg/l, lymphadenopathy, splenomegaly and high IPSSWM score, patients treated with BDR were more likely to have serum IgM level >40 g/l, patients treated with CDR were more likely to have low IPSSWM scores ($P < 0·05$ for all comparisons; Table I). BDR was given more frequently to patients with hyperviscosity, while Benda-R was given more frequently to patients with extramedullary disease, and CDR to patients with neuropathy ($P < 0·05$ for all comparisons). No differences in sex, hemoglobin level, platelet count, bone marrow involvement, and *MYD88* and *CXCR4* mutational status were observed between treatment groups. One hundred and sixteen patients (64%) received maintenance rituximab. The rate of maintenance therapy did not differ between treatment regimens. The median number of cycles of maintenance administered was 6 (range 1–12 cycles).

Table I. Patients' characteristics.

	Total (n = 182)	Benda-R (n = 57)	BDR (n = 87)	CDR (n = 38)	P-value
Age >65 years	87 (48%)	36 (63%)	32 (37%)	19 (50%)	0·01
Male sex	108 (59%)	35 (61%)	53 (61%)	20 (53%)	0·64
Haemoglobin ≤115 g/l	60 (33%)	23 (40%)	27 (31%)	10 (26%)	0·32
Platelet count ≤100 × 10^9/l	18 (10%)	9 (16%)	7 (8%)	2 (5%)	0·20
Serum beta-2-microglobulin >3 mg/l	98 (54%)	39 (64%)	43 (49%)	16 (42%)	0·02
Serum IgM >40 g/l	98 (54%)	21 (37%)	62 (71%)	15 (39%)	<0·001
Marrow involvement ≥50%	88 (49%)	33 (58%)	38 (45%)	17 (45%)	0·29
Lymphadenopathy	54 (30%)	25 (44%)	15 (17%)	14 (37%)	0·001
Splenomegaly	26 (14%)	18 (32%)	6 (7%)	2 (5%)	<0·001
MYD88 L265P mutation	53 (91%)	17 (89%)	23 (88%)	13 (100%)	0·60
CXCR4 mutations	28 (48%)	10 (53%)	11 (42%)	7 (54%)	0·71
IPSSWM					
Low risk	89 (49%)	20 (35%)	45 (52%)	24 (63%)	0·006
Intermediate risk	54 (30%)	17 (30%)	30 (35%)	7 (18%)	
High risk	38 (21%)	20 (35%)	11 (13%)	7 (18%)	
Indication for treatment					
Anaemia	90 (50%)	34 (60%)	41 (47%)	15 (40%)	0·16
Hyperviscosity	43 (24%)	9 (16%)	31 (36%)	3 (8%)	0·001
Constitutional symptoms	30 (17%)	7 (12%)	19 (21%)	4 (11%)	0·18
Extramedullary disease	22 (12%)	14 (25%)	3 (3%)	5 (14%)	0·001
Peripheral neuropathy	17 (9%)	6 (11%)	3 (3%)	8 (22%)	0·006
Best response to therapy					
Complete response	22 (12%)	11 (19%)	9 (11%)	2 (5%)	0·37
Very good partial response	48 (27%)	14 (26%)	20 (24%)	14 (37%)	
Partial response	84 (47%)	28 (49%)	40 (48%)	16 (42%)	
Minor response	10 (6%)	2 (4%)	6 (7%)	2 (5%)	
No response	14 (8%)	2 (4%)	8 (10%)	4 (11%)	
Received maintenance	116 (64%)	35 (61%)	55 (65%)	26 (68%)	0·79

Benda-R, bendamustine and rituximab; BDR, bortezomib, dexamethasone and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia.

Table II. Univariate and multivariate logistic regression models for major response.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age >65 years	1·67 (0·69–4·04)	0·26		
Male sex	0·67 (0·27–1·65)	0·28		
Haemoglobin ≤115 g/l	0·60 (0·25–1·44)	0·25		
Platelet count ≤100 × 10^9/l	2·67 (0·34–21·1)	0·35		
Beta-2-microglobulin >3 mg/l	0·97 (0·41–2·28)	0·93		
Serum IgM >40 g/l	0·32 (0·12–0·86)	0·02	0·28 (0·10–0·80)	0·02
Marrow involvement ≥50%	1·38 (0·58–3·30)	0·47		
Lymphadenopathy	0·67 (0·27–1·64)	0·38		
Splenomegaly	0·60 (0·36–1·78)	0·36		
Low risk IPSSWM	1·00 (Ref)			
Intermediate risk IPSSWM	0·98 (0·36–2·67)	0·97		
High risk IPSSWM	1·03 (0·34–3·15)	0·96		
CDR	1·00 (Ref)			
Benda-R	2·48 (0·65–9·48)	0·18		
BDR	0·92 (0·33–2·63)	0·88		
Maintenance rituximab	12·9 (4·17–39·9)	<0·001	13·9 (4·41–44·1)	<0·001

BDR, bortezomib, dexamethasone and rituximab; Benda-R, bendamustine and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; CI, confidence interval; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia; OR, odds ratio.

