Ibrutinib dose reduction does not affect progression-free survival in patients with Waldenström macroglobulinemia

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Background

- Ibrutinib is an oral Bruton Tyrosine Kinase inhibitor, approved for the treatment of symptomatic Waldenstrom macroglobulinemia (WM) in the US and Europe.
- MYD88 and CXCR4 mutations affect progression-free survival (PFS) in patients with WM.
- In some cases, ibrutinib dose reductions are needed for the management of toxicity.
- However, it is unclear of ibrutinib dose reductions adversely affect PFS in WM patients.

Methods

- We included consecutive patients with a diagnosis of WM who started therapy with ibrutinib.
- We analyzed relevant clinical features and their association with the risk of dose reduction, using logistic regression models, as well as PFS, using Cox proportional-hazard regression models.
- Time to events was estimated using the Kaplan-Meier method.
- P<0.05 were considered statistically significant.

Results

- The median time to ibrutinib dose reduction to 280 mg PO QD was 155 days (95% CI 89-282 days), and median time to dose reduction to 140 mg PO QD was 55 days (95% CI 24-260 days).
- Reasons for ibrutinib dose reduction were cytopenia (n=13; 24%), arrhythmia (n=9; 17%), joint/muscle/bone pain (n=8; 15%), constitutional symptoms (n=6; 11%), skin changes/rash (n=5; 9%), mouth sores (n=4; 7%), gastrointestinal symptoms (n=3; 6%), infections (n=3; 6%), bleeding (n=2; 4%) and AST/ALT elevation (n=1; 2%).

Results

Table 1. Patients' characteristics

Characteristic	Did not reduce N=159	Reduced N=58	p-value
Age, years	65 (43-93)	71 (44-89)	<0.01
Age >65 years	74 (47%)	44 (76%)	<0.01
Male sex	107 (67%)	33 (57%)	0.16
Hemoglobin	10.6 (4-15.7)	9.9 (6.4-13.9)	0.01
Hemoglobin <11.5	107 (68%)	43 (75%)	0.30
Platelets	225 (17-639)	193 (22-606)	0.10
Platelets <100K	18 (12%)	7 (12%)	0.88
B2M	3.4 (1.4-12.4)	4.2 (1.6-14.2)	0.04
B2M >3	88 (64%)	36 (75%)	0.16
IgM	3511 (104-10,321)	3048 (137-9,000)	0.44
IgM >7000	11 (7%)	2 (4%)	0.35
BM involvement	60% (5-95%)	50% (5-95%)	0.52
BMBX >50%	90 (64%)	31 (55%)	0.27
IPSSWM 1	23 (24%)	9 (19%)	0.03
IPPSWM 2	53 (39%)	11 (23%)	
IPSSWM 3	50 (37%)	28 (58%)	
Treatment naïve	49 (31%)	15 (26%)	0.48
Previous lines	2 (1-8)	2 (1-6)	0.53
MYD88 L265P	141 (98%)	49 (98%)	0.97
CXCR4	54 (40%)	15 (33%)	0.39
TTIBR	3.3 (2.4-4.9)	3.7 (2.3-8)	0.32
VGPR	36 (22%)	18 (31%)	<0.01
PR	74 (47%)	36 (62%)	
MR	33 (21%)	4 (7%)	
SD/PD	16 (10%)	0 (0%)	
Major	110 (69%)	54 (93%)	<0.01

Table 2. Logistic regression analysis of the odds of ibrutinib dose reduction

Factor	OR (95% CI)	p-value
Age >65	3.61 (1.83-7.11)	<0.001
Male sex	0.64 (0.35-1.19)	0.16
HB <11.5	1.44 (0.72-2.86)	0.31
PLT <100K	1.07 (0.42-2.72)	0.88
B2M >3	1.70 (0.81-3.57)	0.16
IgM >7000	0.49 (0.11-2.28)	0.36
BMBX >=50%	0.70 (0.37-1.32)	0.27
IPSSWM 2 vs 1	0.76 (0.28-2.03)	0.59
IPSSWM 3 vs 1	2.05 (0.86-4.90)	0.11
Previously treated	1.28 (0.65-2.51)	0.48
MYD88 L265P	1.04 (0.11-10.3)	0.97
CXCR4	0.73 (0.36-1.49)	0.39
Major response	6.01 (2.06-17.5)	0.001

Table 3. Progression-free survival analysis

Factor	HR (95% CI)	p-value
Age >65	1.35 (0.72-2.54)	0.35
Male sex	0.78 (0.40-1.49)	0.45
HB <11.5	2.05 (0.90-4.66)	0.09
PLT <100K	3.91 (1.77-8.66)	0.001
B2M >3	1.17 (0.55-2.52)	0.68
IgM >7000	2.44 (0.86-6.91)	0.09
BMBX >=50%	0.77 (0.39-1.53)	0.46
IPSSWM 2 vs 1	0.93 (0.33-2.63)	0.90
IPSSWM 3 vs 1	2.31 (0.91-5.86)	0.08
Previously treated	1.31 (0.49-3.50)	0.59
MYD88 L265P	0.01 (0.00-0.09)	<0.001
CXCR4	3.02 (1.53-5.96)	0.001
Major response	0.23 (0.12-0.43)	<0.001
Dose reduction	1.19 (0.61-2.35)	0.61

Figure 1. Progression-free survival curves according to ibrutinib dose reduction

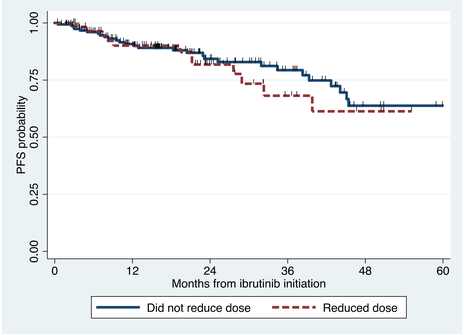
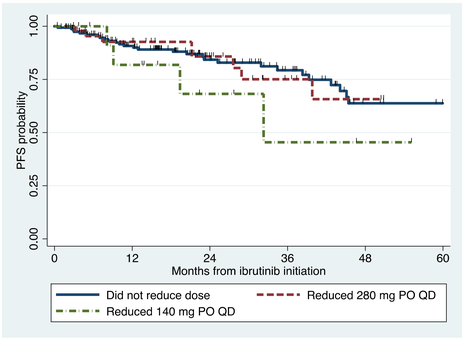


Figure 2. Progression-free survival curves according to ibrutinib dose reduction, including dose of 140 mg PO QD



Conclusion

Ibrutinib dose reduction was needed in 27% of patients with WM, with a median time to dose reduction of 5 months. Patients older than 65 years and patients who had attained major response were more likely to have a dose reduction. With a follow-up time of approximately 2 years, ibrutinib dose reduction was not associated with worse or better PFS in our cohort of patients with WM.

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