

How we manage Bing–Neel syndrome

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Summary

Bing–Neel syndrome (BNS) is an uncommon presentation of Waldenström macroglobulinaemia (WM), seen during the course of the disease in about 1% of patients. BNS occurs when WM cells gain access to the central nervous system (CNS) causing neurological deficits. The diagnosis of BNS is suggested by the presence of radiological abnormalities, such as leptomeningeal enhancement on magnetic resonance imaging and confirmed by the presence of clonal lymphoplasmacytic cells and *MYD88* L265P in the cerebrospinal fluid. The treatment of BNS requires agents with good penetration into the CNS, such as fludarabine, methotrexate and cytarabine. The novel Bruton Tyrosine Kinase inhibitor ibrutinib has shown CNS-penetrating properties, and recent data suggest a therapeutic role in BNS. In this review, we will discuss the clinical and pathological features, diagnostic criteria, treatment options and outcomes of patients with BNS.

Keywords: Waldenström Macroglobulinaemia, Bing–Neel syndrome, ibrutinib.

Over the last 75 years, our understanding of Waldenström macroglobulinaemia (WM) has widened. Nowadays, we recognize WM as a lymphoplasmacytic lymphoma in which the malignant cells produce a monoclonal IgM paraprotein (Swerdlow *et al.*, 2017). The malignant cells can harbour acquired mutations in *MYD88* and *CXCR4*, which can be detected in 90–95% and 30–40% of the cases, respectively (Treon *et al.*, 2012; Hunter *et al.*, 2014). Clinically, WM can be greatly diverse: patients can be asymptomatic, but also can develop anaemia, PN and hyperviscosity among other clinical manifestations. Extramedullary manifestations of WM are rare and could include pleural effusions and renal involvement, as well as central nervous system (CNS) involvement.

In 1936, Drs. Jens Bing and Axel von Neel reported two cases of patients with macroglobulinaemia who developed subacute neurological deficits (Bing & Neel, 1936), an entity which would come to be known as Bing–Neel Syndrome (BNS). The two described patients did not have evidence of myelomatous lesions in their long bones by routine x-ray imaging, and no microscopic evaluation of the bone marrow was performed at the time. It is of great interest that this initial report was published approximately eight years prior to the seminal report of two cases of incipient myelomatosis associated with anaemia, macroglobulinaemia and coagulopathy by Dr. Jan Waldenström (Waldenström, 1944).

Bing–Neel Syndrome is a rare complication of WM, seen in approximately 1% patients, and is associated with substantial morbidity and mortality. BNS can occur at any time during the disease process, and cases have been reported, for example, while patients are responding to systemic therapy, in the absence of systemic disease and as the initial manifestation of WM. The diagnosis of BNS is sometimes elusive and its management has not been standardized, which poses significant challenges. There have been recent initiatives on standardizing diagnostic and response criteria, as well as advances for treatment approaches to BNS (Minnema *et al.*, 2017). The purpose of this review is to provide our approach to the management of patients with BNS.

What are the clinical features of BNS?

Bing–Neel Syndrome should be suspected in patients with WM who develop neurological symptoms concerning for a central process. Two retrospective studies accounting for about 80 patients with a formal diagnosis of BNS have shed some light on the most common neurological deficits seen in these patients. Simon *et al.* (2015) reported balance disorder and gait abnormalities as the most common deficits, occurring in 48% of BNS patients. Cranial nerve deficits and cognitive impairment were reported in 36% and 27% of patients, respectively, while sensory deficits, headaches and back or limb pain were reported at 25%, 18% and 18%, respectively. The study by Castillo *et al.* (2016) reported limb motor deficits and altered mental status, each in 35% of patients, while cranial nerve deficits, sensory deficits and headaches were reported in 29%, 12% and 12% of the patients, respectively. A minority of patients presented with

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seizures associated with brain masses due to BNS, a less common radiological finding that is discussed below. It is important to emphasize that there is not one clinical feature pathognomonic of BNS.

Bing–Neel Syndrome can present at any during the course of the disease in WM patients. In a case series, the median time from WM to BNS diagnosis was 3 years (range 0–16 years), 30% of WM patients had not received systemic therapy for WM prior to the diagnosis of BNS, and one half of these patients was diagnosed with BNS at the time of WM diagnosis (Castillo *et al*, 2016). In this study, another 30% of patients were diagnosed with BNS while receiving active systemic therapy for WM. In another case series, the median time from WM to BNS diagnosis was 4 years (range 1–9 years), and in 36% of patients, BNS was the first manifestation of WM (Simon *et al*, 2015).

