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SHORT REPORT

Haematological Malignancy – Clinical

Zanubrutinib for the treatment of Bing–Neel syndrome

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Summary
Infiltration of the central nervous system by malignant lymphoplasmacytic cells is a rare complication of Waldenström macroglobulinaemia (WM) and is referred to as Bing–Neel syndrome (BNS). Traditionally, the treatment of BNS included chemotherapy, but in more recent years, the oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib has become a standard therapy for WM and the most common therapy for BNS due to the drugs tolerability and ability to cross the blood–brain barrier. Zanubrutinib, a second-generation covalent BTK inhibitor with fewer off-target effects, is also effective in WM. In this series, we report on the successful use of zanubrutinib in nine patients with BNS, of whom five had prior exposure to ibrutinib and four were naïve to BTK inhibitors.

KEYWORDS
Bing–Neel syndrome, ibrutinib, Waldenström macroglobulinaemia, zanubrutinib

INTRODUCTION

Waldenström macroglobulinaemia (WM) is a rare lymphoma characterized by a monoclonal immunoglobulin M (IgM) paraprotein and a lymphoplasmacytic infiltrate in the bone marrow. WM has a variety of manifestations, including anaemia, hyperviscosity and neuropathy, as well as rare manifestations, such as Bing–Neel syndrome (BNS).

BNS occurs in 1% of patients and is defined as infiltration of the central nervous system (CNS) by the malignant lymphoplasmacytic cells of WM.[1] BNS is typically slowly progressive and can present with a variety of neurological symptoms, including gait and balance issues, cranial nerve deficits, limb paralysis or weakness, cognitive deficits, headaches, impaired consciousness or psychiatric symptoms.[1] Due to the rarity of BNS, there are no prospective clinical trials to guide treatment decisions.

Previous series have described the efficacy of cytotoxic therapies, such as high-dose methotrexate, high-dose cytarabine, fludarabine and bendamustine, although these regimens have varying levels of efficacy and significant toxicity.[1–4] More recently, the covalent Bruton tyrosine kinase (BTK) inhibitor ibrutinib, commonly used for the treatment of WM, has become the standard therapy for BNS based on the ability of ibrutinib to cross the blood–brain barrier and achieve clinical, haematological and radiologic responses in BNS.[1,2,4–10] Zanubrutinib, a second-generation covalent BTK inhibitor, has demonstrated efficacy and less toxicity than ibrutinib and was approved by the Food & Drug Administration for treating WM.[2] As zanubrutinib has known CNS penetration,[11,12] we have used this therapy for treating patients with BNS, initially in patients who were intolerant to ibrutinib and later in ibrutinib-naïve patients. Here, we report nine cases of BNS treated with zanubrutinib.

METHODS

Medical records of patients with BNS treated with zanubrutinib at our institution were retrospectively reviewed. Demographic information and clinical characteristics were obtained, in addition to specific data regarding WM diagnosis, treatment, treatment responses and patient outcomes.

Haematological responses were defined as per the 11th International Workshop for WM (IWWM11) response criteria with complete response defined by the absence of monoclonal IgM, serum IgM in the normal range, no evidence of lymphoma on bone marrow aspirate/biopsy and absence of extramedullary disease on imaging; very good partial response defined by ≥90% reduction in serum IgM or a normal serum IgM; partial response as ≥50% to <90% reduction in serum IgM; minor response as ≥25% to <50% reduction in IgM; and stable disease as <25% reduction to <25% increase in serum IgM.[13]

Charts were additionally reviewed to obtain information regarding BNS diagnosis, treatment and responses, including cerebral spinal fluid (CSF) results and CNS imaging. BNS responses were defined as complete remission if there was a resolution of neurological symptoms with normalization of CSF and magnetic resonance imaging (MRI) findings; partial response required improvement in neurological symptoms or complete resolution of symptoms but with maintained radiologic abnormalities; non-response was characterized as persistence or progression of neurologic symptoms, radiologic findings or CSF findings; and relapsed disease required appearance of new symptoms or radiologic findings attributed to BNS.[4]

RESULTS/DISCUSSION

We report here the outcome of nine patients treated for BNS with zanubrutinib (Table 1), including six females (67%). All patients (100%) had *MYD88 L265P*, and zero patients had a *CXCR4* mutation (3 had unknown *CXCR4* status). Three of six patients (50%) had a *TP53* mutation (3 had unknown *TP53* status).

In all patients, the BNS diagnosis followed the WM diagnosis by a median of 4.3 years (range, 0.1–23.1). The median age at BNS diagnosis was 71 years (range, 66–78). Six patients had been previously treated for WM at the time of BNS diagnosis, with a range of 1–6 prior treatments. Median haemoglobin was 11.7 g/dL (range, 10.8–14.2), and serum IgM was 1359 mg/dL (range, 467–4252). BNS was diagnosed based on the following CSF findings in eight patients; 7 (88%) had a B-cell clone detected on flow cytometry, 5 (63%) had malignant cells identified on cytology, 5 (63%) had *MYD88 L265P* detected and 4 (50%) had a B-cell clone detected by *IgH* gene rearrangement. The ninth patient did not have the former testing and was diagnosed based on an elevated CSF IgM and total protein with brain and spine MRI findings consistent with BNS. All patients had brain and spine MRIs, of which five of nine patients (56%) had abnormal findings at the time of BNS diagnosis (example shown in Figure 1). Four patients had findings consistent with leptomeningeal disease, and one involved the brain's central grey, subcortical and deep white matter. Presenting symptoms included paraesthesias, vision changes, balance changes, cognitive changes, vertigo or vestibular dysfunction, aphasia and tremors.

