

Venetoclax for the Treatment of Bing-Neel Syndrome

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Bing-Neel syndrome (BNS) is a rare complication of Waldenström macroglobulinemia characterized by a variety of neurologic symptoms, such as cognitive deficits, gait and balance issues, headaches, seizures, and cranial nerve deficits. According to the consensus panel guidelines from the 12th International Workshop on Waldenström Macroglobulinemia (IWWM-12), a Bruton tyrosine kinase (BTK) inhibitor is the preferred first-line therapy for BNS, with zanubrutinib favored when available. In patients with relapsed disease, additional treatment options, such as bendamustine or fludarabine may be utilized, but treatment options remain limited and additional therapeutic options are needed. Venetoclax, a BCL-2 inhibitor previously shown to be effective for the treatment of relapsed or refractory WM, is known to cross the blood-brain barrier and therefore may be an effective therapy for the treatment of BNS.

Herein, we report our clinical experience with venetoclax as a treatment for BNS in five patients. The median patient age at BNS diagnosis was 61 years (range, 43-73) and four patients were males. *MYD88* mutation was present in three patients (1 unknown, 1 wild-type), one patient had a *CXCR4* mutation (2 unknown), and two had *TP53* mutations (1 wild-type, 2 unknown). Two patients had BNS diagnosed simultaneously with WM, whereas three patients had BNS diagnosed after their WM diagnosis. Two patients had multiple prior lines of therapy for WM prior to BNS diagnosis. Baseline symptoms of BNS are shown in Table 1. Four out of five patients had abnormal brain/spine MRI at the time of BNS diagnosis. All patients had abnormal CSF findings confirming BNS. Prior to venetoclax therapy all patients had previous exposure to a BTK inhibitor, with two patients having developed resistance to BTK inhibition even prior to the diagnosis of BNS. The median prior lines of therapy was 3 (range, 2 to 5). Venetoclax was prescribed at 400 mg daily in three patients (one of whom was taking a weak CYP3A4 inhibitor, ticagrelor) and at 800 mg daily in two patients. The median time on venetoclax was 16 months (range, 7 to 40). Three of the five patients had documented MRI improvement (at 5, 7, and 40 months), three patients had improvement in clinical symptoms, and two had stable symptoms. Treatment was tolerated without Grade ≥ 3 adverse effects, except one patient who had stable BNS and passed away from complications of a COVID-19 infection approximately seven months after starting venetoclax. Two patients had progressive disease, one with isolated BNS progression and one with systemic transformation to DLBCL. Two patients remain on venetoclax with a partial response at 20 and 40 months after treatment initiation.

In this case series, we report results of five patients with BNS treated with venetoclax. Three patients had improvement in MRI findings on venetoclax, three had symptom improvement, and two patients remain on therapy with more than 20 months of disease control. The optimal dose of venetoclax therapy is not known, as patients responded to both 400 and 800 mg daily, but additional exploration of this treatment in BNS is warranted.

Patient	Symptoms at BNS diagnosis	Timing of BNS diagnosis	WM therapy prior to BNS diagnosis	Prior BNS therapy	Brain and spine MRI findings	MRI response after treatment	BNS response	Hematologic response	Approximate time on venetoclax and venetoclax dose	Patient status at time of abstract preparation
1	Tinnitus, imbalance, cognitive impairment, back pain, and decreased hearing	Diagnosed simultaneously with WM	n/a	High dose-MTX, ibrutinib, BR	Multiple areas of leptomeningeal enhancement in the brain and spinal cord, with thickening and enhancement of the right globe, optic nerves, and optic sheath	Improved	Partial response	Very good partial response	16 months / 400 mg daily*	Passed away secondary to progressive BNS
2	Slurred speech, behavioral changes, seizures	Diagnosed simultaneously with WM	n/a	Ibrutinib, CLR131	Diffuse thickening and enhancement of the cauda equina nerve roots	Stable	Partial response	Very good partial response	20+ months (ongoing) / 400 mg daily	Stable BNS on venetoclax
3	Vision changes	Diagnosed after WM	BDR, oprozomib, ibrutinib, BR, loncastuximab	None	Enhancement of the left optic nerve with T2 abnormality of the left optic tract	Improved	Partial response [#]	Very good partial response	10 months / 800 mg daily	Transformation to DLBCL, now s/p chemotherapy and CART cell therapy
4	Headaches, paresthesias, cognitive impairment	Diagnosed after WM	None	MTX, FR, zanubrutinib	Enhancement of the nerve roots of cauda equina and L1-L5	Improved	Partial response	Minor response	40+ months (ongoing) / 400 mg daily	Stable BNS on venetoclax
5	Cognitive impairment	Diagnosed after WM	CaRD, zanubrutinib, BR, IRD	none	Normal	n/a	Stable disease	Stable disease	7 months / 800 mg daily	Passed away related to covid infection

BDR, bortezomib/dexamethasone/rituximab; BR, bendamustine/rituximab; CaRD, carfilzomib/rituximab/dexamethasone; FR, fludarabine/rituximab; IRD, ixazomib/rituximab/dexamethasone; MTX, methotrexate

*on concomitant CYP3A4 inhibitor

[#]patient also received concomitant radiation