Patient-Reported Symptoms During Ibrutinib Holds: A Withdrawal Syndrome

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Background

The Bruton tyrosine kinase (BTK) inhibitor ibrutinib recently became the first approved therapy for patients with Waldenström macroglobulinemia (WM). The management of ibrutinib-related toxicities, such as bleeding and others, are often managed with temporary interruption of therapy. We observed that some WM patients who held ibrutinib developed symptoms during the time they were holding ibrutinib, which then resolved promptly after ibrutinib reinitiation. Our study aims at describing this "ibrutinib withdrawal" phenomenon.

Patients and Methods

We identified patients seen at our institution between May 2012 and April 2017 who met clinicopathological criteria for WM, met consensus criteria to initiate therapy, and received ibrutinib therapy. Medical files were systematically reviewed to identify WM patients who reported new-onset symptoms occurring during a temporary hold of ibrutinib therapy. Pertinent clinical data were gathered. Patient characteristics are summarized descriptively. The univariate association of clinical factors with withdrawal symptoms was evaluated by fitting logistic regression models whenever possible. The outcome of interest was the odds ratio (OR) with 95% confidence interval (CI) of developing withdrawal symptoms.

Results

Table 1. Clinical characteristics of WM patients who temporarily held and did not hold ibrutinib therapy.

Characteristic	Total (n=189)	Did not hold ibrutinib (n=100)	Held ibrutinib (n=89)	P-value
Age at WM diagnosis, years	60 (39-91)	60 (39-91)	60 (42-87)	0.92
Age ≥65 at WM diagnosis	114 (60%)	57 (57%)	57 (64%)	0.32
Age at ibrutinib initiation, years	67 (43-93)	67 (43-93)	67 (43-87)	0.97
Male sex	128 (68%)	66 (66%)	62 (70%)	0.59
Hemoglobin <10 g/dL	74 (39%)	40 (40%)	34 (38%)	0.80
Platelets <100 k/uL	20 (11%)	12 (12%)	8 (9%)	0.50
Serum B2M >3 mg/dL	136 (72%)	67 (67%)	69 (78%)	0.11
Serum IgM ≥4,000 mg/dL	81 (43%)	48 (48%)	33 (37%)	0.13
Bone marrow involvement	60% (5-95%)	50% (5-95%)	60% (5-95%)	0.56
CXCR4 mutation	59 (37%)	34 (43%)	245 (32%)	0.16
Prior treatment	138 (73%)	68 (68%)	70 (79%)	0.10
Time from WM to ibrutinib, months	44 (0.5-302)	37 (0.5-302)	49 (0.5-267)	0.35

Results

Table 2. Clinical characteristics at the time of ibrutinib hold for patients with withdrawal symptoms.

Age/ Sex	Disease status	Tumor genotype MYD88	Tumor genotype CXCR4	Hgb (g/dl)	Serum IgM (mg/dl)	Response	IB hold Reason	IB hold Duration
55/M	RR	MUT	WT	14.1	485	VGPR	Procedure	5 days
69/M	RR	MUT	WT	13.2	66	VGPR	Drug interaction	33 days
45/M	RR	MUT	WT	13.1	2450	MR	Toxicity	5 days
65/M	RR	MUT	MUT	15.4	796	PR	Procedure	5 days
70/M	FL	MUT	WT	11.8	778	PR	Procedure	3 days
79/M	RR	MUT	NA	11.9	1196	PR	Procedure	14 days
70/M	RR	MUT	WT	14.1	1172	PR	Procedure	7 days
77/F	RR	MUT	NA	14.7	365	PR	Procedure	7 days
66/M	FL	MUT	WT	13.7	798	PR	Toxicity	9 days
52/M	RR	MUT	WT	11.6	2804	MR	Toxicity	12 days
51/M	RR	MUT	WT	14.8	323	PR	Toxicity	7 days
75/F	RR	NA	NA	13.2	148	VGPR	Toxicity	14 days
58/M	RR	MUT	WT	13.0	229	VGPR	Procedure	7 days
65/M	RR	MUT	WT	15.2	313	PR	Procedure	6 days
81/F	RR	MUT	WT	12.7	866	PR	Procedure	7 days
50/M	RR	MUT	WT	13.7	2092	MR	Procedure	7 days
67/M	RR	MUT	WT	14.6	871	PR	Toxicity	3 days
78/M	RR	MUT	WT	13.3	195	VGPR	Patient choice	16 days
66/M	FL	MUT	WT	13.2	530	PR	Procedure	7 days
67/M	RR	MUT	MUT	12.3	1370	PR	Toxicity	10 days

