ORIGINAL ARTICLE

Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia

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Abstract

The treatment approaches for Waldenstrom macroglobulinemia (WM) are largely based upon information from single-arm phase II trials, without comparative data. We compared the efficacy of two commonly used regimens in routine practice (bendamustine-rituximab (BR) and dexamethasone, rituximab plus cyclophosphamide (DRC)) and evaluated their activity with respect to the patients' $MYD88^{L265P}$ mutation status. Of 160 consecutive patients, 60 received BR (43 with relapsed/refractory WM) and 100 received DRC (50 had relapsed/refractory WM). In the treatment-naïve setting, overall response rate (ORR) was 93% with BR versus 96% with DRC ($p = 0.55$). Two-year progression-free survival (PFS) with BR and DRC was 88 and 61%, respectively ($p = 0.07$). In salvage setting, ORR was 95% with BR versus 87% with DRC, $p = 0.45$; median PFS with BR was 58 versus 32 months with DRC (2-year PFS was 66 versus 53%; $p = 0.08$). Median disease-specific survival was not reached with BR versus 166 months with DRC ($p = 0.51$). The time-to-event endpoints and depth of response were independent of the $MYD88$ mutation status. Grade ≥ 3 adverse events of both regimens were comparable. A trend for longer PFS was observed with BR although the regimens have comparable toxicities. The activity of BR and DRC appears to be unaffected by patients' $MYD88$ mutation status.

Keywords MYD88 · Drug therapy · Lymphoma · Immunoglobulin M · Lymphoplasmacytic lymphoma

Introduction

Waldenstrom macroglobulinemia (WM) is a unique B cell malignancy characterized by the presence of IgM monoclonal protein and lymphoplasmacytic infiltrate in the bone marrow

[1]. Although the recent discoveries of $MYD88^{L265P}$ and $CXCR4^{WHIM}$ mutations have contributed substantially to our understanding of the WM pathophysiology, WM remains an incurable malignancy [2, 3].

Multiple chemotherapeutic regimens have been used in WM, although the treatment approach has witnessed evolution over time from the use of nucleoside analogs [4] to the incorporation of alkylating agents [5], and subsequently, integration of anti-CD20 monoclonal antibody, rituximab, that now serves as the cornerstone of anti-WM regimens [6]. Ibrutinib, an irreversible Bruton's tyrosine kinase (BTK) inhibitor [7], is the most recent addition to our therapeutic armamentarium against WM. It has demonstrated remarkable efficacy in relapsed/refractory (R/R) patients with WM who harbor the $MYD88^{L265P}$ mutation [8, 9]. However, ibrutinib therapy requires continuous administration until disease

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progression or the development of intolerable side effects, with an estimated annual cost of approximately $122,000 in the USA [10, 11]. In contrast, the estimated costs for a full treatment course (6 cycles) of BR and DRC are $115,000 and $50,000, respectively [12].

Treatment approaches in WM are often derived from small, single-arm clinical trials as few head-to-head comparisons of regimens exist. Bendamustine/rituximab (BR) and dexamethasone/rituximab/cyclophosphamide (DRC) are common fixed duration chemotherapeutic regimens used in previously untreated or R/R WM patient populations, but for which prospective data are only available in the treatment-naïve (TN) setting. Direct comparative data have not been reported for BR and DRC [13, 14].

We compared the efficacy of BR with DRC, two regimens used contemporaneously at a tertiary care center for the management of TN or RR WM patients. Additionally, we report on the activity of these two regimens with respect to the patient's *MYD88* mutation status.

Patients and methods

The medical records of patients with WM who were consecutively seen at Mayo Clinic, between January 1, 2007 and December 31, 2014, were reviewed. The study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki. WM was defined by the presence of 10% or greater monoclonal lymphoplasmacytic cells in the bone marrow and detection of serum monoclonal IgM protein of any size [1]. Symptomatic patients with less than 10% of bone marrow involvement by lymphoplasmacytic lymphoma (LPL) in the relapsed/refractory setting requiring initiation of therapy were also included in the analysis ($n = 2$). Treatment was offered to symptomatic WM patients or those with bulky disease, WM-associated hemolytic anemia, or cytopenias in accordance with the 2nd International WM Workshop (IWWM) Consensus indications for initiation of therapy in WM [15].