Response to therapy

Rates of complete response, very good partial response (VGPR), partial response (PR), minor response and no response to therapy for all patients were 12% (n = 22), 27% (n = 48), 47% (n = 84), 6% (n = 10) and 8% (n = 14), respectively. The rate of overall (minor response or better) and major response (PR or better) for all patients was 92% and 86%, respectively, and the rate of deep response (VGPR or better) was 39%. No difference in rates of response was observed between treatment regimens (Table I). The median times to best response for Benda-R, BDR and CDR were 18 months (95% CI 11–23 months), 20 months (95% CI 14–25 months) and 30 months (95% CI 16–48 months), respectively. Time to best response was significantly longer with CDR than with Benda-R and BDR (log-rank P = 0·003). In univariate and multivariate logistic regression analyses, patients with serum IgM level >40 g/l had lower odds of major response to therapy, whereas patients who received maintenance rituximab had higher odds of major response (Table II). The major response rate for patients who received maintenance rituximab was higher than for patients who did not (97% vs. 68%; Chi square P < 0·001). Age, sex, haemoglobin level, platelet count, serum B2M level, bone marrow involvement, lymphadenopathy, splenomegaly, IPSSWM and therapy were not associated with major response. We also performed univariate and multivariate logistic regression analyses for deep response using the same clinical variables as the analysis for major response. Maintenance rituximab was the only factor associated with higher rates of deep response (45% vs. 29%; adjusted OR 2·07, 95% CI 1·07–4·02; P = 0·03). No other factors were associated with deep response (data not shown).

Progression-free survival analysis

The median PFS for the entire group was 5·8 years (95% CI 4·9–6·8 years). For patients treated with Benda-R, BDR and CDR, the median PFS was 5·5 years (95% CI 4·9–not reached), 5·8 years (95% CI 4·4–7·4 years) and 4·9 years (95% CI 2·8–7·0 years), respectively (Fig 1A). There was a trend towards better PFS for patients who received Benda-R when compared to BDR (log-rank P = 0·10) and CDR (log-rank P = 0·10). There was no difference in PFS between BDR and CDR (log-rank P = 0·69). The median PFS for patients who did and did not receive maintenance rituximab was 6·8 years (95% CI 5·9–not reached) vs. 2·8 years (95% CI 2·1–4·1 years), respectively (Fig 1B). In the univariate analysis, serum B2M level >3 mg/l, serum IgM level >40 g/l and lymphadenopathy were associated with worse PFS, while use of Benda-R and maintenance rituximab were associated with better PFS (Table III). In the multivariate analysis, serum B2M level >3 mg/l and serum IgM level >40 g/l were associated with worse PFS, and both Benda-R and BDR were associated with a better PFS when compared to CDR. Maintenance rituximab as a time-varying covariate was associated with a better PFS (Table III). Adjusting for serum B2M level, serum IgM level and maintenance rituximab, BDR had worse PFS than Benda-R (HR 2·43, 95% CI 1·05–5·63; P = 0·04).

Overall survival analysis

The median follow-up from initiation of treatment for the entire group was 3·5 years (95% CI 3–4 years). The median follow-up times for Benda-R, BDR and CDR were 3 years (95% CI 2–3·5 years), 4 years (95% CI 3–5 years) and 5 years (95% CI 3–7 years), respectively (log-rank P < 0·001). The estimated 5- and 10-year OS rates for all patients were 92% (95% CI 84–96%) and 79% (95% CI 61–89%), respectively; the median OS has not been reached. The estimated 5-year OS rates among patients treated with Benda-R, BDR and CDR were 95% (95% CI 81–99%), 96% (95% CI 85–99%) and 81% (95% CI 60–92%), respectively