Bing–Neel Syndrome symptoms should be appropriately differentiated from the more common WM-related morbidities of IgM-related peripheral neuropathy (PN) and hyperviscosity. IgM-related PN should be suspected in patients who present with symmetrical, length-dependent sensory deficits affecting the limbs in a bilateral and symmetrical manner (D'Sa *et al*, 2017). The progression of the sensory deficits typically occurs over months to years, and nerve conduction studies show a component of demyelination. In some cases, the titres of anti-myelin associated glycoprotein are elevated. As BNS and PN can coexist, BNS should be suspected in patients with PN with asymmetrical distribution, predominant motor deficits or other atypical features. Recurrent nosebleeds, progressive headaches, blurred vision and slow mentation can help differentiate symptomatic hyperviscosity from BNS (Minnema *et al*, 2017). Hyperviscosity should be suspected in patients with a markedly increased serum IgM levels, as symptomatic hyperviscosity is rare in patients with serum IgM level <30 g/l (Gustine *et al*, 2017). A retinal examination can provide valuable information, as changes associated with hyperviscosity, such as retinal haemorrhages and retinal vessel engorgement, tortuosity and “sausaging” can be visualized. Retinal imaging can be obtained, if available.

How do we diagnose BNS?

The diagnosis of BNS is challenging, and it typically involves a combination of clinical suspicion as well as radiological abnormalities and, in the best-case scenario, histological confirmation. To establish a diagnosis of BNS, we routinely perform a brain and spine magnetic resonance imaging (MRI) scan with gadolinium, followed by a lumbar puncture. Cerebrospinal fluid (CSF) is sent for cytology, flow cytometry and polymerase chain reaction (PCR) for *IGH* gene rearrangement and *MYD88* L265P.

Once a diagnosis of BNS is suspected, the next best step is to obtain brain and entire spine MRI with gadolinium administration. The MRI protocol should include fluid-

attenuated inversion recovery and T1-weighted sequences before and after gadolinium injection. Brain and/or spinal MRI abnormalities can be visualized in approximately 80% of patients with BNS (Simon *et al*, 2015; Castillo *et al*, 2016). The most common MRI abnormality is leptomeningeal enhancement, which is seen in about 80% of BNS patients with MRI abnormalities, while brain masses are less common and account for 20% of the cases. MRI should be obtained prior to performing a lumbar puncture, to exclude focal mass effects or obstructive hydrocephalus, as well as to avoid non-specific enhancement that can occur because of CSF sampling. Despite the usefulness of MRI in BNS diagnosis, there is not one radiological finding pathognomonic of BNS. Therefore, MRI does not eliminate the need for CSF examination as an important component of the evaluation for BNS. Other causes of MRI abnormalities, such as infections or cerebrovascular disease, should be evaluated and managed accordingly. Conversely, a normal brain and spine MRI does not reliably exclude a diagnosis of BNS in the appropriate clinical setting. An MRI scan from a patient with BNS affecting the brain and spine is shown in Fig 1A–C. If MRI were not available, computed tomography scanning of the head and spine with intravenous contrast can be considered, although this technique has lower sensitivity than MRI for neuroimaging.

The gold standard for a diagnosis of BNS is the demonstration of WM cells on CSF examination or, less frequently, on a brain tissue biopsy. Cytological examination of the CSF can show atypical lymphocytes with plasmacytic morphology. However, making a diagnosis of BNS based solely on cytological evaluation should be discouraged. The flow cytometric profile of lymphoplasmacytic cells in WM is characterized by positive expression of pan B-cell markers, such as CD19, CD20, CD22, CD79a and CD79b, as well as CD27 and CD52, while positive expression of CD5, CD10 and CD23 is rarely seen (Owen *et al*, 2003). Plasma cells typically express CD138 and IgM. In BNS, the lymphoplasmacytic cells involving the CNS must have a similar profile than the malignant cells in the bone marrow (Simon *et al*, 2015; Castillo *et al*, 2016). Although the presence of WM cells in peripheral blood is infrequent, caution should be exercised to avoid peripheral blood contamination of the CSF sample, which could render a false positive result.