Only the patients who had received at least one complete cycle of BR or DRC were considered evaluable. The BR regimen consisted of bendamustine 90 mg/m^2 IV on days 1 and 2 in addition to rituximab 375 mg/m^2 IV on day 1. The DRC regimen was given as dexamethasone 20 mg IV on day 1, rituximab 375 mg/m^2 IV on day 1, and cyclophosphamide 100 mg/m^2 PO daily on days 1 through 5. BR was given every 4 weeks for up to 6 cycles, while DRC was given every 3 weeks for up to 6 cycles.

Response to treatment was assessed according to the Consensus Response Criteria from the 6th IWWM [16]. Refractory disease was characterized as lack of response to prior therapy or progression within 3 months of last treatment. Overall response rate (ORR) was assessed by measuring the rate of a minor response or better. Major response rate (MRR) was defined as the rate of partial response or better. The time-to-best response was defined as the time from initiation of BR or DRC to the IgM nadir before initiation of another line of therapy.

The *MYD88* mutation status was assessed by the amplification-refractory mutation system (ARMS), a variant of allele-specific polymerase chain reaction (AS-PCR), with an analytical sensitivity of approximately 1% mutation detection in a wild-type background from bone marrow aspirate samples. DNA was extracted using the Qiagen DNeasy kit (Qiagen, Valencia, CA) from bone marrow aspirate sample pellets fixed in methanol–acetic acid. A single-tube multiplex AS-PCR was performed using primers situated in exon 5 of *MYD88* (NM_002468.4), including one primer specifically targeting the c.794T > C; Leu265Pro (L256P) alteration. Reaction products were analyzed using capillary electrophoresis (QIAxcel; Qiagen). Using this methodology, the MYD88 control amplification yielded a PCR product of 141 base pairs (bp), and an additional specific 72-bp product denoting the L265P mutation, if present. The toxicities involved with the two regimens were graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 4.0 [17].

All time-to-event analyses were performed from BR or DRC initiation date using the Kaplan-Meier method and the log-rank test. Progression-free survival (PFS) was defined as the time from initiation of BR or DRC to the time of first event (progression of disease or death). Patients without the event were censored for PFS at the last date they were found to be in remission and alive. Time-to-next therapy (TTNT) was measured from the time of commencement of DRC or BR to initiation of the next treatment regimen or death, whichever came first. Patients who died without receiving the next line of therapy or who were alive without requiring the next line of therapy were censored at the date they were last known to be alive. TTNT is a clinically relevant end point in WM as patients often fulfill the criteria for progressive disease, but remain clinically asymptomatic and are observed until the re-emergence of WM-associated criteria for which re-initiation of therapy is warranted as outlined in the consensus recommendations.

For the calculation of the disease-specific survival (DSS), the patients who died from causes unrelated to WM were censored. The cause of death was considered "WM-related" if death resulted from progressive disease, AL amyloidosis-related end-organ failure, therapy-related myelodysplastic syndrome [MDS], transformation to diffuse large B cell lymphoma [DLBCL], infections, or treatment-related complication and "unrelated" if patients died while WM was in remission, were off therapy, and death occurred from causes other than WM (e.g., stroke, myocardial infarction, or another unrelated cancer) and without evidence of disease progression or

relapse. Two-sided Wilcoxon rank sum test and Fisher's exact test were used to compare the medians of continuous and categorical variables, respectively. The Kaplan-Meier method was utilized for all time-to-event analyses. A p value < 0.05 was considered statistically significant and analysis was performed using JMP 10.0 software (SAS Institute, Cary, NC).