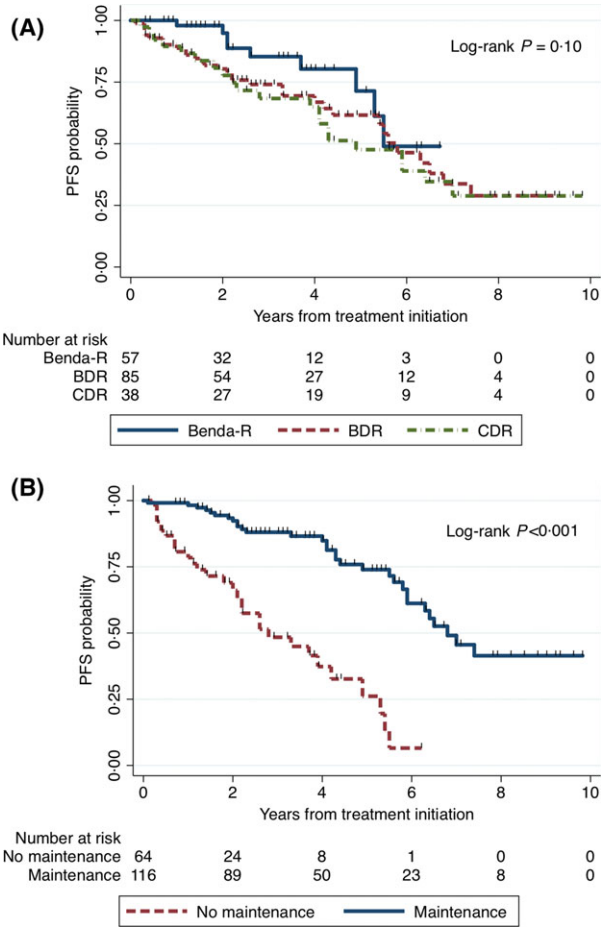

Fig 1. PFS estimates by (A) Benda-R *versus* BDR *versus* CDR, and (B) maintenance rituximab. BDR, bortezomib, dexamethasone and rituximab; Benda-R, bendamustine and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; PFS, progression-free survival. [Colour figure can be viewed at wileyonlinelibrary.com]

(Fig 2A). For patients treated with BDR and CDR, the estimated 10-year OS was 87% (95% CI 67–95%) and 61% (95% CI 26–83%), respectively, and was not evaluable for patients treated with Benda-R. The 5- and 10-year OS rates for patients who received maintenance rituximab were 95% (95% CI 86–98%) and 84% (95% CI 60–94%), respectively, and, for patients who did not receive maintenance rituximab, the corresponding rates were 84% (95% CI 63–94%) and 66% (95% CI 35–85%), respectively (Fig 2B). By univariate analysis, treatment with BDR and use of maintenance rituximab were associated with better OS (Table IV). There was no difference in risk of death between Benda-R and BDR (HR 0·58, 95% CI 0·09–3·89, $P = 0·58$). In the multivariate analysis, treatment with BDR and maintenance rituximab was independently associated with a decreased risk of death. Adjusting for maintenance, the risk of death from any cause was not different between BDR and Benda-R (HR 0·60, 95% CI 0·09–3·96, $P = 0·59$).

Exploratory analyses

Based on the dose of bendamustine administered, we divided patients in two groups: patients who received 90 mg/m^2 per dose ($n = 40$; 70%) and patients who received 60–70 mg/m^2 per dose ($n = 17$; 30%). There were no differences with regards to major response (OR 1·30, 95% CI 0·13–13·4; $P = 0·83$), deep response (OR 0·86, 0·27–2·70; $P = 0·79$), PFS (HR 3·85, 95% CI 0·61–24·4; $P = 0·15$) or OS (HR 3·74, 95% CI 0·22–63·3, $P = 0·36$) between groups. These results did not change when adjusting for maintenance therapy (data not shown).

Based on the number of cycles of bendamustine administered, we divided patients in two groups: patients who received six cycles ($n = 24$; 42%) and patients who received fewer than six cycles ($n = 33$; 58%). There were no differences with regards to major response (OR 2·30, 95% CI 0·22–23·6; $P = 0·48$), deep response (OR 1·15, 040–3·31; $P = 0·80$), PFS (HR 0·71, 95% CI 0·14–3·57; $P = 0·68$) and OS (HR 1·01, 95% CI 0·06–16·4, $P = 0·99$) between groups. These results did not change when adjusting for maintenance therapy (data not shown).

Based on the route of administration of bortezomib, we divided patients in two groups: those that received bortezomib twice weekly ($n = 58$; 67%) and patients who received bortezomib once weekly ($n = 29$; 33%). There were no differences with regards to major response (OR 0·84, 95% CI 0·25–2·81; $P = 0·78$), deep response (OR 0·54, 95% CI 0·20–1·49; $P = 0·24$) and PFS (HR 0·59, 95% CI 0·24–1·44, $P = 0·24$) between groups. These results did not change when adjusting for maintenance therapy (data not shown). HR estimates for OS was not possible as none of the patients receiving once weekly bortezomib have died.

The median PFS in patients who received Benda-R, BDR and CDR without maintenance was 4·9, 2·2 and 1·4 years, respectively (log-rank $P = 0·003$), and in patients who received maintenance rituximab it was NR, 6·5 and 6·4 years, respectively ($P = 0·32$). The median OS for patients who received Benda-R, BDR and CDR without maintenance was NR, NR and 4·4 years, respectively (log-rank $P < 0·001$), and in patients who received maintenance rituximab it was NR for all groups (log-rank $P = 0·33$).