Molecular testing on CSF can provide important support for the diagnosis of BNS, using PCR assays for *IGH* rearrangements and mutated *MYD88* (L265P). In the study by Castillo *et al* (2016), *IGH* rearrangements and the *MYD88* L265P mutation were detected in 94% and 100% of the BNS patients tested. Similarly, caution should be exercised to avoid peripheral blood contamination and subsequent false positive results. Also, false negative results may occur due to low burden of disease in CSF. The identification of an *IGH* rearrangement with the same base sequence in CSF and bone marrow can provide strong evidence in favour of a diagnosis of BNS. Multiple studies have detected the *MYD88* L265P

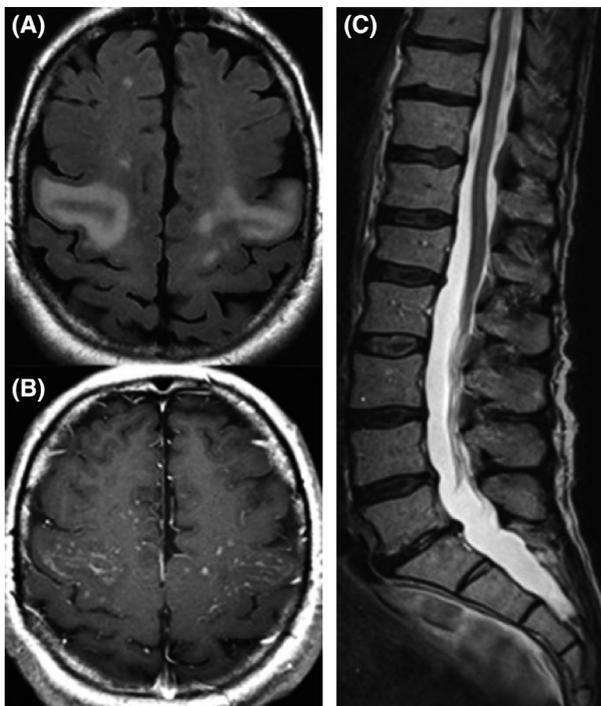


Fig 1. Magnetic resonance imaging abnormalities in Bing-Neel syndrome. (A) Parenchymal involvement of the brain, increased signal abnormalities in both pre-central regions in axial fluid-attenuated inversion recovery (FLAIR) sequence. (B) Brain parenchymal involvement, multiple nodular contrast enhancement in both pre-central regions in axial T1 sequence after contrast media administration. (C) Cauda equina thickening T2 sagittal sequence. Reprinted with permission from: Minnema, M.C., Kimby, E., D'Sa, S., Fornecker, L.M., Poulain, S., Snijders, T.J., Kastiris, E., Kremer, S., Fittsiori, A., Simon, L., Davi, F., Lunn, M., Castillo, J.J., Patterson, C.J., Le Garff-Tavernier, M., Costopoulos, M., Leblond, V., Kersten, M.J., Dimopoulos, M.A. & Treon, S.P. (2017) Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. *Haematologica*, **102**, 43–51.

mutation in 90–95% of patients with WM using high sensitivity PCR assays (Jimenez *et al*, 2013; Mori *et al*, 2013; Poulain *et al*, 2013; Varettoni *et al*, 2013; Schmidt *et al*, 2015). The sole identification of the *MYD88* L265P mutation in the CSF, however, is not diagnostic for BNS, because this mutation can also be detected in a substantial proportion of patients with primary CNS lymphoma (Montesinos-Rongen *et al*, 2011; Gonzalez-Aguilar *et al*, 2012; Nakamura *et al*, 2016). The *MYD88* L265P mutation can also be detected in a minority of patients with chronic lymphocytic leukaemia (CLL) or marginal zone lymphoma (MZL) and low-grade lymphoproliferative disorders, in which CNS involvement can also rarely develop (Jesioneck-Kupnicka *et al*, 2013; Ueba *et al*, 2013; Rossi *et al*, 2014; Strati *et al*, 2016; Wanquet *et al*, 2016; Ayanambakkam *et al*, 2018).

