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Impact of ibrutinib dose intensity on patient outcomes in previously treated Waldenström macroglobulinemia

Short title

Ibrutinib dose intensity in Waldenström

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In 2015, the Bruton tyrosine kinase (BTK) inhibitor ibrutinib became the first approved therapy for symptomatic Waldenström macroglobulinemia (WM) [1]. Temporary interruption of therapy is recommended to manage treatment-related toxicities and when patients undergo invasive procedures [2]. In a previous study, a lower dose intensity (DI) of ibrutinib therapy was associated with a shorter progression-free survival (PFS) in 195 patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who participated in the RESONATE study [3]. However, the impact of interrupted therapy with ibrutinib has not been evaluated in patients with WM. We examined the importance of ibrutinib dose intensity in previously treated WM patients who received therapy in the multicenter study that supported regulatory approval (ClinicalTrials.Gov ID NCT01614821) [4].

Medical records of subjects who participated in this trial were reviewed and pertinent clinical data were collected surrounding ibrutinib temporary drug holds. Treatment adherence to ibrutinib was documented during the clinical trial and was measured by overall DI. Overall DI was defined as the proportion of administered versus planned daily 420-mg doses from initiation of therapy until last dose received. We also evaluated the 8-week DI and 6-month DI, which were defined as the proportion of administered versus planned daily 420-mg doses within the first 8 weeks and 6 months, respectively, from initiation of ibrutinib therapy. Response was assessed based on current criteria [5]. Comparison between groups were evaluated using Chi-square or Fisher exact tests. PFS was defined as the time in months from ibrutinib initiation until disease progression or death from any cause and was estimated using the Kaplan-Meier method.

Comparisons between groups were made using the log-rank test. Survival outcomes were analyzed using Cox proportional-hazard regression models and reported as hazard ratio (HR) with 95% confidence interval (CI). Assessment of *MYD88* and *CXCR4* mutations were performed as previously described [6, 7].

Sixty-three WM patients were enrolled and began therapy with ibrutinib at 420 mg once daily. Of these patients, 20 (32%) had an overall DI of 100%, 37 patients (59%) had an overall DI of 95-99%, and 6 patients (10%) had an overall DI below 95%. Only 1 patient (1.6%) had an overall DI below 80%. After a median of 3.9 years of ibrutinib therapy, the mean overall DI was 97%. Nineteen patients (30%) had low overall DI (mean DI ≤97%), and 44 patients (70%) had high overall DI (mean DI >97%). Patients with low overall DI were more likely to be 65 years or older at the time of ibrutinib initiation compared to patients with high overall DI (68% vs. 36%; p=0.03). No other differences could be demonstrated between patients with low versus high overall DI (**Table 1**). The median drug hold length was 6 days (range, 2-50 days). Ibrutinib DI was decreased due to toxicity in 57%, and due to surgical procedures in 43% of patients.

At the time of this report, the median follow-up time is 48 months (95% CI 47-50 months). Twenty-four patients (38%) have progressed, and the median PFS has not yet been reached. The median PFS was significantly shorter in patients with low overall DI versus high overall DI (median, 22 months vs. not reached; log-rank p=0.001; **Figure 1A**). The HR for PFS in patients with low overall DI was 3.59 (95% CI 1.58-8.14; p=0.002) when compared with patients with high overall DI. In a multivariate analysis

adjusting for age, serum IgM, hemoglobin and beta-2-microglobulin levels, low DI was the only independent variable associated with worse PFS (HR 3.34, 95% CI 1.34-8.30; p=0.009).

Based on genomic profiling, 37 patients (59%) were *MYD88*^{MUT}*CXCR4*^{WT}, 21 patients (33%) were *MYD88*^{MUT}*CXCR4*^{WHIM}, and 5 patients (8%) were *MYD88*^{WT}*CXCR4*^{WT}. Subgroup analyses showed a significant difference in PFS for *MYD88*^{MUT}*CXCR4*^{WT} patients with low DI versus high DI (median, 35 months vs. NR; p=0.007; **Figure 1B**). The HR for PFS in patients with low overall DI was 4.83 (95% CI 1.38-16.9; p=0.01) when compared with patients with high overall DI. There was a trend in *MYD88*^{MUT}*CXCR4*^{WHIM} patients (median, 14 months vs. not reached; log-rank p=0.05; **Figure 1C**). The HR for PFS in patients with low overall DI was 3.37 (95% CI 0.95-12.0; p=0.06) when compared with patients with high overall DI. No difference could be demonstrated in *MYD88*^{WT}*CXCR4*^{WT} patients (median 5 months vs. NR; HR 1.09, 95% CI 0.09-13.3; p=0.95), but the sample was too small to make reliable estimates.