Results

Patient and disease characteristics

Of 160 symptomatic patients with WM, 60 (38%) received BR while the remaining 100 (62%) patients received the DRC regimen. Of the 60 patients in the BR group, 44 (73%) patients were treated in the R/R setting. Of 100 patients in the DRC group, 50 (50%) patients were treated in the R/R setting. BR was the 2nd line (range 2–11) therapy in 21 (47%) patients (median of 2 prior line of therapy), while DRC was 2nd line (range 2–8) in 29 (58%) patients (median of 1 prior lines of therapy) in the R/R population. Rituximab monotherapy was the only prior line of therapy in 8 (20%) patients in the BR group and 20 (40%) in the DRC group ($p = 0.66$). Baseline characteristics at the time of BR or DRC initiation are shown in Table 1. Six patients had received both BR and DRC during their disease course and overlapped between the two cohorts. Two patients with less than 10% of bone marrow involvement by LPL were included in the analysis. One of them with constitutional symptoms and extensive lymphadenopathy was treated with DRC, while the remaining patient had renal involvement by LPL and was treated with BR.

Treatment-NAÏVE setting

Among the previously untreated patients, the median IgM levels decreased from 3785 mg/dL (range 375 to 10,200 mg/dL) to 724 mg/dL (range 81 to 3250 mg/dL; $p = 0.0001$) at best response with BR. Similarly, the reduction in IgM after DRC was from 4130 mg/dL (range 871 to 9860 mg/dL) to 1250 mg/dL (range 25 to 7180 mg/dL; $p = 0.001$) at best response. The median time-to-best response was 6.1 months (range 1 to 25) with BR group versus 11 months (range 0.5–47) with DRC ($p = 0.13$).

For the patients treated with BR, the ORR and MMR were 93 and 86%, respectively. VGPR was achieved by 4 patients (29%), PR by 8 patients (57%), and MR by 1 patient (7%). Progressive disease without any initial response was noted in 1 patient (7%) who received BR. For patients treated with DRC, ORR was 96% and MRR was 87%. VGPR was achieved by 8 patients (17%), PR was seen in 32 (70%) patients, and MR in 4 (9%) patients. Stable disease was seen in 1 (4%) patient (Fig. 1). ORR ($p = 0.55$) and MRR ($p = 1.0$) were similar in patients treated with frontline BR or DRC. VGPR or

better response rate was similar in patients treated with BR or DRC ($p = 0.44$).

The duration of follow-up from BR and DRC in the TN patients was similar: median 30 months (95% CI, 13–53) versus 30 months (95% CI, 21–36), respectively. The 2-year progression-free survival (PFS) was 88 and 61% in the BR and DRC groups, respectively ($p = 0.07$); the median PFS for the cohort on BR was not reached (95% CI: NR-NR), while it was 34 months (95% CI, 23-NR) for the DRC group. The 2-year TTNT was 87 and 76% (Fig. 2) in the BR and DRC groups, respectively ($p = 0.41$). The median TTNT and disease-specific survival (DSS) were not reached with either regimen (TTNT 95% CI: NR-NR for BR and 36.8-NR for DRC, $p = 0.44$; DSS 95% CI, 16.8-NR for BR and NR-NR for DRC, $p = 0.94$).

Relapsed/refractory setting

In the relapsed/refractory setting, the median IgM levels decreased from 3880 mg/dL (range 61 to 8600 mg/dL) to 659 mg/dL (range 128 to 4120 mg/dL; $p = 0.0001$) at best response with BR and from 3870 mg/dL (range 514 to 10,000 mg/dL) to 1846 mg/dL (range 177 to 5830 mg/dL; $p = 0.001$) with DRC. The median time-to-best response was 7 months (range 1 to 39) with BR and 7 months (range 0.5 to 28) with DRC ($p = 0.77$).

Patients treated with BR achieved an ORR of 95%, and the MRR was 81%. CR was seen in 1 (3%) patient, VGPR in 14 (38%) patients, PR in 15 (41%) patients, and MR in 5 (13%) patients. Two (5%) patients treated with BR progressed without any initial response. For patients who were treated with DRC, the ORR was 87% and the MRR was 68%. VGPR was achieved in 2 (4%) patients, PR in 30 (64%) patients, and MR in 9 (19%) patients. SD was seen in 4 (9%) patients, while the remaining 2 (4%) patients had progressive disease (PD) (Fig. 1). No difference was seen in ORR ($p = 0.45$) and MRR ($p = 0.21$) in patients treated with BR or DRC in the relapsed/refractory setting. In contrast to the treatment-naïve setting, the rate of VGPR or better response in the relapsed/refractory setting was higher in patients treated with BR compared to DRC (41 vs. 4%, $p = 0.0001$).