Data on the prevalence of *CXCR4* mutations in BNS are rather limited. *CXCR4* mutations can be detected in 30–40% of patients with WM (Hunter *et al*, 2014; Roccaro *et al*,

2014). These mutations are localized in the C-terminal of the *CXCR4* gene and more than 30 mutations have been described (Xu *et al*, 2016). Sanger sequencing is a commonly employed method for detecting *CXCR4* mutation but has a lower sensitivity than PCR-based assays for detection of the mutation and is not available in most clinical laboratories. *CXCR4* mutations were not detected in the few BNS patients tested (Poulain *et al*, 2014; Mason *et al*, 2017), which could have been false negative results given the concerns with sensitivity described above. The development of PCR-based and next generation sequencing techniques with deeper penetration could help to improve the detection rate of *CXCR4* mutations in the CSF of patients with BNS.

Cerebrospinal fluid protein electrophoresis and immunofixation could be of help when making a diagnosis of BNS but these assays are not readily available in most clinical laboratories, and the diagnostic value of these tests in BNS is still under investigation. In our practice, we do not routinely use CSF protein electrophoresis and immunofixation for the diagnosis of BNS.

How do we treat BNS?

Treatment should be recommended in symptomatic patients with a definitive diagnosis of BNS. It is unclear at the moment if asymptomatic patients with evidence of WM cells in the CNS should be treated. The goal of therapy in BNS should be to reverse the patient's clinical symptoms and hopefully induce a prolonged progression-free survival (PFS). As with systemic WM, a complete eradication of the disease is not mandatory, as long as the patients are clinically benefiting from therapy. The armamentarium against BNS is, as expected, limited to agents with CNS penetration: intrathecal chemotherapy and radiation therapy. Given the scarcity of patients with BNS and lack of consensus recommendations on therapy, the treatment of BNS is not standardized.

The use of high-dose methotrexate or high-dose cytarabine in BNS stems from the experience on the treatment of patients with primary CNS lymphoma (Poulain *et al*, 2014; Simon *et al*, 2015; Castillo *et al*, 2016). Although effective, these agents are toxic, and the administration of these treatments is usually provided in an inpatient setting. High-dose methotrexate can be associated with renal toxicity, myelosuppression and mucositis. High-dose cytarabine can cause myelosuppression and cerebellar toxicity. It is our recommendation to reserve these treatments for patients with relapsed disease who are considered fit for intensive therapy.

Other effective agents against BNS, but with lower toxicity, include bendamustine, fludarabine and cladribine. A number of reports have suggested activity of bendamustine in patients with lymphoproliferative disorders involving the CNS. However, there are limited data on the CNS-penetrating ability of bendamustine. A recent study in patients with primary CNS lymphoma treated with bendamustine showed a low area under the curve exposure ratio (Kim *et al*, 2018).

Bendamustine has been used, however, with responses in several patients with BNS, both in the frontline as well as in the relapsed setting (Simon *et al*, 2015; Varettoni *et al*, 2015; Castillo *et al*, 2016). The toxicity profile of bendamustine includes rash, constipation and a small risk of secondary myeloid neoplasms. The nucleoside analogues, fludarabine and cladribine, also have CNS penetration. This was initially supported by the increased risk of neurotoxicity in patients exposed to high doses of these drugs (Cheson *et al*, 1994). In a study of 21 patients with astrocytoma and solid cancers metastatic to the brain, CNS concentrations of cladribine appeared to be dose-dependent (Saven *et al*, 1993). Clinically, fludarabine was shown to be effective in patients with CLL or MZL involving the CNS (Knop *et al*, 2005; Matmati *et al*, 2010). In patients with BNS, both cladribine and fludarabine have induced clinical benefit based on prior reports (Richards, 1995; Delgado *et al*, 2002; Simon *et al*, 2015; Castillo *et al*, 2016; Vos *et al*, 2016). However, these agents carry a specific toxicity profile characterized by an increased risk of immunosuppression, myelosuppression, secondary myeloid neoplasms and refractory cytopenias.