Table III. Univariate and multivariate Cox proportional-hazard regression models for progression-free survival.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age >65 years	0·98 (0·59–1·63)	0·95		
Male sex	0·89 (0·53–1·47)	0·65		
Haemoglobin ≤115 g/l	1·05 (0·62–1·80)	0·85		
Platelet count ≤100 × 10^9/l	0·59 (0·21–1·64)	0·32		
Beta-2-microglobulin >3 mg/l	1·80 (1·08–3·00)	0·03	2·24 (1·28–3·93)	0·005
Serum IgM >40 g/l	1·54 (0·93–2·56)	0·09	1·90 (1·10–3·30)	0·02
Marrow involvement ≥50%	1·11 (0·68–1·84)	0·67		
Lymphadenopathy	1·82 (1·08–3·09)	0·03	1·71 (0·96–3·05)	0·07
Splenomegaly	1·78 (0·89–3·56)	0·11		
Low risk IPSSWM	1·00 (Ref)			
Intermediate risk IPSSWM	1·48 (0·85–2·59)	0·17		
High risk IPSSWM	1·13 (0·57–2·27)	0·73		
CDR	1·00 (Ref)		1·00 (Ref)	
Benda-R	0·49 (0·22–1·09)	0·08	0·18 (0·07–0·43)	<0·001
BDR	0·90 (0·52–1·57)	0·72	0·55 (0·30–0·99)	0·046
Maintenance rituximab*	0·18 (0·10–0·31)	<0·001	0·54 (0·45–0·66)	<0·001

BDR, bortezomib, dexamethasone and rituximab; Benda-R, bendamustine and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; CI, confidence interval; HR, hazard ratio; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia.
*Maintenance rituximab was considered a time-varying covariate in the multivariate analysis

Discussion

Herein, we present results from a retrospective study that examined the efficacy of three combination regimens with and without maintenance rituximab as primary therapy in patients with symptomatic WM. Our study provides additional insights to the available data on primary therapy for WM. Our results can be summarized as follows: (i) primary therapy with Benda-R, BDR and CDR produces high response rates with more rapid time to best response seen with Benda-R and BDR than with CDR; (ii) PFS appears longer in WM patients treated with Benda-R and BDR when compared to CDR; (iii) OS appears longer in WM patients treated with BDR than with CDR; and (iv) WM patients who received maintenance rituximab had deeper responses to therapy as well as superior PFS and OS than patients who did not receive maintenance, adjusting for treatment regimen.

Our findings in WM patients who received CDR are consistent with the results of a prospective study from Greece (n = 72) as well as a recent retrospective study from the US (n = 50) (Dimopoulos *et al*, 2007; Kastritis *et al*, 2015; Paludo *et al*, 2017). In these studies, the ORR to CDR ranged between 80% and 90% with a median PFS of about 3 years. Of note, none of these studies followed induction CDR with maintenance rituximab. It is possible that the median PFS of 5 years observed in our study (n = 37) reflects that about 70% of patients treated with CDR at our institution received maintenance rituximab.

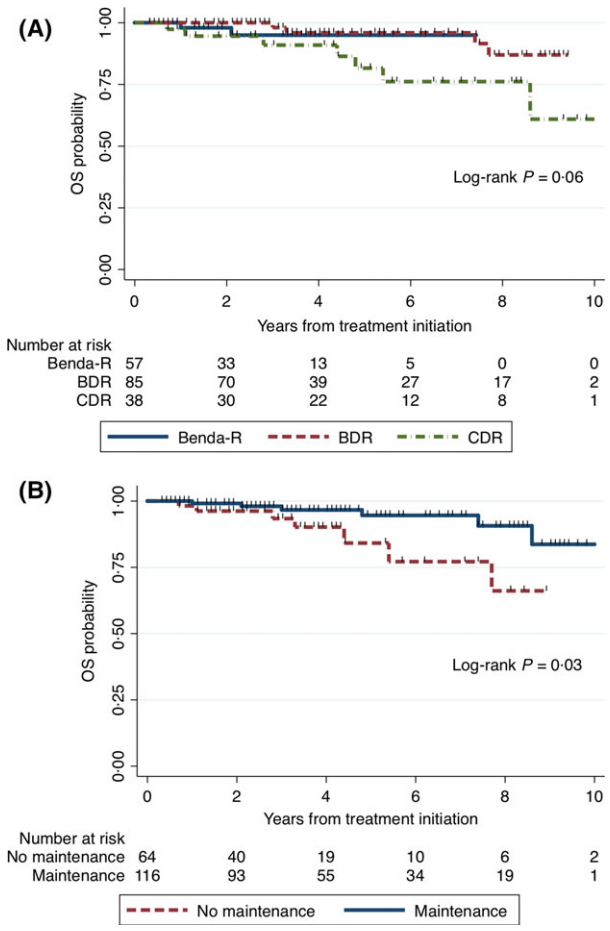

Fig 2. OS estimates by (A) Benda-R *versus* BDR *versus* CDR, and (B) maintenance rituximab. BDR, bortezomib, dexamethasone and rituximab; Benda-R, bendamustine and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; OS, overall survival. [Colour figure can be viewed at wileyonlinelibrary.com]

Two prospective studies from Greece (n = 59) and the US (n = 23) have reported findings for WM patients who were treated with BDR (Treon *et al*, 2009, 2015a; Dimopoulos *et al*, 2013; Gavriatopoulou *et al*, 2017). The ORR also ranged between 80% and 90% with a median PFS of 3·5 years in the Greek study and 5·5 years in the US study. There were differences in the design of these studies that might have accounted for the difference in PFS. The US study used twice weekly dosing of bortezomib and 1 year of maintenance therapy. Our study (n = 88) shows a median PFS for BDR of 5·8 years, which could reflect that 64% of these patients received also rituximab maintenance.