Patients received zanubrutinib 320 mg once daily (2 patients), 160 mg twice daily (6 patients) and 80 mg twice daily (1 patient) due to frailty and cytopenias related to ibrutinib. At the time of zanubrutinib initiation, four patients had never had BNS treatment. Five patients had prior BNS therapy. One patient previously treated with ofatumumab plus methotrexate (1 cycle), and then, 1 month of 420 mg ibrutinib was transitioned to zanubrutinib due to the improved safety profile. Four other patients had well-controlled BNS on ibrutinib. Three patients had received 420 mg ibrutinib daily, and one patient received 280 mg ibrutinib daily due to thrombocytopenia at the higher dose. All four patients transitioned to zanubrutinib due to adverse events associated with ibrutinib, including palpitations/atrial fibrillation, back pain, skin rash, reflux and constipation. These adverse events all improved with transition to zanubrutinib.

For those on ibrutinib before initiating zanubrutinib (range: 1 month to 5.6 years), all patients had improved neurologic symptoms on ibrutinib. After the transition to zanubrutinib, one patient maintained a PR of their BNS but had systemic WM progression from a previous haematological VGPR at 5.9 months after a total of approximately 6 years on BTK inhibitor therapy. One patient achieved a haematological VGPR, as well as a PR of BNS, which was maintained approximately 2 years until the patient died due to causes unrelated to WM or BNS. While on zanubrutinib, two additional patients maintained a PR of their BNS, both achieving additional improvement in neurological symptoms. They both achieved and have maintained a PR of BNS and a VGPR of their systemic disease and remain on zanubrutinib at 15.9 months and 31.3 months later respectively. The fifth patient had significant neurological deficits present at that time of transition from ibrutinib to zanubrutinib (only 1 month after starting ibrutinib) and the patient has now continued zanubrutinib for 19.4 months with complete resolution of neurologic symptoms and MRI brain abnormalities consistent with a PR of their BNS. Of note, CSF testing was not repeated in these nine patients, so achievement of a CR of BNS was not possible, as current criteria require repeat CSF to document the absence of malignant cells.

Of the four patients with previously untreated BNS, all achieved a PR of their BNS and had improvement in neurological symptoms at a median of 6.4 months (range: 0.3–11.7) after initiating zanubrutinib. The one patient with abnormal CNS imaging had an improvement of these findings on repeat imaging at 6 months. All four patients remain on zanubrutinib, with a median time on therapy of 26.2 months (range: 12.6–41.8).

Due to deeper responses and an improved safety, zanubrutinib became a first-line treatment option for WM.[11] Zanubrutinib is known to cross the blood–brain barrier; therefore, this therapy has been explored in treating CNS lymphoma.[12] A case report was published describing the efficacy of zanubrutinib in one woman with relapsed BNS, and more recently, two abstracts were presented describing 15 patients and 11 patients with BNS treated with zanubrutinib.[14–16]

We previously described the persistence of residual malignant cells in the CSF in half of BNS patients treated with ibrutinib despite durable clinical and radiological improvement in more than 80% of patients.[5] A similar finding was reported in a series of BNS patients treated with

TABLE 1 Clinical characteristics and outcomes of nine patients with Bing–Neel syndrome treated with zanubrutinib.

Patient	Presenting symptoms at BNS diagnosis	Prior BNS therapy	Time on ibrutinib (months)	MRI findings at time of zanubrutinib initiation	MRI after treatment	BNS response	Haematological response	Time on zanubrutinib (months)/ zanubrutinib dose	Patient status at time of manuscript preparation
Previously untreated BNS									
1	Paraesthesias in the lower extremities, vision changes	None	n/a	Enhancement of nerve roots in cauda equina and epidural enhancement at the thoracic spine	Improvement in nerve root and epidural enhancement	PR	VGPR	13.6/160 m BID	Stable BNS on zanubrutinib
2	Balances issues, memory loss	None	n/a	None	n/a	PR	VGPR	15.1/160 mg BID	Stable BNS on zanubrutinib
3	Fatigue, balance issues, lightheadedness, paraesthesia in the lower extremities	None	n/a	None	n/a	PR	SD	41.8/320 mg daily	Stable BNS on zanubrutinib
4	Dizziness, vestibular dysfunction	None	n/a	None	n/a	PR	PR	12.6/160 mg BID	Stable BNS on zanubrutinib
Prior exposure to ibrutinib									
5	Confusion, amnesia, aphasia	1 cycle MTX/ ofa then ibrutinib	1	Multifocal enhancing lesions in the cerebral hemispheres with lepto- and pachymeningeal enhancement over the frontal lobe	Complete resolution	PR	Unconfirmed CR	19.4/160 mg BID	Stable BNS on zanubrutinib
6	Peripheral neuropathy, memory issues, vertigo	Ibrutinib	2	Diffuse pachymeningeal enhancement	Complete resolution	PR	VGPR	31.3/160 mg BID	Stable BNS on zanubrutinib
7	Aphasia, confusion	Ibrutinib	8	None	n/a	PR	VGPR	11.2/320 mg daily	Death due to unrelated cause
8	Peripheral neuropathy, confusion, memory issues	Ibrutinib	5	None	n/a	PR	PR	15.9/160 mg BID	Stable BNS on zanubrutinib
9	Tremors and upper extremity weakness	Ibrutinib	67.5	None	n/a	PR	VGPR	5.9/80 mg BID	Transitioned to alternate therapy due to relapse of systemic WM