The mean 8-week DI was 96% (range 61-100%). Fifty-one patients (81%) had an 8-week DI >96%, and 5 patients (8%) had an 8-week DI <80%. The mean 6-month DI was 98% (range 84-100%). Fifty-one patients (81%) had a 6-month DI >98%, and no patients had a 6-month DI of <80%. The 8-week and 6-month DI below the mean were not associated with worse PFS (log-rank p=0.75 in both cases). We also evaluated the median DI (99%) as a cutoff for our survival analysis; 32 patients (51%) had a median DI >99%, and 31 patients (49%) had a median DI ≤99%. There was no statistical

difference in median PFS between patients with median DI >99% and median DI ≤99% (not reached vs. 47 months; log-rank p=0.17).

Among patients who held ibrutinib (n=50; 79%), those who missed doses for 8 consecutive days or more (n=26; 41%) experienced a shorter PFS compared to patients who missed less than 8 consecutive days (n=24; 38%) with a median PFS of 35 months versus NR; p=0.005; **Figure 1D**). The HR for PFS in patients who held ibrutinib for 8 or more days was 4.07 (95% CI 1.44-11.5; p=0.008) when compared to patients who held for less than 8 days. In *MYD88*^{MUT}*CXCR4*^{WT} patients, holding for 8 days or more was associated with a median PFS of 48 months vs. NR in patients who held for less than 8 days (log-rank p=0.01; **Figure 1E**). The HR for PFS in patients who held ibrutinib for 8 or more days was 8.56 (95% CI 1.02-72.0; p=0.04) when compared to patients who held for less than 8 days. In *MYD88*^{MUT}*CXCR4*^{WHIM} patients, holding ibrutinib for 8 days or longer was associated with a median PFS of 22 months vs. NR in patients who held for less than 8 days (log-rank p=0.07; **Figure 1F)**. The HR for PFS in patients who held ibrutinib for 8 or more days was 3.49 (95% CI 0.85-14.4; p=0.08) when compared to patients who held for less than 8 days. There was a weak positive correlation between holding ibrutinib and low DI (Pearson's r=0.24).

An increase in serum IgM level was observed on 62 occasions at the next response assessment after a drug hold. The median increase in serum IgM level was 51% (range, 5-552%), and 37 increases (60%) met criteria for progressive disease (PD). Following the reinitiation of ibrutinib, the median time to a response of stable disease (SD) or

better was 127 days, and was significantly longer for patients with the *MYD88*^{MUT}*CXCR4*^{WHIM} versus *MYD88*^{MUT}*CXCR4*^{WT} tumor genotype (212 vs. 109 days; p<0.001).

Our retrospective analysis of this single-arm prospective study suggests that WM patients with mean overall DI lower than 97% had shorter PFS and a risk of progression 3 times higher than in patients with mean overall DI 97% or higher. In addition, holding ibrutinib for longer than 1 week at any time during the entire treatment duration appeared associated with a 4-fold increased risk of progression. Our stratified analyses based on tumor genotype showed similar results for overall DI and ibrutinib hold lasting longer than 1 week. Our findings are in line with a previous study evaluating the impact of ibrutinib dose intensity in patients with CLL [3], and suggest that ibrutinib holds should be minimized, and ibrutinib restarted as soon as clinically indicated to achieve optimal patient outcomes. However, low DI at 8 weeks or 6 months did not adversely impact PFS in our cohort, when compared to a study in CLL [3]. A potential explanation is the longer median PFS in patients with low DI in our cohort of 22 months versus 7 months in the CLL study. Temporary interruption of ibrutinib therapy was associated with transient increases in serum IgM level, and more than half of WM patients temporarily holding ibrutinib would experience disease progression based on current criteria [5]. However, a response is regained in virtually all cases at ibrutinib reinitiation, as previously reported [8]. The time to response after progression during a temporary hold appears longer for WM patients with the *MYD88*^{MUT}*CXCR4*^{WHIM} tumor genotype. We acknowledge the limitations of our study, which include the small sample and

smaller subset analyses, which could have introduced bias into our results. One could also argue that the low DI seen in our study might not reflect a real-world experience and could make the interpretation of our results challenging. On the other hand, missing data was minimized given the prospective nature of the parent study, and the median follow-up time is the longest reported in WM patients. In conclusion, our study suggests that, similar to CLL patients, low DI adversely impacts PFS in WM patients. Ibrutinib therapy is indefinite and compliance should be strongly emphasized to optimize outcomes.