Finally, the data on the use of Benda-R as primary therapy in WM is supported by a subset analysis of a randomized controlled study (n = 20) from Germany and preliminary data on a prospective study on primary therapy with Benda-R (n = 182) followed by maintenance rituximab (Rummel *et al*, 2012, 2013). In these studies, the ORR was reported at 90% and the median PFS was approximately 5 years, which was longer than with the combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Our study (n = 57) shows an ORR of 95% and a median PFS of 5·5 years. About 60% of WM patients treated with Benda-R in our study received maintenance rituximab.

The use of maintenance rituximab following a rituximab-containing regimen in WM patients has been controversial, as no prospective study has been done exclusively in WM. A number of studies have evaluated maintenance rituximab after rituximab-containing regimens in the more common follicular lymphoma and have shown an improvement in PFS although OS benefit has not been demonstrated (Salles *et al*, 2011; Barta *et al*, 2016). A previous retrospective study showed PFS and OS benefit in favour of maintenance rituximab over observation in WM patients (Treon *et al*, 2011). However, in that study, the prognostic modelling was univariate and included both untreated and previously treated patients. In our study, we show that maintenance rituximab provides deeper responses and PFS and OS benefits. We fully adjusted our analyses for pertinent clinical variables, as well for each regimen received as induction. Additionally, to deal with immortal bias, we analysed maintenance rituximab as a time-varying covariate in our statistical modelling. An ongoing prospective study is evaluating maintenance rituximab in WM patients (Rummel *et al*, 2012).

Our study, however, is not without limitations. The retrospective nature of this study makes it prone to missing data and selection bias. However, our rate of missing data was less

Table IV. Univariate and multivariate Cox proportional-hazard regression models for overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age >65 years	2·15 (0·70–6·61)	0·18		
Male sex	2·35 (0·64–8·57)	0·19		
Haemoglobin ≤115 g/l	0·42 (0·09–1·91)	0·27		
Platelet count ≤100 × 10^9/l	UTC			
Beta-2-microglobulin >3 mg/l	2·34 (0·72–7·62)	0·16		
Serum IgM >40 g/l	1·30 (0·43–4·00)	0·64		
Lymphadenopathy	1·74 (0·57–5·34)	0·33		
Splenomegaly	1·48 (0·33–6·77)	0·61		
Marrow involvement ≥50%	0·32 (0·09–1·18)	0·10		
Low risk IPSSWM	1·00 (Ref)			
Intermediate risk IPSSWM	1·18 (0·37–3·72)	0·78		
High risk IPSSWM	0·45 (0·05–3·64)	0·45		
CDR	1·00 (Ref)		1·00 (Ref)	
Benda-R	0·39 (0·08–1·99)	0·26	0·24 (0·05–1·27)	0·09
BDR	0·27 (0·08–0·92)	0·04	0·14 (0·03–0·61)	0·009
Maintenance rituximab*	0·32 (0·11–0·95)	0·04	0·72 (0·55–0·93)	0·01

BDR, bortezomib, dexamethasone and rituximab; Benda-R, bendamustine and rituximab; CDR, cyclophosphamide, dexamethasone and rituximab; CI, confidence interval; HR, hazard ratio; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia; UTC, unable to calculate.

*Maintenance rituximab was considered a time-varying covariate in the multivariate analysis.

than 3%, with exception of *MYD88* and *CXCR4* mutational status. In addition, the age and sex distribution, treatment indications and other factors were otherwise representative of the clinical features of the general population with WM. An obvious major limitation is the lack of randomization, which is identifiable by the imbalances between the groups of patients treated with CDR, BDR and Benda-R. However, we addressed this limitation by performing a multivariate analysis that took into account the most relevant clinical factors that could impact response, PFS and OS. Finally, the results of our exploratory analyses might have been underpowered and should be considered with caution.

Based on the results of our study, one could argue that both BDR and Benda-R induce faster and more prolonged responses than CDR, and should be considered as reasonable primary therapy options for patients with WM. Given that the efficacy of BDR and Benda-R is similar, one could further personalize treatment recommendations based on the toxicity profile of these regimens, which have been well established. One of the most important adverse events associated with BDR therapy is neuropathy, which can be minimized, although not eliminated, with subcutaneous and/or weekly administration of bortezomib. On the other hand, bendamustine, although well tolerated overall, can be associated with a small but real risk of secondary leukaemia. Given the characteristics of these regimens, it is our practice to offer BDR to younger patients and Benda-R to elderly patients. CDR, although less effective, has a benign toxicity profile with manageable cytopenias and gastrointestinal symptoms, and is also a reasonable treatment option.