Mounting data have suggested clinical efficacy of the oral Bruton Tyrosine Kinase (BTK) inhibitor, ibrutinib, in patients with CLL and mantle cell lymphoma involving the CNS, as well as in patients with primary CNS lymphoma (Bernard *et al*, 2015; Chamoun *et al*, 2017; Wanquet *et al*, 2017). Ibrutinib was also shown to be effective in BNS patients, based on early reports (Cabannes-Hamy *et al*, 2016; Castillo *et al*, 2016). The CNS penetration properties of ibrutinib were formally evaluated in a patient with BNS who was refractory to high-dose methotrexate and rituximab and had relapsed shortly after bendamustine and intrathecal liposomal cytarabine (Mason *et al*, 2017). The patient was started on ibrutinib 560 mg by mouth once daily. Within 4 months of ibrutinib, there was clinical and radiological improvement. Synchronous measurements of plasma and CSF concentrations of ibrutinib showed a percentage CSF/plasma of 2.2–3.5% a few hours after dosing with ibrutinib. The level of ibrutinib in CSF was above the 50% inhibitory concentration (IC₅₀) for BTK inhibition. Additional reports have further reported the efficacy of ibrutinib on BNS patients with tumoural forms, as well as in the frontline setting (Boudin *et al*, 2018; O'Neil *et al*, 2018; Plander *et al*, 2018; Tallant *et al*, 2018).

A recent report on 28 patients treated with single agent ibrutinib have provided additional insights on the safety and efficacy of this agent in BNS patients (Castillo *et al*, 2019). The median age at BNS diagnosis was 65 years with male predominance (57%). The median time from WM diagnosis to BNS diagnosis was 4 years, and 36% of patients were diagnosed with BNS within 12 months of WM diagnosis. The most common neurological symptoms at ibrutinib initiation included motor, cognitive and sensory deficits. Cytological and flow cytometric abnormalities were seen in all patients, MRI abnormalities in 89%, and the MYD88 L265P

was detected in the CSF of all the patients tested. All patient received single agent ibrutinib, 46% at 560 mg and 54% at 420 mg by mouth once daily. Ibrutinib was the first BNS treatment in 39% of patients. Within 3 months of therapy, 85% of patients experienced symptomatic improvement, 60% radiological improvement and 58% had cytological CSF clearance. Approximately 40% of patients had CSF persistence of disease despite improvement and/or resolution of symptoms and radiological abnormalities. These benefits were sustained over time, with a 2-year event-free survival (EFS) probability of 80%. EFS was defined as time from ibrutinib initiation to unacceptable toxicity, disease progression or death from any cause. There was no detectable difference in EFS based on ibrutinib dose (560 mg or 420 mg daily). Grade 3 or 4 adverse events on ibrutinib included infections, neutropenia, bleeding and cardiac arrhythmia.

Rituximab monotherapy is not readily advised in BNS patients given its limited CNS penetration. However, rituximab could be considered as an adjunct to ibrutinib, fludarabine or bendamustine, for example, in patients who also need systemic control of the disease. Systemic rituximab therapy can be associated with infusions reactions, serum IgM flare and increased risk of infections. The experience with intrathecal rituximab in BNS is limited. Intrathecal rituximab was shown to be effective in patients with other B-cell lymphomas involving the CNS, but has been associated with toxicity (Villela *et al*, 2008; Kim *et al*, 2011; Bromberg *et al*, 2012; Czyzewski *et al*, 2013; Ceppi *et al*, 2016), and could be considered in the relapsed or palliative setting. Intrathecal chemotherapy has been associated with short-lived clinical benefit in patients with BNS, and it is better reserved for use in combination with systemic therapy or in the palliative setting. Radiotherapy can also be used in BNS patients, especially in cases with symptoms related to localized involvement of the CNS, such as exclusive cauda equina involvement.

Our recommendation is to treat BNS patients with ibrutinib in the frontline setting, if available and not previously used for the treatment of systemic WM. Fludarabine, bendamustine, cladribine, high-dose methotrexate and high-dose cytarabine are treatment options that can be considered in the relapsed setting. As with systemic therapy, stem cell toxic agents should be avoided in young patients. There are no data to suggest that BNS patients with brain masses or leptomeningeal enhancement should be treated differently, except for the use of intrathecal chemotherapy, which would be indicated in the latter. Our recommended treatment algorithm is shown in Fig 2.

How do we assess response to treatment in BNS?