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Authorship contribution

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

Disclosures

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References

1. FDA News Release. FDA explands aproved use of Imbruvica for rare form of non-Hodgkin lymphoma. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm432123.htm . Accessed on December 14, 2017.
2. Castillo JJ, Palomba ML, Advani R, Treon SP. Ibrutinib in Waldenström macroglobulinemia: latest evidence and clinical experience. Ther Adv Hematol. 2016;7(4):179-186.
3. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. Blood. 2017;129(19):2612-2615.
4. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015;372(15):1430-1440.
5. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. Br J Haematol. 2013;160(2):171-176.

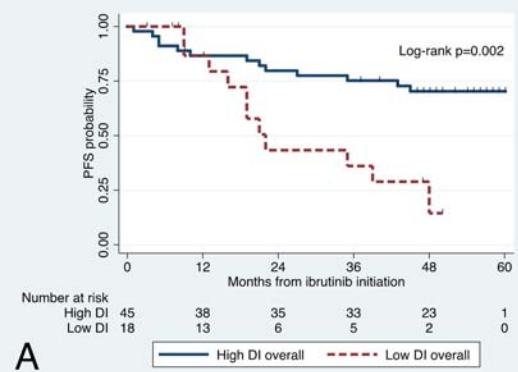
6. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood. 2014;123(11):1637-1646.
7. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013;121(11):2051-2058.
8. Gustine JN, Meid K, Dubeau T, et al. Ibrutinib discontinuation in Waldenstrom macroglobulinemia: Etiologies, outcomes, and IgM rebound. Am J Hematol. 2018;93(4):511-517.

Table 1. Patients' baseline characteristics according to ibrutinib dose intensity

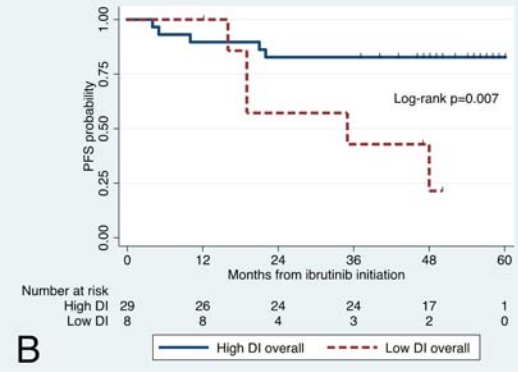
Characteristic	**High overall DI (n=44)**	**Low overall DI (n=19)**	**P-value**
Age ≥65 years	16 (36%)	13 (68%)	0.03
Male sex	34 (77%)	14 (74%)	0.76
Hemoglobin level <10 g/dl	15 (34%)	10 (53%)	0.26
Platelet count <100 K/uL	3 (7%)	4 (21%)	0.18
Serum β2-microglobulin >3.0 mg/l	33 (75%)	11 (58%)	0.23
Serum IgM level >4,000 mg/dl	18 (41%)	8 (42%)	1.00
Bone marrow involvement ≥50%	27 (61%)	10 (53%)	0.58
Lymphadenopathy	27 (61%)	10 (53%)	0.58
Splenomegaly	3 (7%)	4 (21%)	0.18
Number of prior therapies >2	17 (39%)	10 (53%)	0.41
MYD88 L265P mutation	40 (91%)	18 (95%)	1.00
CXCR4 mutation	12 (27%)	9 (47%)	0.15
Best response			
Very good partial response	13 (30%)	5 (26%)	0.73
Partial response	22 (50%)	9 (47%)	
Minor response	6 (14%)	2 (11%)	
Stable disease	3 (7%)	3 (16%)	

Figure legend

Figure 1. Progression-free survival estimates in patients with 63 patients with relapsed and/or refractory Waldenstrom Macroglobulinemia treated with ibrutinib. Kaplan-Meier curves are shown according to ibrutinib overall dose intensity in (A) all patients, (B) *MYD88* mutated/*CXCR4* wild type patients, and (C) *MYD88* mutated/*CXCR4* mutated patients, and according to holding ibrutinib for 8 consecutive days at any time during treatment in (D) all patients, (E) *MYD88* mutated/*CXCR4* wild type patients, and (F) *MYD88* mutated/*CXCR4* mutated patients.