The estimated median follow-up from BR was 32 months (95% CI, 26–41) and 51 months (95% CI, 38–55) from DRC ($p = 0.26$). The median PFS for patients treated with BR was 58 months (95% CI, 23-NR) and the 2-year PFS was 66%. In comparison, for patients treated with DRC, median PFS was 31 months (95% CI, 15–50) and the 2-year PFS was 53%, $p = 0.08$. The median TTNT from BR was 60 months (95% CI, 45-NR; 2-year TTNT was 75%), while the median TTNT from DRC was 50 months (95% CI, 34–60; 2-year TTNT was 68%, $p = 0.24$). The median DSS in the BR group was NR (95% CI, 135-NR) and 166 months (95% CI, 111-NR) in the DRC group ($p = 0.51$).

Table 1 Baseline characteristics at BR or DRC initiation

Parameter, median (range)*	BR ($n = 60$)	DRC ($n = 100$)	p value
Age, years	66 (30–85)	68 (37–95)	0.90
Male gender, n (%)	41 (68)	58 (58)	0.24
Hemoglobin, g/dL	10.6 (6–15)	10.5 (5–15)	0.91
Platelet count, $\times 10^9$/L	194 (23–535)	196 (22–609)	0.75
B2 microglobulin, mcg/mL	3.8 (1.6–8)	3.4 (1.6–14)	0.58
IPSSWM score, n (%)			
High	20 (49)	44 (55)	0.51
Intermediate	12 (29)	21 (26)	0.72
Low	9 (22)	15 (19)	0.67
IgM, mg/dL	3795 (61–10,200)	4085 (514–10,000)	0.32
BM involvement, % (range)	60 (5–99)	50 (5–90)	0.32
MYD88^{L265P}, n (%)	14 (74)	24 (83)	0.48
Relapsed/refractory, n (%)	44 (73)	50 (50)	0.004
Treatment regimens prior to BR or DRC in R/R patients, n (%)**			
Rituximab monotherapy	27 (45)	34 (68)	
Chlorambucil	4 (7)	8 (16)	
R-CVP	4 (7)	5 (10)	
Fludarabine	2 (3)	4 (8)	
Everolimus	3 (5)	3 (6)	
Cladribine	2 (3)	2 (4)	
ASCT	3 (5)	2 (4)	
R-CHOP	5 (8)	0	
DRC	6 (10)	–	
FR	3 (5)	0	

*Unless specified otherwise

**Included only regimes used in more than one patient

BM bone marrow; *TOI* treatment of interest; *MYD88* myeloid differentiation primary response 88 gene; *R-CVP* rituximab, cyclophosphamide, vincristine, prednisone; *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; *ASCT* autologous stem cell transplant; *FR* fludarabine, rituximab

The proportion of patients with relapsed/refractory disease was significantly higher in the BR cohort (Table 1). Importantly, in a bivariate analysis of the entire cohort for PFS, incorporating the setting (TN vs. R/R) and the regimen involved (BR vs. DRC), the latter emerged as a significant factor [hazard ratio 0.52 (95% CI, 0.3–0.9), $p = 0.019$] in favor of BR.

Six patients received both BR (as salvage therapy in all 6 patients) and DRC (as salvage in 5 of 6 patients). In all patients, DRC was used earlier in the disease course than BR. All patients achieved at least a minor response (ORR 100%) when treated with either DRC or BR. One patient who achieved a PR with prior DRC had a VGPR to BR. At the time of analysis, all patients had progressed after DRC compared to only 1 patient after BR. The median PFS from DRC was 29 months (95% CI, 9–57) compared to NR (95% CI, 15-NR) from BR, $p = 0.78$.

