Abstract: P1145

Title: ZANUBRUTINIB IN BING-NEEL SYNDROME: EFFICACY AND TOLERABILITY

Abstract Type: Poster Presentation

Topic: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical

Background:

Bing-Neel syndrome (BNS) is a rare complication of Waldenström macroglobulinemia (WM), in which malignant lymphoplasmacytic lymphoma (LPL) cells invade the central nervous system (CNS). There are no prospective trials on BNS treatment. Bruton's tyrosine kinase inhibitors (BTKi) are an effective and safe treatment for WM and are known to penetrate the blood-brain barrier. Ibrutinib, a first generation BTKi, was reported to yield rapid clinical and radiological improvement in the majority of BNS patients; however, off-target activity results in frequent adverse events (AEs). Zanubrutinib, a next-generation covalent BTKi, demonstrated a trend towards faster and deeper responses, with a more favorable toxicity profile compared to ibrutinib in a comparative trial in WM.

Aims:

We aimed to assess the efficacy of zanubrutinib treatment on neurological symptoms, radiological abnormalities, and cerebrospinal fluid (CSF) involvement, as well as its safety and tolerability, in patients with BNS.

Methods:

In this retrospective study, participating centers were asked to report all consecutive BNS patients treated with at least one dose of zanubrutinib. Patients receiving concurrent chemotherapy were excluded. After written informed consent, data from electronic health records on clinical, radiological and CSF examinations were collected. AEs were graded according to the CTCAE, v5.0. Data collection is currently ongoing and will be updated at the time of the meeting.

Results:

Currently, 15 BNS patients from 1 UK and 3 Dutch centers are included (Table 1). In 13 cases (86.7%), BNS was identified in previously diagnosed LPL and in 2 as new-onset LPL. Ten patients (66.7%) were previously treated for LPL at time of BNS diagnosis. Eight patients (53.3%) had previously received treatment for BNS, including chemo-immunotherapy (n=7) and ibrutinib (n=2). Median age at start of zanubrutinib was 68 years (IQR 63-75). All patients received 320mg zanubrutinib daily.

At initiation of zanubrutinib, 12 patients (80%) had neurological symptoms, including sensory deficits (n=6), motor deficits (n=5), memory loss (n=5), upper and/or lower limb ataxia (n=4), seizures (n=4), radicular pain (n=4), cranial nerve deficits (n=3), behavioral changes (n=3), headache (n=3), decreased consciousness (n=2) and vertigo (n=1). There was radiological evidence of CNS involvement in 12 patients (80%), including leptomeningeal (n=9), cauda equina (n=6), intraparenchymal (n=5), and/or cranial nerve (n=4) enhancement, and hydrocephalus (n=2). Cytologic assessment and/or flow cytometry of CSF was positive for clonal B cells in 10/13 tested cases (76.9%). Molecular analysis of CSF was positive for MYD88L265P in 10/10 (100%) tested cases at BNS diagnosis and/or start of zanubrutinib.

Median follow-up time was 7.7 months (IQR 5.6-12.3), all patients are alive and still on zanubrutinib treatment. Of 12 patients with neurological symptoms at baseline, 11 (91,7%) experienced clinical improvement with complete resolution of symptoms in 5. Out of 5 patients with repeated CSF analysis, 3 demonstrated persistent detectable clonal LPL cells. Of 12 patients with MRI abnormalities, 6 had radiological improvement, repeated MRI is awaited in the remaining 6. No relapses have occurred. There was 1 AE grade ≥3 (9.1%, febrile

neutropenia with temporary zanubrutinib dose reduction).

Summary/Conclusion:

Zanubrutinib achieved a clinical response in 92% of BNS patients and was accompanied by acceptable toxicity. Our preliminary findings indicate that zanubrutinib may be an effective and well-tolerated treatment modality for BNS.

AB and JvdM contributed equally to this work

Table 1: Baseline characteristics and BNS treatment outcome per case

Case	Sex; age at start zanubrutinib	Prior LPL treatment	Prior BNS treatment	Best clinical response *	Best radiological response *	Best cytological response in CSF *	Follow-up, months
1	M; 67	RCP, ofatumumab-bendamustine	-	Resolution	Resolution	Resolution	14
2	M; 60	BDR, rituximab, bendamustine	-	Improvement	*No abnormalities at start*	Persisting	4
3	F; 75	DRC	-	Improvement	Improvement	Persisting	8
4	M; 68	-	Ibrutinib	Resolution	Awaited	*No abnormalities at start*	7
5	M; 74	CyBorD	-	Resolution	Improvement	Awaited	13
6	M; 68	R-bendamustine	MATRix	Improvement	Awaited	*No CSF analysis at start*	8
7	M; 74	DRC	HD-MTX-AraC-Rituximab	*No abnormalities at start*	*No abnormalities at start*	Awaited	14
8	M; 50	RT, R-CVP	R-AraC-MTX	Resolution	Improvement	*No CSF analysis at start*	4
9	M; 62	R-bendamustine	R-AraC-MTX, R-ICE	*No abnormalities at start*	Awaited	Persisting	12
10	M; 67	R-bendamustine; DRC	R-AraC-MTX	Resolution	Improvement	Resolution	12
11‡	M; 60	-	R-AraC-MTX, R-ICE	*No abnormalities at start*	Awaited	Awaited	7
12	M; 76	-	-	Improvement	*No abnormalities at start*	Awaited	1
13	M; 63	Rituximab	Steroids, ibrutinib, fludarabine, MTX	Improvement	Improvement	Awaited	23
14	F; 77	-	-	Awaited	Awaited	Awaited	0
15	M; 77	-	-	Improvement	Awaited	Awaited	6

* Case 11 concerns an IgG-secreting LPL. All other cases are WM.

AraC: cytarabine, BDR: bortezomib-dexamethasone-rituximab, BNS: Bing-Neel syndrome, CyBorD: Cyclophosphamide-Bortezomib-Dexamethasone, CSF: cerebrospinal fluid, F: female, HD: high-dose, ICE: Iphosphamide-Carboplatin-Etoposide, IgG: immunoglobulin G, LPL: lymphoplasmacytic lymphoma, M: male, MATRix: methotrexate-cytarabine-thiotepa-rituximab, MTX: methotrexate, R: Rituximab, RCP: rituximab-cyclophosphamide-prednisone, R-CVP: rituximab-cyclophosphamide-vincristine-prednisone, RT: radiotherapy, WM: Waldenström macroglobulinemia

Keywords: Lymphoplasmacytic lymphoma, Bruton's tyrosine kinase inhibitor (BTKi), CNS lymphoma, Waldenstrom's macroglobulinemia