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Report of Consensus Panel 2 from the 12th International Workshop on the management of Bing-Neel syndrome in patients with Waldenstrom's Macroglobulinemia

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ABSTRACT

Consensus panel 2 from the 12th International Workshop on Waldenstrom Macroglobulinemia was tasked with updating the guidelines on the diagnosis and management of patients with Bing-Neel syndrome (BNS). In this panel we have summarized the clinical symptoms that may be present with BNS, discussed the criteria required for diagnosis of BNS, made recommendations for follow-up imaging, and proposed revised guidelines for response assessment in BNS. The key recommendations from the 12th International Workshop on WM (IWWM-12) Consensus panel 2 include: (1) the establishment of zanubrutinib as a standard therapy for treatment of BNS; (2) recommendations on imaging and CSF evaluation during treatment and follow-up of BNS; and (3) revised response criteria in view of new data showing that malignant cells can persist in the CSF of many patients treated with BTK-inhibitors. New categorical response categories proposed include that for a Clinical Complete Response and Progressive Disease.

Introduction

Central nervous system (CNS) involvement by the malignant lymphoplasmacytic cells of Waldenström macroglobulinemia (WM), known as Bing Neel Syndrome (BNS), is a rare complication that occurs in approximately 1% of patients with WM [1,2]. BNS can manifest with a heterogeneous spectrum of clinical symptoms, resulting in variable morbidity and mortality outcomes [3–5]. Due to the rarity of this disorder there are no large databases or prospective trials available to guide diagnosis, treatment, and follow-up testing in these patients. The prior consensus guideline provided direction on the diagnosis, treatment and response criteria for BNS [6]. Since the development of the prior guideline, BTK inhibitors have been adopted as a standard therapy for BNS and new insights on treatment goals and optimal response

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evaluation have been gained. This consensus panel proposes new guidelines for BNS diagnosis and management incorporating more recently available therapies and the experience gained in recent years regarding BNS.

What are the symptoms of Bing Neel syndrome (BNS) and in whom should BNS be suspected?

BNS can present with a variety of neurologic symptoms and may differ based on the area of CNS involvement. For example, meningeal involvement may present with headache, nausea/vomiting, cranial neuropathies or vision changes. Parenchymal involvement of the medulla or brain may present with changes in cognition, dementia, seizures, impaired consciousness, motor deficits including paralysis, or aphasia. A combination of these symptoms may occur in patients with simultaneous parenchymal and leptomeningeal disease [7]. Sensory symptoms may also occur and may be mistaken for peripheral neuropathy, which is common in WM. Peripheral neuropathy that is not length-dependent or is asymmetric should raise suspicion for BNS, which can occur independent of or concomitantly with peripheral neuropathy.

Ocular involvement has been reported in approximately 4% to 6% of BNS cases with various clinical presentations, such as optic nerve involvement, infiltration of orbital fat, and distinct orbital masses [3,5,8–13]. Other WM-related entities such as symptomatic hyperviscosity or ocular involvement by diffuse large B cell lymphoma can cause similar symptoms, so we recommend thorough assessment by an ophthalmologist in any case with visual changes to assess the etiology of these symptoms.

BNS can occur in patients with IgM MGUS, in those without a prior diagnosis of MGUS or WM, or in those with known WM that is either previously untreated or treated. BNS can develop during active WM-directed therapy. BNS was the first manifestation of WM in 36% of patients in a French series of patients with BNS and in those with a prior diagnosis of WM the interval between this diagnosis and the onset of BNS was long (median 8.9 years) [4]. This study also found that BNS occurred in some patients without any other evidence of systemic WM progression. Therefore, unexplained, persistent neurologic symptoms in a patient with IgM MGUS or WM should warrant evaluation for BNS.

What are the diagnostic criteria and what are the diagnostic tests that need to be performed?