Abbreviations: BID, twice daily; BNS, Bing–Neel syndrome; CR, complete response; MTX, methotrexate; n/a, not applicable; PR, partial response; SD, stable disease; VGPR, very good partial response.

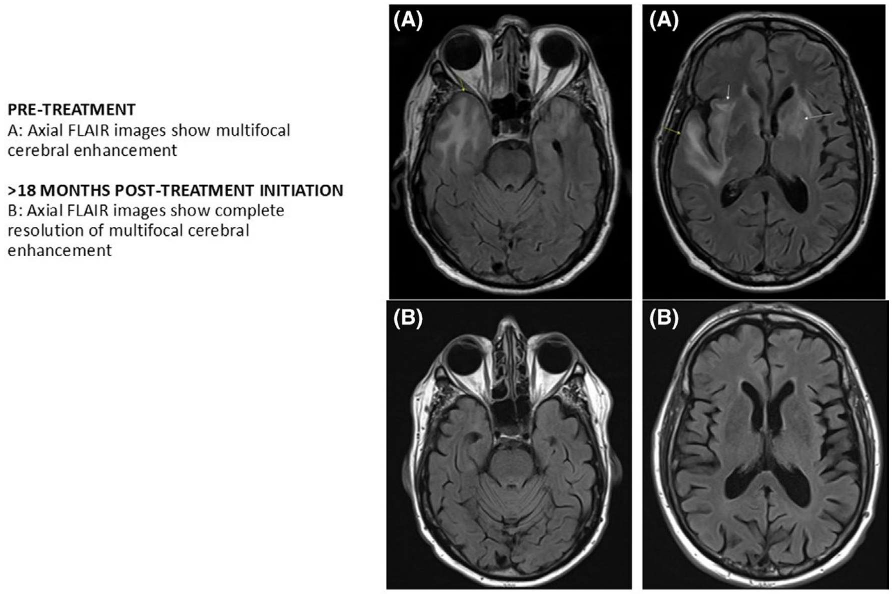

FIGURE 1 Brain magnetic resonance imaging (MRI) example.

chemotherapy.[2] Based on these findings, CSF clearance is not typically used to assess response in BNS, akin to extramedullary disease or bone marrow burden not being used to assess response in WM.[13] In our practice, we no longer monitor CSF disease burden in BNS patients who are improving symptomatically and radiologically.

In this series, we have demonstrated the efficacy of zanubrutinib in nine patients with BNS who were previously treated with ibrutinib or BTK inhibitor naïve. All nine patients maintained or achieved a PR of their BNS on zanubrutinib, and no one had progression of their BNS at the time of this report. Since zanubrutinib dosing in this small cohort varied, we are unable to comment on a difference in efficacy based on dosing, but we do favour maintaining a full dose of 160 mg twice daily or 320 mg once daily, when possible, to help maximize CNS penetration. All five patients that transitioned from ibrutinib maintained a PR of their BNS and three of these patients had continued improvement in neurological symptoms after initiating zanubrutinib. Based on our findings, zanubrutinib can be considered an effective treatment option for newly diagnosed BNS or for patients transitioning from ibrutinib due to the potential for or the presence of adverse effects.

AUTHOR CONTRIBUTIONS

CAF, JJC, SPT and SS cared for patients. JS and SS wrote the original manuscript. AR-G collected data for this project. All others edited and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

JJC received research funds or honoraria from Abbvie, AstraZeneca, Beigene, Cellectar, Johnson & Johnson, Kite, Loxo, Mustang Bio, Nurix and Pharmacyclics. SS received research funds or honoraria from ADC Therapeutics, Beigene and Cellectar. ST received research funding and/or consulting fees from Abbvie/Pharmacyclics Inc., Janssen Oncology Inc., Beigene Inc., Eli Lilly Pharmaceuticals, Bristol Myers Squibb and Ono Pharmaceuticals. ST is a named inventor of MYD88 and CXCR4 testing for WM and has assigned all interests to their institution.

DATA AVAILABILITY STATEMENT

All data collected for this series are included in the manuscript.

PATIENT CONSENT STATEMENT

All patients consented to data collection for research purposes.

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