Ibrutinib is Highly Active as First Line Therapy in Symptomatic Waldenström's Macroglobulinemia

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Background

Activating somatic mutations in MYD88 and CXCR4 are present in 95-97% and 40-45% of untreated patients with Waldenström's macroglobulinemia (WM), respectively. MYD88 mutations trigger pro-survival signaling through Bruton's Tyrosine Kinase and Hematopoietic Cell Kinase, both direct targets of ibrutinib (Yang Blood 2013; 2016). CXCR4 mutations confer *in vitro* and clinical drug resistance to ibrutinib in previously treated WM patients (Cao Leukemia 2014; Treon NEJM 2015). Prior studies have demonstrated ibrutinib produces overall and major responses in 90% and 70-75% of previously treated WM patients (Treon NEJM 2015; Dimopoulos Lancet Oncol 2017). However, ibrutinib as primary therapy in symptomatic patients with WM has not been previously reported.

Patients and Methods

We conducted a prospective, single-arm phase II study evaluating ibrutinib in symptomatic, previously untreated WM patients. All patients had a clinicopathological diagnosis of WM, and met criteria for treatment initiation based current international guidelines (Owen BJH 2013; Kyle Semin Oncol 2003). Ibrutinib at a daily dose of 420 mg was administered orally until disease progression or unacceptable toxicity. Dose reduction was permitted. MYD88 and CXCR4 mutation status were determined by allele-specific polymerase chain reaction (AS-PCR) and Sanger sequencing methods, as previously described (Xu Blood 2013; BJH 2015). **Data cutoff was July 15, 2017.**

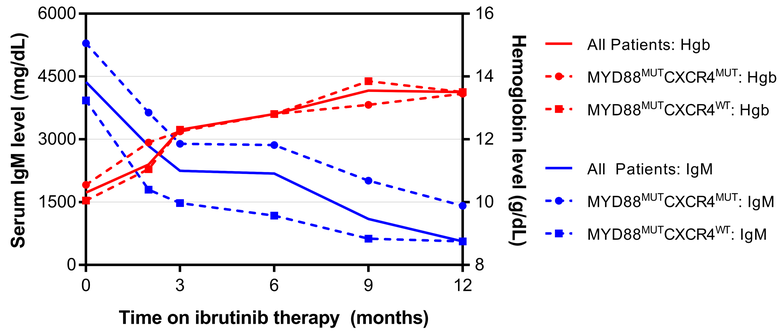
Results

Table 1. Baseline clinical characteristics.

Characteristic	Patients (N=30)
Age, years	67 (43-83)
Male sex	23 (77%)
IPSSWM score	
Low	5 (17%)
Intermediate	11 (37%)
High	14 (47%)
Serum IgM level, mg/dl	4369 (844-10,321)
Hemoglobin level, g/dl	10.3 (7.5-14.5)
Serum β2-microglobulin, mg/l	3.8 (2.0-7.6)
Adenopathy ≥1.5 cm	10 (30%)
Splenomegaly ≥15 cm	5 (17%)
Bone marrow involvement, %	65 (5-95)
MYD88 mutation	30 (100%)
CXCR4 mutation	14 (47%)

Results

Figure 1. Median serum IgM and hemoglobin levels in response to ibrutinib therapy.



The median time on ibrutinib therapy was 8.1 months (range 2.0-16.4 months), and was similar for $CXCR4^{WT}$ and $CXCR4^{MUT}$ patients (9.4 vs. 8.0 months, respectively; p=0.98). At best response, the median serum IgM level declined from 4,380 to 1,786 mg/dl; median hemoglobin level increased from 10.3 to 13.6 g/dl; and median bone marrow involvement decreased from 65% to 20% (p≤0.0001 for all comparisons). Decreased or resolved adenopathy (n=7; 70%) and splenomegaly (n=4; 80%) was observed in most patients with baseline extramedullary disease.

Table 2. Response rates and kinetics to ibrutinib therapy.

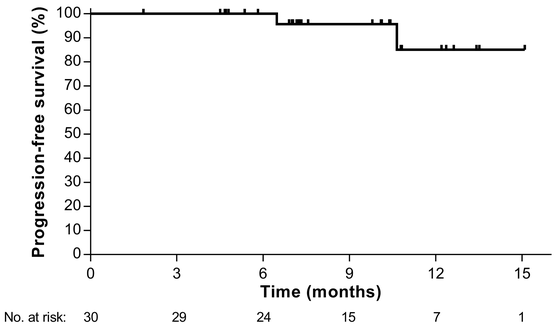
	All Patients (n=30)	$MYD88^{MUT}$ $CXCR4^{WT}$ (n=16)	$MYD88^{MUT}$ $CXCR4^{MUT}$ (n=14)	P-value
Overall responses (%)	97	100	93	0.47
Major responses (%)	80	88	71	0.38
Very good partial responses (%)	17	25	7	0.34
Median time to response (months)				
Minor response (≥MR)	1.0	1.0	2.0	0.10
Major response (≥PR)	2.0	2.0	8.0	0.05

MR: minor response; PR: partial response

Two patients met progression criteria while on active therapy, both of whom were CXCR4 mutated, and one of whom self-held protocol therapy for >2 weeks due to travel. The latter patient continues treatment for clinical benefit per protocol. Four study patients are off protocol therapy due to progression (n=1); withdrawal of consent due to travel (n=1); reversible grade 3 drug-induced hepatitis (n=1); and unrelated grade 4 ventricular arrhythmia (n=1). One patient required dose reduction for vasculitic rash/foot pain (to 140 mg/day). All patients are alive as of study cutoff date of July 15, 2017.

Results

Figure 2. Kaplan-Meier curve for progression-free survival.



All patients were MYD88 mutated.

Table 3. Adverse events associated with ibrutinib therapy.

Event or Abnormality, N (%)	Grade 2	Grade 3	Total Grades 2-4
Alanine transaminase elevation	0	1 (3)	1 (3)
Arthralgias	1 (3)	0	1 (3)
Asparate transaminase elevation	0	1 (3)	1 (3)
Atrial fibrillation	2 (6)	0	2 (6)
Bruising	1 (3)	0	1 (3)
Drug-induced hepatitis	0	1 (3)	1 (3)
Foot pain	0	1 (3)	1 (3)
Hypertension	2 (6)	1 (3)	3 (10)
Muscle cramps	1 (3)	0	1 (3)
Neutropenia	3 (10)	0	3 (10)
Procedural hemorrhage	1 (3)	0	1 (3)
Thrombocytopenia	0	1 (3)	1 (3)
Upper respiratory infection	1 (3)	0	1 (3)
Urinary tract infection	2 (6)	0	2 (6)
Vasculitic rash	1 (3)	0	1 (3)

*Listed are adverse events that were deemed by the investigators to be possibly, probably, or definitely associated with the study drug; no related grade 4 toxicities were observed.

Conclusion

Our findings provide the first report of activity and safety of ibrutinib in symptomatic, previously untreated patients with WM, and demonstrate that ibrutinib is highly active and well-tolerated as a single agent, with no unexpected toxicities. Delays in ibrutinib response are associated with expression of mutated CXCR4.

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