The initial evaluation in a patient with suspected BNS should involve brain and whole spine MRI images before and after gadolinium contrast administration. While most patients will show abnormalities on MRI, a nonaberrant MRI does not rule out BNS [3,4]. BNS-related aberrancies may involve leptomeningeal/dural and/or parenchymal infiltration of the brain and/or spine. Additionally, cerebral spinal fluid (CSF) should be sampled with the CSF sent for the following studies: cytology, flow cytometry, MYD88 L265P mutational PCR, and/or immunoglobulin heavy chain (IgH) gene rearrangement testing. CSF cytology may demonstrate atypical lymphocytes with plasmacytoid differentiation. Flow cytometry may detect a monoclonal B-cell population with light chain restriction. MYD88 PCR will often detect a MYD88 mutation, and the IgH gene rearrangement testing may detect a B-cell clone even in those cases in which flow cytometry does not detect a clonal population or the disease is MYD88 wild-type.

CSF total protein, IgM level and cell count with differential may also be helpful in diagnosis, as any of these laboratory results may be abnormal in BNS, but without evidence for specific thresholds. A recent case series of 46 patients reported a median CSF protein of 1.4 g/L (range, 0.25-4.69), CSF IgM of 4.13 g/L (0.147-475), and CSF leukocyte count of 15.5 cells/mm^3 (1-153) [5]. Additionally, immunofixation of the CSF, as well as the IgM index, calculated as "(CSF IgM [mg/L]/serum IgM [g/L])/(CSF albumin [mg/L]/serum albumin [g/L])" may be useful in detecting the presence of excess or clonal IgM in the CNS [14]. When interpreting results of the CSF sample, clinicians should be aware of possible bloody contamination of the CSF, especially for the very sensitive molecular tests. Of note, some of the above tests can be abnormal in other entities as well, such as MYD88 positive primary CNS lymphoma, so if suspicion for high grade lymphoma exists this should be excluded with additional work-up as the treatment course should be modified if high-grade lymphoma is found.

In many cases, cytology, flow cytometry, MYD88 and IgH gene rearrangement testing is abnormal and the diagnosis of BNS can be confirmed with high specificity. In cases in which only the high sensitivity MYD88 PCR is abnormal we recommend correlation with additional CSF testing, MRI imaging, and the clinical symptoms to ensure that a diagnosis of BNS is accurate as MYD88 testing in the absence of other clinical signs/symptoms may not be sufficient for BNS diagnosis.

In cases with a parenchymal lesion without circulating disease in the CSF or when a lumbar puncture is not safe to perform due to bleeding risk or high intracranial pressure, a brain biopsy is recommended. Immunohistochemistry should be performed to assess B-cell and plasma cell antigens, such as CD19, CD20, CD79b, and CD38, alongside molecular testing to evaluate for MYD88 mutations and IGH gene rearrangements. In these cases, it is helpful to correlate the brain biopsy results with the bone marrow biopsy results to confirm that the clone is related to the patient's systemic disease. Of note, if a prior bone marrow biopsy was not performed, the patient should have a bone marrow biopsy with MYD88 testing to confirm the diagnosis of WM.

What is the prognosis of a patient with BNS, concerning life expectancy and neurological response?

Due to the availability of effective therapies, the survival of BNS patients is thought to be similar to survival of those patients with WM without BNS. With currently applied therapies, reported overall survival rates in BNS cohorts range from 80% at 2 years, ±88% at 3 years, and 93% at 3 years [5,15,16].

Neurologic symptoms may improve in some patients, but due to the lower regenerative capacity of the nervous system some symptoms may remain. Published studies are mostly retrospective and do not always provide information on improvement. In the ibrutinib series most patients (85%) had improvement or resolution of their neurologic symptoms within 3 months, with complete resolution of symptoms seen in 18% of patients [15]. High rates of clinical improvement have also been reported in patients treated with zanubrutinib, although long term follow-up to assess overall survival is not yet available.

What are the treatment goals in regards to symptoms, cerebral spinal fluid response, imaging, and hematologic responses?

Treatment should be initiated only in those patients with symptomatic BNS. In those patients with neurologic symptoms, the goal of treatment is to prevent progression of neurological symptoms and, for most patients, also improving clinical/neurologic symptoms. As with WM, there is no known cure for BNS, so prolonging progression free survival and maintaining quality of life is paramount. Complete eradication of the disease is not required to achieve a clinical response, as it is known that with the most effective therapies in BNS, ibrutinib and zanubrutinib, approximately 50% of patients continue to show malignant cells on CSF. In addition, MRI changes may not completely revert to normal but im-

Table 1
Proposed IWWM-12 response criteria for Bing-Neel syndrome.

