Ibrutinib Therapy in Patients with Waldenstrom Macroglobulinemia: outcomes outside of clinical trial setting

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Background: Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor was approved for the treatment of Waldenstrom Macroglobulinemia (WM) in January, 2015 based on the findings of a clinical trial of 63 previously-treated patients with WM.[1] Data on outcomes with this agent outside of clinical trials are limited.

Methods: Medical records of patients with WM seen consecutively between 02/01/2015 and 05/15/2018 at Mayo Clinic, MN were reviewed and patients with WM treated with ibrutinib at any point during their disease course were included. Refractoriness to prior therapy was defined as disease progression on therapy or within two months of stopping treatment. The response rates were assessed by WM VI International Workshop criteria. Adverse events were graded using National Cancer Institute Common Toxicity Criteria for Adverse Events v4.03. All time-to-event analyses were performed from the time of initiation of ibrutinib using the Kaplan-Meier method.

Results: Forty-five patients [previously treated, n=39 (87%), treatment-naïve, n=6] had received ibrutinib for WM. The median age was 66 years (range: 52-81 years) and the median ECOG performance score was 1 (range: 0-3) at the time of initiation of ibrutinib. Median number of therapies prior to ibrutinib for the previously-treated patients was 2 (range: 1-9) and 45% had received ≥3 prior lines of therapy. Of the 45 patients, 28 patients (23 previously treated, 5 treatment-naïve) had data for response assessment and 30 patients had toxicity data.

The baseline characteristics and laboratory parameters at initiation of ibrutinib are outlined in **Table 1a** and prior therapies, including refractoriness are mentioned in **Table 1b.** Overall response rates (ORR) was 86% and major-response rate (MRR) was 68%; ORR was100% and 83%, respectively in patients who received ibrutinib primary versus salvage therapy. Time to first and best response was 2.9 months (95% CI: 1.0-3.9) and 12.8 months (95% CI: 3.0-13.6), respectively. Clinically relevant endpoints in patients who received ibrutinib are outlined in **Table 2.** Adverse effects due to ibrutinib are mentioned in **Table 3.**

At the time of last follow-up, 16 (33%) patients had discontinued ibrutinib therapy. The reason for discontinuation was progression (n=6), elevated liver enzymes (n=3), cognitive changes (n=1), inability to achieve a deeper response than minor response (n=1), atrial fibrillation (n=3), consolidation with ASCT after achieving PR with ibrutinib (n=1), and severe fatigue (n=1). Ten patients were evaluable for IgM rebound after ibrutinib discontinuation. Of those, four (40%) had sudden increase in IgM level [median: 150% from the IgM level soon after ibrutinib discontinuation (range: 22%-502%)], within a median of 2 months (range: 1-3 months) and one required plasmapheresis for symptomatic hyperviscosity. At the date-of-last follow-up, two patients had died one of whom was on ibrutinib therapy at the time of death [pontine hemorrhage not related to AVM (n=1) and transformation to diffuse-large-B-cell-lymphoma, (n=1)].

Conclusions: Ibrutinib is an effective agent in WM patients with $MYD88^{L265P}$mutation. Our data regarding outcomes in non-trial setting appear comparable to the results observed in the pivotal clinical trial. [1] Hematologists should be aware of unique toxicities as well as IgM rebound following abrupt discontinuation of ibrutinib.

Table 1a: Baseline characteristics and laboratory parameters at ibrutinib initiation

Parameter	Patients, n=28[a]
Hemoglobin, median (range), g/dL	10.7 (6-16)
Platelet count, median (range), g/dL	215 (29-517)
Serum kappa FLC in kappa restricted disease, median (range), mg/dL	3.3 (0.3-60.5)
Serum lambda FLC in lambda restricted disease, median (range), mg/dL	6.17 (6.17-6.17)
Kappa Free light chain involved, n (%)	17 (61)
Involved/uninvolved free light-chain ratio	3.0 (1.1-1592)
IgA, median (range), mg/dL	39 (5-325)
IgG, median (range), mg/dL	436 (13.6-1920)
IgM, median (range), mg/dL	2520 (97-8130)[b]
M-spike (g/dL)	1.6 (0.1-5.7)
$MYD88^{L265P}$ mutation (%)	94[b]
Viscosity (cp)	2.2 (1.1-4.2)
Lactate dehydrogenase (U/L)	163.5 (96-604)
Urine protein (g/24h)	0.3 (0.02-2.3)
Beta 2 microglobulin (ug/mL)	4.07 (2.2-11.7)
Marrow Lymphoplasmacytic lymphoma cells, median % (range)	30 (0-90)

a: $MYD88^{L265P}$ mutation status was available in 16 patients and of those, 15 had L265P mutation while 1 was wild type.
b: One patient with normal serum IgM and renal AL amyloidosis was given ibrutinib therapy

Table 1b: Previous treatment lines in patients who received ibrutinib

Treatment before ibrutinib, n=45	Patients exposed (%)	% refractory
Rituximab monotherapy	49	4
BR	18	2
DRC	16	0
Lenalidomide-based regimen	4	0
Bortezomib-based regimen	20	7
Autologous stem cell transplant	14	0

BR: bendamustine and rituximab, DRC: Dexamethasone rituximab and cyclophosphamide

Table 2: Clinically relevant end points

Clinically relevant and point	Entire cohort, n=28	Ibrutinib as 1st line, n=5 (18%)	Ibrutinib as subsequent line, n=23 (82%)
ORR, (%)	86	100	83
Major response rate	68	80	65
CR, (%)	-	-	-
VGPR, (%)	4	0	4
PR, (%)	75	80	61
MR, (%)	21	20	17
Time to 1st response, months (95% CI)	2.9 (1.0-3.9)	3.0 (1.0-17)	2.7 (0.9-4.0)
Time to best	12.8 (3.0-13.6)	15.6 (3.0-18.5)	11.3 (3.0-13.2)

response, months (95% CI)			
Median follow-up, months (95% CI)	19 (8.7-22.2)	18.5 (4.0-38)	19.5 (8.75-22)
PFS, months (95% CI) Proportion of patients alive and without progression at 6, 12, 18 months	NR (27-NR) 96%, 87%, 77%	NR (NR-NR) 100%, 100%, 100%	NR (15-NR) 91%, 85%, 72%
DOR, months (95% CI)	NR (26-NR)	NR (NR-NR)	NR (12-NR)
OS, months (95% CI) Proportion of patients surviving at 18 months	NR (95% CT: NR-27) 94%	NR (95% CT: NR-NR) 100%	27 (95% CI: 27-NR) 93%

CI: Confidence Interval, NR: Not reached, ORR: Overall response rate, CR: Complete response, VGPR: Very good partial response, PR: Partial response, MR: Minimal response, PFS: Progression free survival, DOR: Duration of response, OS: Overall survival.

Table 3: Adverse effects in patients due to ibrutinib therapy

Adverse effect	Patients, (%), n=30
Anemia	10
Patients in grade ≤3	7
Patients in grade >3	3
Thrombocytopenia	7
Number of patients in grade ≤3	3
Number of patients in grade >3	3
Neutropenia	7
Number of patients in grade ≤3	3
Number of patients in grade >3	3
Diarrhea	4
Atrial fibrillation	10
Fatigue	17
Rash	10
Hemorrhage	3
Neuropathy	3
Headache	3
Transaminitis	10
Cognitive changes	3

Reference

1. Treon, S.P., et al., *Ibrutinib in Previously Treated Waldenström's Macroglobulinemia.* New England Journal of Medicine, 2015. **372**(15): p. 1430-1440.