Duration of therapy

Outcomes based on the duration of therapy were analyzed comparing patients who received 6 versus 4 cycles of therapy, either in the treatment-naïve or relapsed/refractory setting. Thirty-one patients (52%) on BR regimen received a full 6-cycle course while the remaining 29 (48%) patients received

an abbreviated course. A total of 14 (23%) patients received 4 cycles of therapy. Out of the 14 patients who received 4 cycles of BR, the indication for a shorter treatment course could be ascertained in 8 patients, of whom 7 patients had a pre-planned abbreviated course, while treatment-related toxicity led to shortening of the course in 1 patient. The MRR was similar with the use of 6 cycles (93%) or 4 cycles (90%, $p = 1.0$). A trend towards higher deep response (CR+VGPR) rates was seen with 6 cycles (46%) compared to 4 cycles (20%, $p = 0.25$). Median PFS from BR was not reached for either group [6 cycles (95% CI, 23-NR) vs. 4 cycles (95% CI, 14-NR), $p = 0.3$]. For patients treated with DRC, 52 (52%) received 6 cycles while 3 (3%) patients received 4 cycles of therapy. Out of those 3 patients, one patient received only 4 cycles of therapy due to disease progression. The sample size of DRC-treated patients who received 4 cycles of therapy was too small to conduct a meaningful analysis.

MYD88^{L265P} status

The *MYD88* mutation status was available in 48 patients of the entire cohort. Of those, 19 had received BR and 29 had received DRC in the primary or salvage setting. *MYD88*^{L265P} mutation was noted in 14 (74%) patients treated with BR and 24 (83%) patients treated with DRC. The time-to-event
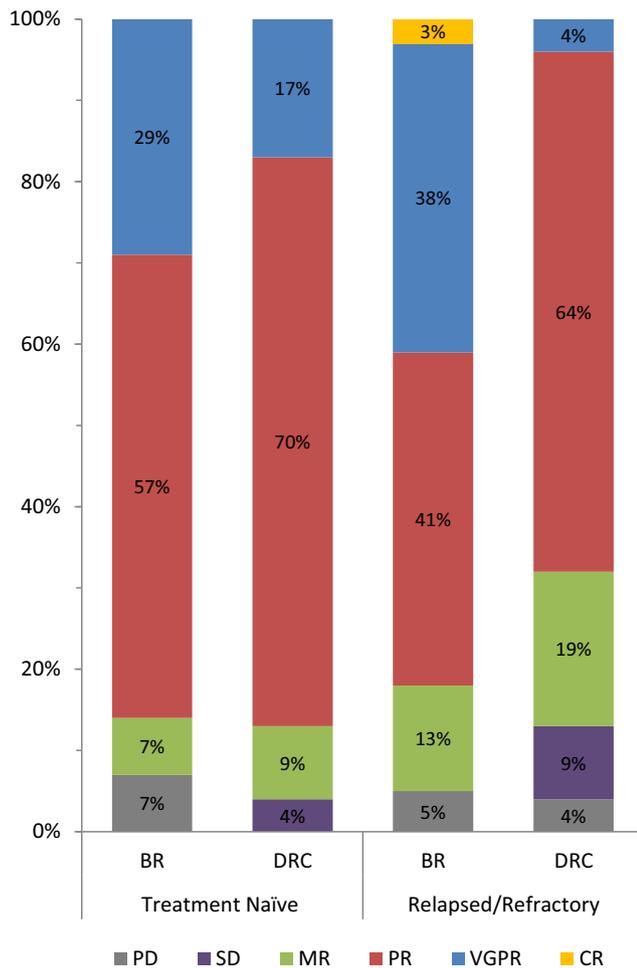
Fig. 1 Best response rates from BR and DRC. CR complete response, VGPR very good partial response, PR partial response, MR minor response, SD stable disease, PD progressive disease

outcomes (i.e., PFS, TTNT, and DSS) were similar in patients with *MYD88* mutated or wild-type. The ORR in *MYD88*^{L265P} patients was 92% compared to 100% in *MYD88*^{WT} patients, $p = 1.0$.