Categorical BNS response	Proposed revision for BNS categorical response	Previous BNS categorical response
Complete response (CR)	Resolution of all reversible neurologic symptoms related to BNS with normalization of CSF, including negative cytology, flow cytometry and MYD88 testing, and normalization of MRI findings, if applicable. Absence of new neurologic symptoms or MRI findings.	Resolution of all neurologic symptoms with normalization of the CSF and MRI findings.
Clinical complete response (CCR)	Resolution of all reversible neurologic symptoms and resolution of MRI abnormalities attributed to BNS.	Not defined in previous criteria.
Partial response (PR)	Improvement, but not complete resolution of reversible neurologic symptoms related to BNS.	Improvement in neurologic symptoms, but with maintained radiologic abnormalities with negative CSF.
Nonresponse	No improvement in neurologic symptoms related to BNS.	Persistence or progression of neurologic symptoms, radiologic findings or CSF findings.
Progressive disease	Appearance of new or progression of neurologic symptoms related to BNS or worsening of MRI findings attributed to BNS.	(Only relapse defined) Reappearance of new signs and symptoms attributed to BNS or progression or new findings on MRI attributed to BNS.

provement of the MRI findings is seen in the majority of patients [15,16].

Systemic hematologic responses may, but do not always, correlate with the susceptibility of the malignant cells in the CSF to a particular therapy. Therefore, it is important to track also the hematologic response with routine IgM measurements. Signs of systemic disease progression should raise suspicion that the BNS may also progress and in that setting there should be a low threshold to consider repeat CNS imaging and a change in therapy if neurologic symptoms develop.

This consensus panel proposes that the response criteria for BNS be altered from that previously considered the standard (Table 1) [6]. This is mainly due to the disconnect between clinical response and CSF clearance and the inability to quantify CSF response. We propose the following IWWM-12 revised response criteria which are summarized in Table 1, alongside the previous criteria. New categories denoting Clinical Complete Response, and Progressive Disease has been added in the revised response criteria.

As mentioned, the goal of treatment is improvement in symptoms, so in those patients with incidentally discovered BNS or patients with symptoms related to other neurological causes, treatment of BNS is not indicated.

How do we manage and treat BNS both first line and in the relapse setting?

BTK inhibitors have become the most frequently used treatment for BNS. Ibrutinib, a first generation BTK inhibitor, became the first FDA approved therapy for the treatment of WM based on the high response rates [17,18]. Due to the known ability of ibrutinib to cross the blood-brain barrier, this therapy has been used in BNS with approximately 85% of patients having improvement or resolution of neurologic symptoms and with enhanced safety profile compared to high dose chemotherapy [15,19–22]. More recently, zanubrutinib, a second generation BTK inhibitor with an improved safety profile compared to ibrutinib, has shown to be at least equally effective as ibrutinib in patients with WM. Multiple case series have reported the efficacy of this therapy in BNS as well, with clinical response ranging from 73% to >90% [16,22–25]. A small series of 9 patients included 5 patients that transitioned from ibrutinib to zanubrutinib, as well 4 patients with treatment naïve BNS [23]. All 9 patients maintained or improved control of BNS with zanubrutinib therapy. The 4 patients with treatment naïve disease had a median time on therapy of 26.2 months with no patients having BNS progression at time of publication.

Tirabrutinib, a second-generation covalent BTK inhibitor with proven efficacy in WM has been approved for clinical use in Japan [26]. High blood brain barrier penetration rate was reported in a prior clinical trial of refractory CNS lymphoma [27]. It has also been reported to have efficacy in treatment of some naïve and relapsed BNS, but is not widely available for use [28,29]. BTK inhibitors can be used in both treatment naïve and relapsed disease if the LPL cells still remain sensitive to BTK inhibition.