We acknowledge that it is a common practice in the US to offer single agent rituximab as primary therapy in WM patients (Olszewski *et al*, 2016). However, we consider single agent rituximab a less effective therapy in WM, which is associated with an ORR of 30–40% and median PFS ranging between 1 and 2 years (Gertz *et al*, 2004; Treon *et al*, 2005). In addition, the use of single agent rituximab has been associated with IgM flares, a unique complication seen in patients with WM (Ghobrial *et al*, 2004; Treon *et al*, 2004). Although not reflective of rapid disease progression, IgM flares can induce abrupt increases of 25–300% in baseline serum IgM levels that can induce hyperviscosity and make WM patients with neuropathy or cryoglobulinaemia more symptomatic. However, patients with low burden of disease or who might not tolerate chemoimmunotherapy can be considered for single agent rituximab therapy.

As none of the treatment options discussed here are curative, the treatment of patients with WM has to be personalized. Components of the decision-making process should include the patient's disease presentation, the efficacy and toxicity of the regimen to be used and patient's preferences and goals of care. Of interest, a recent population-based study showed that the inclusion of rituximab in the primary therapy of patients with WM is associated with a benefit in OS (Olszewski *et al*, 2017). In light of the approval of ibrutinib for the treatment of patients with symptomatic WM and emerging data on the use of ibrutinib as primary therapy (Treon *et al*, 2015b, 2017; Dimopoulos *et al*, 2017), additional research is needed to further refine our treatment

options, which should take into account not only efficacy and toxicity but also cost.

Authorship contribution

JJC and JNG designed the study, performed the analysis and drafted the manuscript. LX, GY and ZRH performed molecular testing in patients' samples. All the authors took care of the patients, gathered the data, and critically reviewed and approved the final manuscript.

Disclosures

JJC has received honoraria and/or research funds from Abbvie, Gilead, Janssen, Millennium and Pharmacyclics. SPT has received honoraria and/or research funds from Pharmacyclics. JJC is supported by the WMR fund.

References

Barta, S.K., Li, H., Hochster, H.S., Hong, F., Weller, E., Gascoyne, R.D., Habermann, T.M., Gordon, L.I., Colocci, N., Bengtson, E.M., Horning, S.J. & Kahl, B.S. (2016) Randomized phase 3 study in low-grade lymphoma comparing maintenance anti-CD20 antibody with observation after induction therapy: a trial of the ECOG-ACRIN Cancer Research Group (E1496). *Cancer*, **122**, 2996–3004.

Castillo, J.J., Olszewski, A.J., Kanan, S., Meid, K., Hunter, Z.R. & Treon, S.P. (2015) Overall survival and competing risks of death in patients with Waldenstrom macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. *British Journal of Haematology*, **169**, 81–89.

Dimopoulos, M.A., Anagnostopoulos, A., Kyrtsonis, M.C., Zervas, K., Tsatalas, C., Kokkinis, G., Repoussis, P., Symeonidis, A., Delimpasi, S., Katodritou, E., Vervessou, E., Michali, E., Pouli, A., Gika, D., Vassou, A., Terpos, E., Anagnostopoulos, N., Economopoulos, T. & Pangalis, G. (2007) Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *Journal of Clinical Oncology*, **25**, 3344–3349.

Dimopoulos, M.A., Garcia-Sanz, R., Gavriatopoulou, M., Morel, P., Kyrtsonis, M.C., Michalis, E., Kartasis, Z., Leleu, X., Palladini, G., Tedeschi, A., Gika, D., Merlini, G., Kastritis, E. & Sonneveld, P. (2013) Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood*, **122**, 3276–3282.

Dimopoulos, M.A., Trotman, J., Tedeschi, A., Matous, J.V., Macdonald, D., Tam, C., Tournilhac, O., Ma, S., Oriol, A., Heffner, L.T., Shustik, C., Garcia-Sanz, R., Cornell, R.F., de Larrea, C.F., Castillo, J.J., Granell, M., Kyrtsonis, M.C., Leblond, V., Symeonidis, A., Kastritis, E., Singh, P., Li, J., Graef, T., Bilotti, E., Treon, S., Buske, C. & iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia. (2017) Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncology*, **18**, 241–250.

Gavriatopoulou, M., Garcia-Sanz, R., Kastritis, E., Morel, P., Kyrtsonis, M.C., Michalis, E., Kartasis, Z., Leleu, X., Palladini, G., Tedeschi, A., Gika, D., Merlini, G., Sonneveld, P. & Dimopoulos, M.A. (2017) BDR in newly diagnosed patients with WM: final analysis of a phase 2 study after a minimum follow-up of 6 years. *Blood*, **129**, 456–459.