RR: relapsed/refractory; FL: frontline; MUT: mutated; WT: wild-type; VGPR: very good partial response; PR: partial response; MR: minor response;

From the patients who held ibrutinib, 20 (22%) reported withdrawal symptoms. Of these patients who experienced withdrawal symptoms, 17 (85%) were receiving ibrutinib in the relapsed/refractory setting, and 3 (15%) in the frontline setting. All patients were holding ibrutinib for the first time since treatment initiation. The median drug hold length was 7 days (range 3-33 days).

The median time to symptom development was 2 days (range 0-5 days) from the start of the drug hold. Four patients with fever were admitted to the hospital, and after exhaustive workup, no infectious etiology was identified. All patients reported resolution of symptoms the same day ibrutinib was restarted following the drug hold. Nine patients had subsequent drug holds, and reported the same symptoms during the hold period. Two patients known to develop these symptoms were treated with corticosteroids during a subsequent hold and reported symptomatic relief.

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Results

Table 3. Patient-reported symptoms during a temporary ibrutinib hold.

Symptom, N (%)	Grade 1	Grade 2	Total Grades 1-2
Fever	10 (50)	7 (35)	17 (85)
Body aches	7 (35)	2 (10)	9 (45)
Night sweats	3 (15)	3 (15)	6 (30)
Arthralgias	4 (20)	1 (5)	5 (25)
Chills	2 (10)	2 (10)	4 (20)
Headache	2 (10)	2 (10)	4 (20)
Fatigue	3 (15)	1 (5)	4 (20)
Weakness	1 (5)	1 (5)	2 (10)

Table 4. Clinical characteristics of WM patients who did and did not develop withdrawal symptoms.

Characteristic	Total (n=89)	Asymptomatic (n=69)	Withdrawal (n=20)	P-value
Age at WM diagnosis, years	60 (42-87)	60 (42-87)	60 (44-75)	0.93
Age ≥65 at WM diagnosis	57 (64%)	45 (65%)	12 (60%)	0.67
Age at ibrutinib initiation, years	67 (43-87)	68 (43-87)	66 (44-80)	0.56
Male sex	62 (70%)	47 (68%)	15 (75%)	0.56
Hemoglobin <10 g/dL	34 (38%)	25 (36%)	9 (45%)	0.48
Platelets <100 k/uL	8 (9%)	8 (12%)	0 (0%)	0.11
Serum B2M >3 mg/dL	69 (78%)	51 (74%)	18 (90%)	0.13
Serum IgM ≥4,000 mg/dL	33 (37%)	30 (43%)	3 (15%)	0.02
Bone marrow involvement	60% (5-95%)	60% (5-95%)	60% (5-95%)	0.82
CXCR4 mutation	25 (32%)	23 (37%)	2 (12%)	0.047
Prior treatment	70 (79%)	53 (77%)	17 (85%)	0.43
Time from WM to ibrutinib, months	49 (0.5-267)	58 (0.5-267)	43 (0.5-202)	0.84
Time on ibrutinib, months	23.0 (1.8-59.9)	23.1 (1.8-59.9)	23.0 (4.3-58.8)	0.84
VGPR on ibrutinib	13 (15%)	7 (10%)	6 (30%)	0.02
PR on ibrutinib	57 (64%)	43 (62%)	14 (70%)	
MR on ibrutinib	15 (17%)	15 (22%)	0 (0%)	
SD on ibrutinib	4 (4%)	4 (6%)	0 (0%)	

VGPR: very good partial response; PR: partial response; MR: minor response; SD: stable disease

Odds ratios for withdrawal symptoms:
Serum IgM ≥4,000 mg/dl: OR 0.23 (95% CI 0.06-0.86; p=0.03); **VGPR:** OR 2.63 (95% CI 0.76-9.15; p=0.10); **CXCR4 mutation:** OR 0.23 (95% CI 0.05-1.08; p=0.06).

Conclusion

We describe patient-reported symptoms that develop in about 20% of WM patients who held ibrutinib therapy. Such symptoms ensue within 2 days of holding ibrutinib and resolve rapidly following reinitiation of therapy. Clinicians should be aware of this phenomenon which may represent an ibrutinib withdrawal syndrome.