In cases of relapsed disease, when BTK inhibitors are unavailable or ineffective, or when the patient's BNS and/or WM is refractory to a covalent BTK inhibitor, there are multiple chemotherapy-based regimens that have sufficient blood-brain barrier penetration and proven efficacy in BNS based on prior cases reports and series. Bendamustine and fludarabine-based regimens, often in combination with rituximab, can be administered as finite therapies in the outpatient setting and have shown high response rates, albeit with significant toxicity, such as infection and stem cell toxicity [3,4,30]. High dose methotrexate and high dose cytarabine can also be utilized for BNS but may not be appropriate for frail patients or those with impaired renal function, and typically requires repeated hospitalizations for administration. Intrathecal monotherapy is not typically recommended except in cases with meningeal disease only when other systemic therapies are not viable options.

Radiotherapy can also be utilized in select cases that require urgent local control, such as in those patients with orbital involvement with risk of visual impairment.

What therapies are in development and may play a role in the future treatment of BNS?

BTK degraders are a novel therapy currently being explored in B-cell malignancies, including WM. Early data with this class of drugs demonstrate CNS penetration, particularly with the BTK degrader NX-5948 which is currently in a clinical trial that allows enrollment of patients with WM, other B-cell malignancies, and patients with primary or secondary CNS lymphoma (NCT05131022) [31,32]. Additional BTK degraders, such a NX-2127 and BGB-16673, are also being utilized in clinical trials and may play a future role in BNS treatment (NCT04830137, NCT05006716, NCT06634589, NCT05294731).

The BCL-2 inhibitor, venetoclax has been effectively used for the treatment of relapsed or refractory WM [33]. Venetoclax has known penetration of the blood-brain barrier and is a suitable candidate to be explored as a potential treatment for BNS [34,35]. Pirtobrutinib, a noncovalent BTK inhibitor, has shown to be effective in WM and has become a standard WM therapy in multiple areas of the world [36]. Its penetration of the blood-brain barrier has not yet been described, but should be explored in the future as potential treatment of CNS involvement by WM or other lymphomas.

Additional therapies that may be explored in the future for BNS are CART cell therapies, which have known CNS activity and case reports documenting activity in WM [37,38], and the IRAK-4 inhibitor, CA-4948, which has also been shown to cross the blood brain barrier and may be effective in WM due to known dysregulation of IRAK signaling in WM [39,40].

How do we assess response in patients with treated BNS and what is the recommended follow up (frequency, measurements, neurologic evaluation)?

Ideally imaging would show a response to therapy, but imaging changes are often delayed or may not correlate with clinical response. Therefore, we do not recommend continued imaging to routinely assess disease response. We recommend 1 repeat brain and spine MRI when a patient has achieved a good clinical remission, has achieved a stable clinical response, or if the patient is not responding at 3 to 6 months after treatment initiation as prior cases series have reported a time of 3 to 6 months for symptom and imaging improvement [15,23]. If initial repeat imaging shows stability or disease improvement then no repeat imaging is required after that time if the patients continues to have stable or improved neurologic symptoms.

We do not routinely recommend repeating lumbar punctures with CSF for response assessment analysis due to the risks associated with this procedure and the established understanding that approximately half of patients will have persistently abnormal CSF without clearance of malignant cells. This is particularly relevant for patients treated with BTK inhibitors, as these therapies increase the risk of procedure-related bleeding and have been associated with IgM rebound during treatment holds [41–43]. Therefore, we do not recommend routine repeat CSF testing in patients that are clinically responding to treatment. Instead, we recommend clinical monitoring for improvement of neurologic symptoms. A repeat lumbar puncture may be considered appropriate if the clinician is considering therapy cessation, in the absence of symptomatic improvement, if there is suspicion of an alternative diagnosis (ie, transformation to an aggressive lymphoma or infection), or other select cases.

Conclusions

BNS is a rare but treatable disease if recognized. BTK inhibitors are the first treatment choice due to high clinical response and low toxicity of treatment. These new consensus guidelines are meant to be of help to clinicians treating BNS patients and are updated with new insights gained from newly reported case series and patient cases.

Declaration of competing interest

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