Gertz, M.A., Rue, M., Blood, E., Kaminer, L.S., Vesole, D.H. & Greipp, P.R. (2004) Multicenter phase 2 trial of rituximab for Waldenstrom macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). *Leukaemia & Lymphoma*, **45**, 2047–2055.

Ghobrial, I.M., Fonseca, R., Greipp, P.R., Blood, E., Rue, M., Vesole, D.H., Gertz, M.A. & Eastern Cooperative Oncology Group. (2004) Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*, **101**, 2593–2598.

Kastritis, E., Gavriatopoulou, M., Kyrtsonis, M.C., Roussou, M., Hadjiharissi, E., Symeonidis, A., Repoussis, P., Michalis, E., Delimpasi, S., Tsatalas, K., Tsirigotis, P., Vassou, A., Vervessou, E., Katodritou, E., Gika, D., Terpos, E. & Dimopoulos, M.A. (2015) Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenstrom macroglobulinemia: final analysis of a phase 2 study. *Blood*, **126**, 1392–1394.

Kyle, R.A., Treon, S.P., Alexanian, R., Barlogie, B., Bjorkholm, M., Dhodapkar, M., Lister, T.A., Merlini, G., Morel, P., Stone, M., Branagan, A.R. & Leblond, V. (2003) Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Seminars in Oncology*, **30**, 116–120.

Morel, P., Duhamel, A., Gobbi, P., Dimopoulos, M.A., Dhodapkar, M.V., McCoy, J., Crowley, J., Ocio, E.M., Garcia-Sanz, R., Treon, S.P., Leblond, V., Kyle, R.A., Barlogie, B. & Merlini, G. (2009) International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*, **113**, 4163–4170.

Olszewski, A.J., Treon, S.P. & Castillo, J.J. (2016) Evolution of management and outcomes in Waldenstrom macroglobulinemia: a population-based analysis. *Oncologist*, **21**, 1377–1386.

Olszewski, A.J., Chen, C., Gutman, R., Treon, S.P. & Castillo, J.J. (2017) Comparative outcomes of immunochemotherapy regimens in Waldenstrom macroglobulinaemia. *British Journal of Haematology*, **179**, 106–115.

Owen, R.G., Treon, S.P., Al-Katib, A., Fonseca, R., Greipp, P.R., McMaster, M.L., Morra, E., Pangalis, G.A., San Miguel, J.F., Branagan, A.R. & Dimopoulos, M.A. (2003) Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Seminars in Oncology*, **30**, 110–115.

Owen, R.G., Kyle, R.A., Stone, M.J., Rawstron, A.C., Leblond, V., Merlini, G., Garcia-Sanz, R., Ocio, E.M., Morra, E., Morel, P., Anderson, K.C., Patterson, C.J., Munshi, N.C., Tedeschi, A., Joshua, D.E., Kastritis, E., Terpos, E., Ghobrial, I.M., Leleu, X., Gertz, M.A., Ansell, S.M., Morice, W.G., Kimby, E., Treon, S.P. & Macroglobulinaemia VIIWoW. (2013) Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *British Journal of Haematology*, **160**, 171–176.

Paludo, J., Abeykoon, J.P., Kumar, S., Shreders, A., Ailawadhi, S., Gertz, M.A., Kourelis, T., King, R.L., Reeder, C.B., Leung, N., Kyle, R.A., Buadi, F.K., Habermann, T.M., Dingli, D., Witzig, T.E., Dispenzieri, A., Lacy, M.Q., Go, R.S., Lin, Y., Gonsalves, W.I., Warsame, R., Lust, J.A., Rajkumar, S.V., Ansell, S.M. & Kapoor, P. (2017) Dexamethasone, rituximab and cyclophosphamide for relapsed and/or refractory and treatment-naive patients with Waldenstrom macroglobulinemia. *British Journal of Haematology*, **179**, 98–105.

Rummel, M.J., Lerchenmuller, C., Greil, R., Gorner, M., Hensel, M., Engel, E., Jaeger, U., Breuer, F., Hertenstein, B., Prummer, O., Buske, C., Barth, J., Burchardt, A.C. & Brugger, W. (2012) Bendamustin-rituximab induction followed by observation or rituximab maintenance for newly diagnosed patients with Waldenstrom' macroglobulinemia: results from a prospective, randomized, Multicenter Study (StiL NHL 7-2008 -MAINTAIN-; ClinicalTrials.gov Identifier: nCT00877214). *Blood*, **120**, 2739.

Rummel, M.J., Niederle, N., Maschmeyer, G., Banat, G.A., von Grunhagen, U., Losem, C., Kofahl-Krause, D., Heil, G., Welslau, M., Balser, C., Kaiser, U., Weidmann, E., Durk, H., Ballo, H., Stauch, M., Roller, F., Barth, J., Hoelzer, D., Hinke, A., Brugger, W. & Study group indolent Lymphomas (StiL). (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*, **381**, 1203–1210.

