Ibrutinib for the Treatment of Bing-Neel Syndrome

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Background

- Bing-Neel syndrome (BNS) is a rare complication of Waldenstrom macroglobulinemia (WM), in which WM cells gain access to the CNS causing neurological deficits[1].
- Treatment options in patients with BNS are limited
- Ibrutinib, an oral BTK-inhibitor, and the only approved therapy in WM, can penetrate into the CNS[2], but data on BNS is lacking.

Aim

To evaluate the efficacy of ibrutinib in patients with BNS

Methods

- Retrospective study in 2 centers
- Diagnosis of BNS was established in pts with WM by radiological and/or cytological evidence of CNS involvement by WM
- Response was assessed based on recently published criteria[3]
- Ibrutinib was given at 420-560 mg PO qd until disease progression or intolerable toxicity

Results – Patients Characteristics

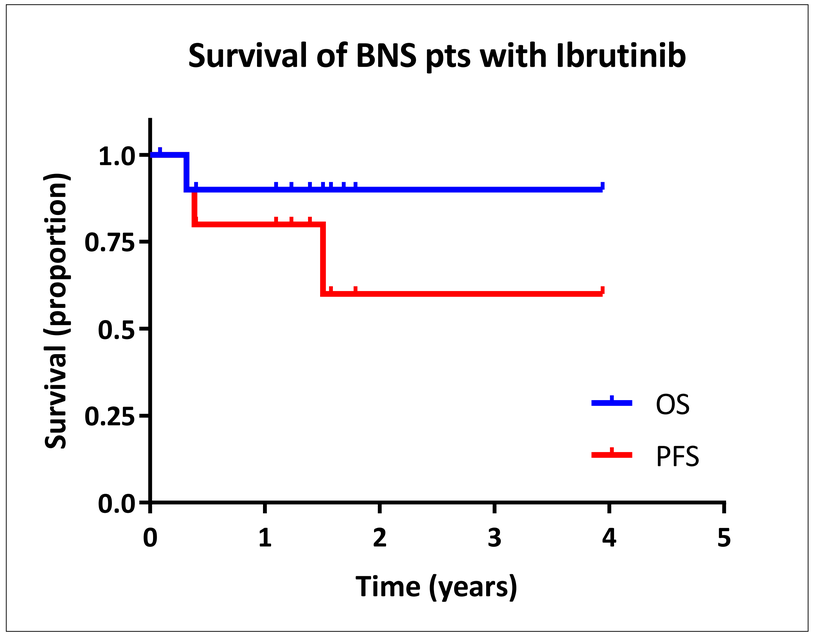
- 11 patients are reported; median age @ WM diagnosis was 60 years (48-73)
- Median lines of therapy for WM prior to BNS diagnosis was 2 (0-7);
  4 patients (36%) were untreated prior to BNS
- The median age @ BNS diagnosis was 65 years (49-78), with a median of 6.6 years from WM to BNS diagnosis (0.1-15)
- Most common BNS symptoms were motor (n=7), sensory (5), and cognitive (4) deficits, and seizures (3).
- MRI findings included leptomeningeal enhancement (6) and brain masses (4)
- CSF cytology was positive in 7 pts, confirmed by flow cytometry in all 7.
- Biopsies were performed in 3 patients and confirmed Dx
- Dx was based on MRI-only in 1 pt
- Median serum IgM prior to ibrutinib initiation was 1218 mg/dl (range 616-3330 mg/dl), and Hb was 11.8 g/dl (9.2-13.5 g/dl).
- Median lines for BNS prior to Ibrutinib was 1 (0-4); it was the first line in 5 pts

No.	Age at WM Dx	Sex	Prior Rx for WM[$]	Time to BNS (y)	Prior Rx for BNS[#]	Presenting symptoms	MRI findings	CSF	IgM (mg/dl)	Hb (g/dl)	Ibrutinib Dose (mg)
1	53	M	3	12.7	1	Ataxia	Mass	+	1000	12	420
2	62	M	0	0.6	0	Sensory neuropathy	Enhancement	+	3330	11	420
3	49	F	3	3.9	1	SM neuropathy	Enhancement	+	1370	9	420
4	56	M	5	9.6	0	None	Peri-optic masses	NA	2030	12	420
5	56	M	0	9.4	4	Hearing loss, ataxia, cognitive	Enhancement & mass	NA	1012	13	560
6	60	F	0	0.1	0	Sensory neuropathy	Normal	+	735	13	560
7	61	F	3	15.0	0	Cognitive, aphasia, seizure	Enhancement & masses	-	1078	14	560
8	72	M	7	6.6	0	SM neuropathy, progressive tremor	Enhancement	+	1789	12	420
9	48	F	0	1.0	3	Seizure, tremor, dysarthria	Dural mass	+	1218	12	560
10	73	F	1	3.0	1	Cognitive, SM neuropathy	Enhancement	+	1538	9	560
11	65	M	2	9.9	2	Ataxia, cognitive	Enhancement	+	616	13	560

[$]Including alkylators (n=11), anti-CD20 antibodies (11), nucleoside analogues (4), proteasome inhibitors (2), immunomodulators (2), and autologous transplant (1) [#]Including high-dose methotrexate (n=5), intrathecal chemotherapy (2), bendamustine (1) and radiation therapy (2). [*]SM, sensory-motor

Response Assessment

- Symptoms improved in 8 of 9 patients with available data
- At best response, median IgM and Hb levels were 384 mg/dl (222-3330 mg/dl) and 13.3 g/dl (range 9.2-15 g/dl), respectively.
- MRI findings improved in 7/8 patients and were stable in 1
- CSF studies cleared in 2 patients and were stable in 2 patients.
- To date, 4 pts have stopped ibrutinib: 2 with PD - next lines were MTX/TMZ and FR; 1 d/t intolerance for BNS (→ BR); and 1 died with suspected BNS progression.



- 1-year & 2-year PFS rate were 69% (95% CI 30-89%) and 57% (22%-81%).
- 2-year OS rate was 90% (95% CI 47-99%).

Conclusion

Ibrutinib is a safe and effective treatment option for patients with BNS

References

[1]Castillo et al. Br J Haematol 2016; [2]Mason et al. Br J Haematol 2016; [3]Minnema et al. Haematologica 2016

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There are no relevant conflicts of interest to disclose