PFS probability
1.00
0.75
0.50
0.25
0.00
Log-rank p=0.002
0
12
24
36
48
60
Months from ibrutinib initiation
Number at risk
High DI 45 38 35 33 23 1
Low DI 18 13 6 5 2 0
High DI overall
Low DI overall

A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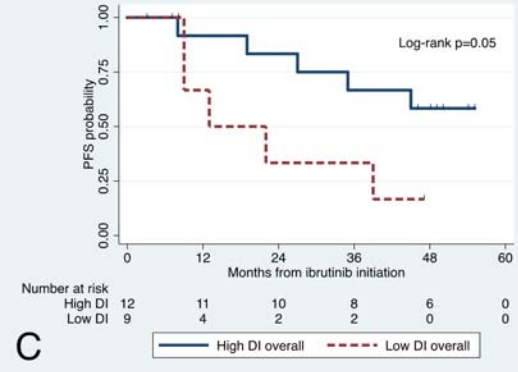
0.75
0.50
0.25
0.00
Log-rank p=0.007
0
12
24
36
48
60
Months from ibrutinib initiation
Number at risk
High DI 29 26 24 24 17 1
Low DI 8 8 4 3 2 0
High DI overall
Low DI overall

B


PFS probability
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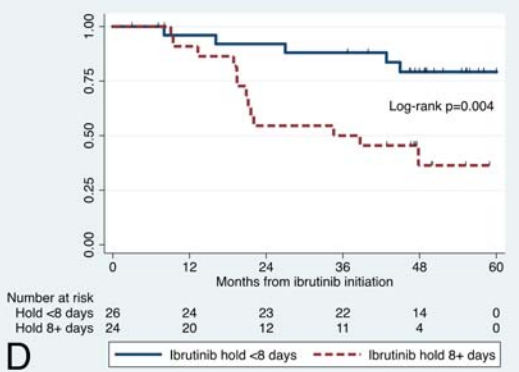
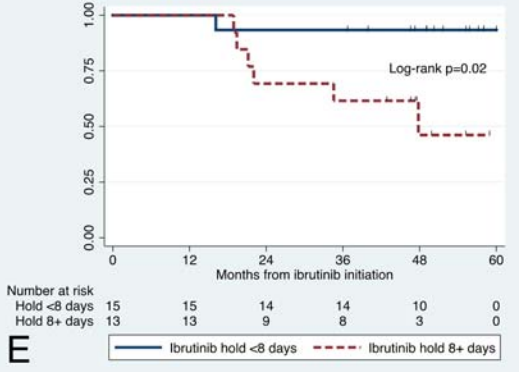
0.75
0.50
0.25
0.00
Log-rank p=0.05
0
12
24
36
48
60
Months from ibrutinib initiation
Number at risk
High DI 12 11 10 8 6 0
Low DI 9 4 2 2 0 0
High DI overall
Low DI overall

C


1.00
0.75
0.50
0.25
0.00
Log-rank p=0.004
0
12
24
36
48
60
Months from ibrutinib initiation
Number at risk
Hold <8 days 26 24 23 22 14 0
Hold 8+ days 24 20 12 11 4 0
Ibrutinib hold <8 days
Ibrutinib hold 8+ days

D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0.50
0.25
0.00
Log-rank p=0.02
0
12
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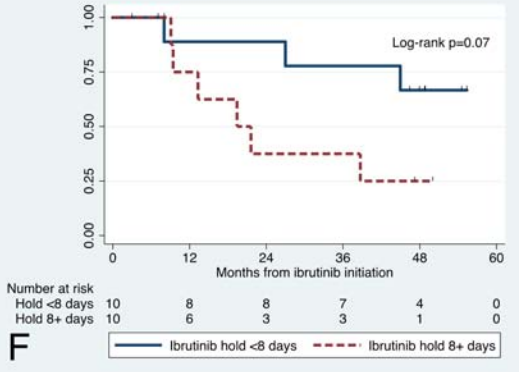
Months from ibrutinib initiation
Number at risk
Hold <8 days 15 15 14 14 10 0
Hold 8+ days 13 13 9 8 3 0
Ibrutinib hold <8 days
Ibrutinib hold 8+ days

E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0.25
0.00
Log-rank p=0.07
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Months from ibrutinib initiation
Number at risk
Hold <8 days 10 8 8 7 4 0
Hold 8+ days 10 6 3 3 1 0
Ibrutinib hold <8 days
Ibrutinib hold 8+ days

F