Salles, G., Seymour, J.F., Offner, F., Lopez-Guillermo, A., Belada, D., Xerri, L., Feugier, P., Bouabdallah, R., Catalano, J.V., Brice, P., Caballero, D., Haioun, C., Pedersen, L.M., Delmer, A., Simpson, D., Leppa, S., Soubeyran, P., Hagenbeek, A., Casasnovas, O., Intragumtornchai, T., Ferme, C., da Silva, M.G., Sebban, C., Lister, A., Estell, J.A., Milone, G., Sonet, A., Mendila, M., Coiffier, B. & Tilly, H. (2011) Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*, **377**, 42–51.

Swerdlow, S.H., Campo, E., Pileri, S.A., Harris, N.L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G.A., Zelenetz, A.D. & Jaffe, E.S. (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, **127**, 2375–2390.

Treon, S.P., Branagan, A.R., Hunter, Z., Santos, D., Tournhilac, O., Anderson, K.C. & Waldenstrom's Macroglobulinemia Clinical Trials G. (2004) Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenstrom's macroglobulinemia. *Annals of Oncology*, **15**, 1481–1483.

Treon, S.P., Emmanouilides, C., Kimby, E., Kelliher, A., Preffer, F., Branagan, A.R., Anderson, K.C. & Frankel, S.R. (2005) Extended rituximab therapy in Waldenstrom's macroglobulinemia. *Annals of Oncology*, **16**, 132–138.

Treon, S.P., Ioakimidis, L., Soumerai, J.D., Patterson, C.J., Sheehy, P., Nelson, M., Willen, M., Matous, J., Mattern, J. 2nd, Diener, J.G., Keogh, G.P., Myers, T.J., Boral, A., Birner, A., Esseltine, D.L. & Ghobrial, I.M. (2009) Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *Journal of Clinical Oncology*, **27**, 3830–3835.

Treon, S.P., Hanzis, C., Manning, R.J., Ioakimidis, L., Patterson, C.J., Hunter, Z.R., Sheehy, P. & Turnbull, B. (2011) Maintenance Rituximab is associated with improved clinical outcome in rituximab naive patients with Waldenstrom Macroglobulinaemia who respond to a rituximab-containing regimen. *British Journal of Haematology*, **154**, 357–362.

Treon, S.P., Meid, K., Gustine, J., Patterson, C.J., Matous, J.V., Ghobrial, I.M. & Castillo, J.J. (2015a) Long-term outcome of a prospective study of bortezomib, dexamethasone and rituximab (BDR) in previously untreated, symptomatic patients with Waldenstrom's macroglobulinemia. *Blood*, **126**, 1833.

Treon, S.P., Tripsas, C.K., Meid, K., Warren, D., Varma, G., Green, R., Argyropoulos, K.V., Yang, G., Cao, Y., Xu, L., Patterson, C.J., Rodig, S., Zehnder, J.L., Aster, J.C., Harris, N.L., Kanan, S., Ghobrial, I., Castillo, J.J., Laubach, J.P., Hunter, Z.R., Salman, Z., Li, J., Cheng, M., Clow, F., Graef, T., Palomba, M.L. & Advani, R.H. (2015b) Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *New England Journal of Medicine*, **372**, 1430–1440.

Treon, S.P., Gustine, J., Meid, K., Dubeau, T., Severns, P., Patterson, C.J., Xu, L., Yang, G., Liu, X., Demos, M., Kofides, A., Chen, J.J., Munshi, M., Tsakmaklis, N., Chan, G., Yee, A.J., Raje, N., O'Donnell, E., Hunter, Z.R. & Castillo, J.J. (2017) Ibrutinib is highly active as first line therapy in symptomatic Waldenstrom's macroglobulinemia. *Blood*, **130**, 2767.

Xu, L., Hunter, Z.R., Yang, G., Zhou, Y., Cao, Y., Liu, X., Morra, E., Trojani, A., Greco, A., Arcaini, L., Varettoni, M., Brown, J.R., Tai, Y.T., Anderson, K.C., Munshi, N.C., Patterson, C.J., Manning, R.J., Tripsas, C.K., Lindeman, N.I. & Treon, S.P. (2013) MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood*, **121**, 2051–2058.

Xu, L., Hunter, Z.R., Tsakmaklis, N., Cao, Y., Yang, G., Chen, J., Liu, X., Kanan, S., Castillo, J.J., Tai, Y.T., Zehnder, J.L., Brown, J.R., Carrasco, R.D., Advani, R., Sabile, J.M., Argyropoulos, K., Lia Palomba, M., Morra, E., Trojani, A., Greco, A., Tedeschi, A., Varettoni, M., Arcaini, L., Munshi, N.M., Anderson, K.C. & Treon, S.P. (2016) Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom macroglobulinaemia. *British Journal of Haematology*, **172**, 735–744.