Impact of Ibrutinib Dose Intensity on Patient Outcomes in Previously Treated Waldenström Macroglobulinemia

Joshua N. Gustine, Kirsten Meid, Toni Dubeau, Patricia Severns, M. Lia Palomba, Ranjana H. Advani, Steven P. Treon, and Jorge J. Castillo

Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; Stanford Medical Center, Palo Alto, CA; Memorial Sloan Kettering, New York, NY

Background

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib recently became the first approved therapy for patients with symptomatic Waldenström macroglobulinemia (WM). Temporary interruption of therapy is recommended to manage treatment-related toxicities and when patients undergo invasive procedures. However, the impact of interrupted therapy with ibrutinib has not been evaluated in patients with WM. We therefore examined the clinical implications of dose intensity in previously treated WM patients treated with ibrutinib in the multicenter phase 2 trial supporting regulatory approval (Treon NEJM 2015).

Patients and Methods

Sixty-three patients with WM were enrolled and began therapy with ibrutinib 420 mg once daily. Patient charts were retrospectively analyzed and pertinent clinical data were collected surrounding ibrutinib drug holds. Treatment adherence to ibrutinib was documented during the clinical trial, and was measured by overall dose intensity ($DI_{overall}$). DI was defined as the proportion of administered versus planned doses from initiation of therapy until last dose received. Response was assessed based on current guidelines (Owen BJH 2013). Time to events was estimated using the Kaplan-Meier method, and comparisons between groups were made using the log-rank test.

Results

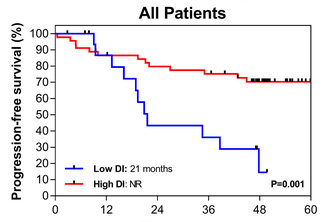
Table 1. Baseline clinical characteristics at the initiation of ibrutinib therapy.

Characteristic	Low $DI_{overall}$ (n=18)	High $DI_{overall}$ (n=45)	P-value
Age ≥65 years	13 (72%)	16 (36%)	0.01
Male sex	14 (78%)	34 (76%)	0.99
Hemoglobin level <10 g/dl	10 (56%)	15 (33%)	0.15
Platelet count <100 K/uL	4 (22%)	3 (7%)	0.10
Serum β2-microglobulin >3.0 mg/l	11 (61%)	33 (73%)	0.37
Serum IgM level >4,000 mg/dl	8 (44%)	18 (40%)	0.78
Bone marrow involvement ≥50%	10 (56%)	28 (62%)	0.78
Extramedullary disease	12 (67%)	28 (62%)	0.78
Number of prior therapies >2	10 (56%)	17 (38%)	0.26
MYD88 mutation	17 (94%)	41 (91%)	0.99
CXCR4 mutation	9 (50%)	12 (27%)	0.09

The mean $DI_{overall}$ was 97% after a median 3.9 years of ibrutinib therapy. Eighteen patients (29%) had a $DI_{overall}$ below the mean (low DI), and 45 patients (71%) had a $DI_{overall}$ above the mean (high DI).

Results

Figure 1. Progression-free survival according to mean dose intensity.



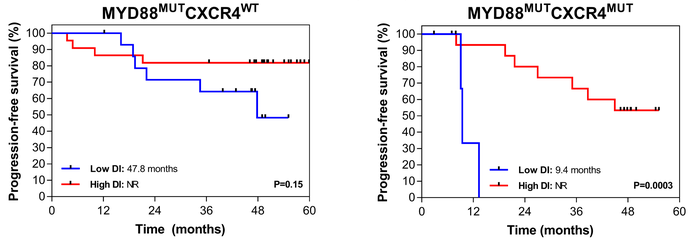
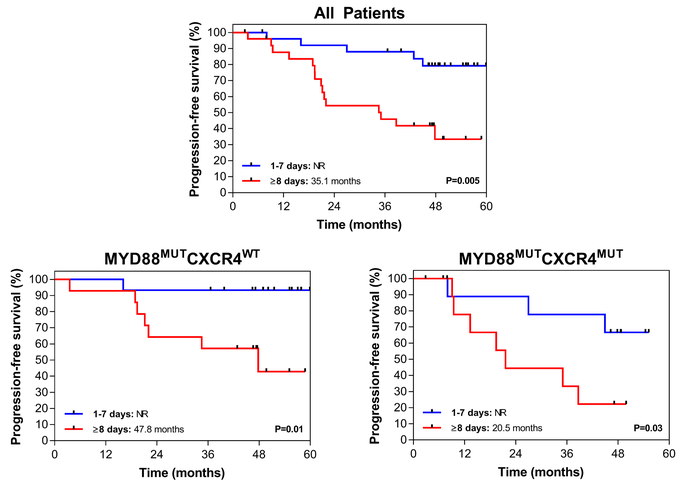


Figure 2. Progression-free survival according drug hold length among patients who held ibrutinib at least once.

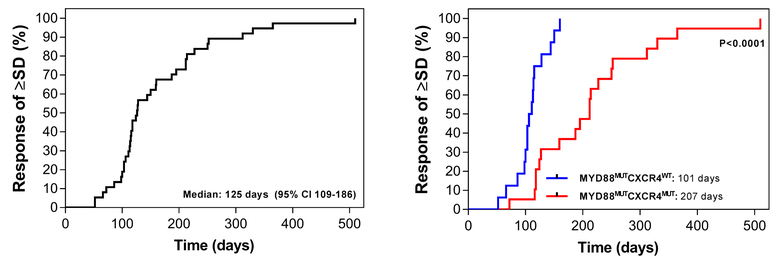


Results

Fifty patients (79%) held ibrutinib at least once, and there were 102 drug hold events in total. The median drug hold length was 6 days (range, 2-50 days). An increase in serum IgM level was observed on 63 occasions at the next response assessment after a drug hold. The median increase in serum IgM level was 50% (range, 4-555%), and 37 increases (59%) met criteria for progressive disease (PD).

Following the reinitiation of ibrutinib, the median time to a response of stable disease (SD) or better was 125 days (95% CI 109-186 days) for patients who met PD criteria, and was significantly longer for patients with the $MYD88^{MUT}CXCR4^{MUT}$ versus $MYD88^{MUT}CXCR4^{WT}$ tumor genotype (207 vs. 101 days; p<0.0001).

Figure 3. Time to a response of stable disease or better after meeting criteria for progressive disease following a temporary drug hold.



Conclusion

Temporary interruption of ibrutinib therapy is associated with transient increases in serum IgM level which appear to persist longer for patients with the *MYD88*^{MUT}*CXCR4*^{MUT} tumor genotype. Patients with DI higher than 97% had longer PFS, and holding ibrutinib >1 week during the entire treatment duration was associated with increased PFS events. These findings suggest ibrutinib holds should be minimized and ibrutinib restarted as soon as clinically indicated to achieve optimal patient outcomes.

For reprints, please contact jorgej_castillo@dfci.harvard.edu.