The median PFS for *MYD88*^{L265P} patients was 45 months (95% CI, 21–59) compared to 34 months (95% CI, 9-NR) in *MYD88*^{WT} patients, $p = 0.30$. The median TTNT for *MYD88*^{L265P} patients was 56 months (95% CI, 41-NR) compared to 36 months (95% CI, 9–37) in *MYD88*^{WT} patients, $p = 0.14$.

Safety

Table 2 summarizes toxicities that were attributable to BR or DRC. Grade 3 or higher adverse events for patients with TN or RR WM were similar in patients treated with BR or DRC. The most common grade 3 or higher adverse events related to BR were neutropenia (11%), infections (5%), thrombocytopenia (2%), and nausea/vomiting (2%). Grade 3 or more adverse events associated with DRC were neutropenia (20%),

thrombocytopenia (7%), infections (3%), and hypotension (1%). No deaths related to therapy were recorded with either regimen.

Therapy-related MDS or transformation to high-grade lymphoma occurred in 5 (8%) patients at a median of 30 months (range 17–59) after BR and 5 (5%) patients at a median of 7 months (range 5–12) after DRC ($p = 0.5$). Of the patients who developed t-MDS or transformed to high-grade lymphoma, 4 patients in the BR group and 5 in the DRC group also received alkylating agents and/or nucleoside analogs prior to the establishment of t-MDS or transformation to high-grade lymphoma. No patients with t-MDS progressed to AML.

Stem cell mobilization and harvest was successful after BR and DRC in all 14 and 17 patients, respectively, in whom this procedure was attempted. The median CD34+ cell count collected was 6.41×10^6 cells/kg in patients treated with BR and 6.64×10^6 cells/kg in patients treated with DRC ($p = 0.98$). A total of 13 patients (7 in the BR group and 6 in the DRC group) ultimately underwent ASCT for the treatment of WM.

Discussion

The lack of consensus regarding the optimal treatment approach to treating patients with WM is in part due to the scarcity of direct comparisons between the therapeutic regimens. With exception of a few phase III clinical trials [5, 14, 18], the data on treatment options in WM are derived from phase II or single-arm clinical trials [19] and are usually extrapolated from TN to R/R setting, or vice-versa. BR and DRC are no exception to this approach. We attempted to fill the void created by the lack of a randomized trial comparing the 2 regimens. Our retrospective study directly compared the effectiveness of BR with DRC used contemporaneously and suggests that both are very active approaches with comparable toxicities. BR, however, showed a trend towards better PFS, both in previously untreated and R/R patient population. This superiority of PFS however did not translate into improved DSS with BR, likely a consequence of availability of effective salvage therapies in this indolent malignancy [6]. This has also been noted in a recent updated of BR versus R-CHOP in indolent lymphomas, including WM [20].

Bendamustine has structural similarities of both alkylating agents and purine analogs [21] and demonstrates incomplete cross resistance with other alkylating agents [22]. Following the promising results of a phase II trial [23], the bendamustine and rituximab combination was evaluated in phase III setting [14] against R-CHOP in previously untreated patients with indolent and mantle cell lymphomas, including 41 patients with WM. While the ORR with BR was 96% compared to 94% with R-CHOP [24], the median PFS was remarkably longer with BR (69 months) compared to R-CHOP (28 months) in patients with WM, with toxicity profile

Fig. 2 Progression-free survival and time-to-next therapy in treatment-naïve and relapsed/refractory patients. Treatment naïve: (a) median PFS in for the cohort on BR is not reached (95% CI: NR-NR) versus 34 months (95% CI: 23-NR) for DRC, *p* = 0.13. (b) Median TTNT is NR (95% CI: NR-NR) with BR and NR (95% CI, 36.8-NR) with DRC, *p* = 0.44. Relapsed/refractory: (c) median PFS for patients treated with BR is 58 months (95% CI, 23-NR) versus 31 months (95% CI, 15–50) with DRC group, *p* = 0.08. (d) The median TTNT from BR is 60 months (95% CI, 45-NR), while the median TTNT from DRC is 50 months (95% CI, 34–60), *p* = 0.24. PFS progression-free survival; TTNT time-to-next therapy; BR bendamustine, rituximab; DRC dexamethasone, rituximab, and cyclophosphamide; m months
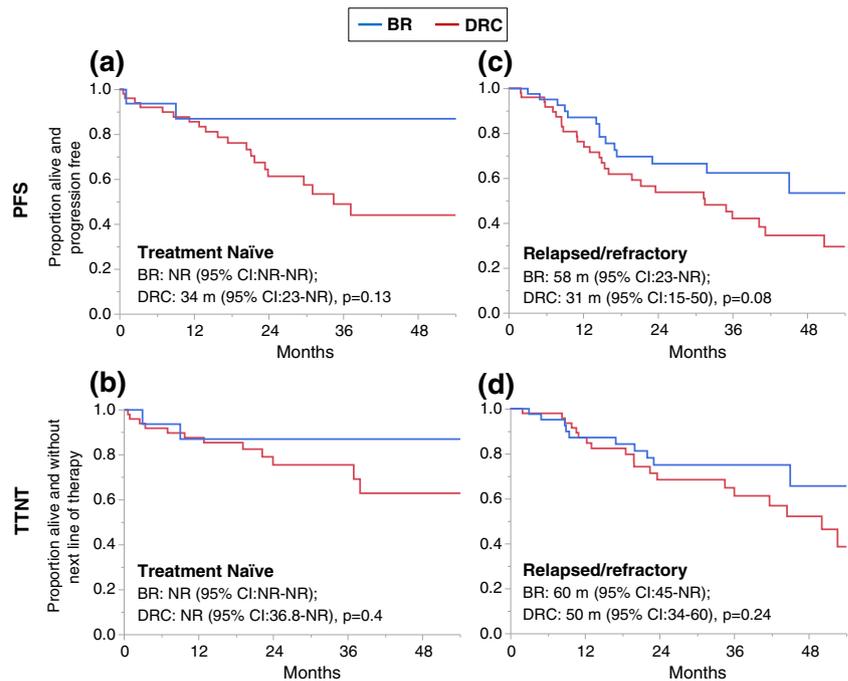
favoring the BR arm as well [14]. The use of R-CHOP as the comparator arm in patients with WM, despite the inferiority of the CHOP backbone to more effective contemporaneous regimes for WM and increased toxicity, including vinca alkaloid-associated neuropathy and anthracycline-associated cardiomyopathy, is a drawback of this trial [6, 25]. Two additional retrospective studies of R/R patients with WM who were treated with BR demonstrated the effectiveness of this combination with an ORR of 80% (CR 7%, VGPR 15%, PR 52%, and MR 6%) to 83% (VGPR 17% and PR 66%) [26, 27]. The estimated 2-year PFS was approximately 60% in one study and the median PFS was estimated at 13 months in the second study [26, 27]. In the previously untreated populations, our study showed similar ORR in patients treated with BR compared to the phase III clinical trial of BR vs. R-CHOP

[24]. In the R/R populations, we observed slightly better response rates than prior retrospective studies [26, 27]. With a longer follow-up, the 2-year PFS seen in our study was similar to the previously estimated PFS seen in TN and R/R WM patients [24, 26, 27].

The DRC regimen was designed specifically for the treatment of WM patients after the 2nd International Workshop in WM as a stem cell-sparing regimen with minimal myelo and immunosuppressive properties [13]. It has only been prospectively studied in a single phase II trial of previously untreated WM patients [13] [28]. DRC was shown to be active, with an ORR of 83% (CR 7%, PR 67%, and MR 9%) and grade ≥ 3 adverse events were seen in only 13% of patients. The median PFS was 35 months (2-year PFS of 67%). Our study showed slightly better ORR and similar 2-year PFS when DRC was used in the TN setting. Additionally, it showed comparable results when patients in the R/R setting.

Our study showed remarkable activity of both regimens, irrespective of the disease setting (TN vs. R/R) at the time of treatment. The ORR achieved with BR and DRC were comparable within the TN and R/R cohorts. A trend towards a better PFS with BR both in the TN and R/R setting was observed. PFS was significantly longer in patients treated with BR when we combined TN and R/R patients, despite a higher proportion of R/R patients comprising the BR group. Although slightly better TTNT was seen in patients treated with BR compared to DRC, no significant difference was noted. Furthermore, BR and DRC are found

Table 2 Toxicities for the entire cohort

Toxicity, %	BR		DRC	
	All	Grade ≥ 3	All	Grade ≥ 3
Neutropenia	39	11	39	20
Thrombocytopenia	26	2	20	7
Nausea/vomiting	9	2	7	0
Fever/chills	5	0	3	0
Headache	2	0	4	0
Hypotension	2	0	3	1
Infections	19	5	15	3

to be equally effective in $MYD88^{L265P}$ or $MYD88^{WT}$ patients as suggested by similar response rates or time-to-event outcomes as frontline or salvage therapy. No impact of $MYD88$ mutation status was seen in a preliminary analysis of patients treated with FCR as part of the R2W clinical trial, although only 3 patients harbored the $MYD88^{WT}$ genotype (personal communication) [29]. In contrast to ibrutinib therapy, in which discontinuation was followed by an increase in IgM levels in WM or rebound leukocytosis in CLL within a week [30, 31], a decline in the IgM levels was observed in the vast majority of patients on BR or DRC even after completion of therapy as suggested by the prolonged time-to-best response seen in our study.

With respect to the duration of therapy, a course of 4 cycles of BR appears to be equivalent to that of 6 cycles as suggested by comparable MRR and PFS although the limited number of patients in this subset analysis precludes any definitive conclusions. There was, however, a trend towards deeper responses noted with the longer BR treatment course, although this observation may be a reflection of continuation of therapy by the treating physicians beyond 4 cycles in patients who were exhibiting signs of continued response. Our subset analysis supports the comparable effectiveness of a lower cumulative dose of bendamustine that was recently reported, with MRR of 95 and 89% with 6 or 4 cycles of BR, respectively, for the treatment of WM [32].

Grade ≥ 3 adverse events were comparable in both regimens. No stem cell toxicity was noted as evident by uniformly successful peripheral blood stem cell collection after BR or DRC. Both regimens are also reasonable options in the elderly, transplant ineligible patient as suggested by similar ORR, PFS and TTNT seen in patients 65 years or older at time of BR or DRC commencement.

While the inherent biases associated with a retrospective study and limited sample size are limitations of our report, our off-study approach is comparable to the results of previously reported prospective clinical trials of BR or DRC. Generally, the patients in clinical trials are fitter [33], thereby introducing a selection bias as well. The CR rate reported in our study was likely underestimated since a bone marrow biopsy in patients who were responding to therapy based on IgM levels was not routinely performed. Low CR rates have also been reported in prospective trials of DRC (CR rate of 7%) in treatment-naïve patients with WM [13]. Similarly, post-treatment imaging studies were not routinely performed in all responders, thereby limiting the assessment of extramedullary disease response. Given the heterogeneity between the TN and relapsed/refractory patient-populations, we elected not to formally compare these two sub-groups that received a given regimen (BR or DRC). Our allele-specific PCR assay's analytical sensitivity is 1% and the prevalence of MYD88L265P mutation reported in our study is comparable to that reported by other studies [34, 35]. The AS-PCR assay used in our institution is a validated test that is routinely used in clinical practice across multiple institutions in the USA. However, due to small number of patients in whom data regarding MYD88 mutation status were available, caution should be exercised in the interpretation of this analysis. No definite conclusions can be made until external validation of this particular finding is undertaken in an independent cohort of patients [36, 37]. We now favor the use of BR as first line therapy in patients with WM given its association with a prolonged PFS and TTNT, deep responses, and favorable toxicity profile [25]. Both regimens are widely available and are also adequate treatment options in the relapsed/refractory setting. Our findings also suggest that the patients relapsing post DRC appear to be easily salvageable with BR.

In conclusion, BR and DRC are well tolerated, stem cell sparing, active regimens administered for a fixed duration for the treatment of WM patients. A trend towards superior PFS was seen with the use of BR, without associated increased toxicity. In contrast to ibrutinib, the $MYD88$ mutation status does not appear to impact the activity of BR or DRC.

Compliance with ethical standards

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