Until recently, the response criteria for BNS had not been standardized. As part of the 8th International Workshop for WM in Amsterdam, a Task Force was formed, which

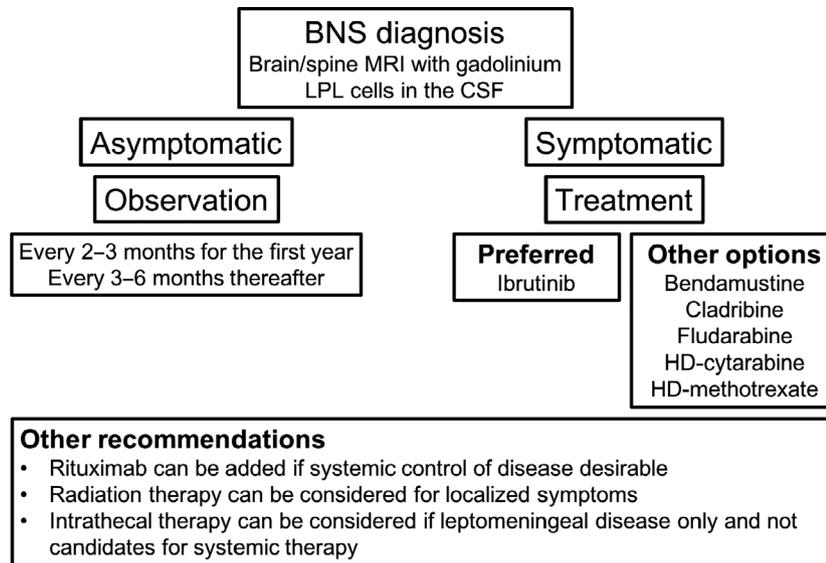


Fig 2. Recommended treatment algorithm for patients with Bing–Neel syndrome. BNS, Bing–Neel syndrome; CSF, cerebrospinal fluid; HD, high-dose; LPL, lymphoplasmacytic lymphoma; MRI, magnetic resonance imaging.

Table I. Response criteria for patients with Bing–Neel syndrome, based on the recommendations of the 8th International Workshop for Waldenström Macroglobulinaemia Task Force on Bing–Neel syndrome (Minnema *et al*, 2017).

Response category	Definition
Complete response	Resolution of all reversible clinical symptoms with normalization of CSF MRI findings. MRI findings may show minimal residual abnormalities on T2 or FLAIR. The absence of new clinical signs, symptoms and new contrast enhancing MRI findings are required for attaining complete response.
Partial response	Improvement but no complete resolution of all reversible clinical symptoms, or complete resolution of all reversible clinical symptoms but with maintained radiological abnormalities, excluding minimal residual abnormalities on T2 or FLAIR. The CSF findings should be negative.
Non-response	Persistence or progression of neurological symptoms, radiological or CSF findings.
Relapse	Reappearance of new signs and symptoms attributed to BNS; or detection by cytological, and/or flow cytometry, and/or molecular techniques of BNS disease; or progression or new findings attributed to BNS by MRI examination of the brain and/or spine.

BNS, Bing–Neel syndrome; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

comprised haematologists, oncologists, neurologists and radiologists, to establish diagnostic criteria, treatment recommendations and response criteria for patients with BNS. The response criteria proposed by this Task Force are shown in Table I.

Complete response is defined by complete resolution of symptoms and radiological anomalies along with CSF clearance from malignant cells. While achieving complete response is highly desirable, it should not be considered the goal of treatment in BNS. On the other hand, we should avoid overtreatment in these patients. The goal of treatment in BNS, as in WM, should be achieving sustained long-term, symptom-free intervals. A partial response is defined by symptomatic and radiological improvement along with CSF clearance from malignant cells. A few case series, however, have suggested that the CSF of patients with BNS might not clear from malignant cells despite patients experiencing

symptomatic and radiological improvement on therapy (Castillo *et al*, 2016; Castillo *et al*, 2019). This specific group of patients, based on current response criteria, would be classified as non-responders, which might not be reflective of the clinical benefit derived from therapy. Additional research is needed to recategorize BNS patients with symptomatic and radiological improvement but persistence of CSF disease as partial responders.

Monthly monitoring with blood counts, serum IgM levels and symptom assessment for the first 6 months of therapy can be considered, followed by quarterly evaluations afterwards. Brain and/or spine MRI, as well as CSF cytology and flow cytometry can be monitored every 6 months for the first 2 years after initiation of therapy. Thereafter, MRI and CSF monitoring be performed as clinically indicated for symptom reappearance. Upon reappearance of pre-existing neurological deficits or development of new symptoms, the

patient should be fully re-evaluated with brain and spine MRI as well as CSF examination.

What is the prognosis of patients with BNS?

Data on the prognosis of BNS patients is rather limited. In the study by Simon *et al.* (2015), the median follow-up time was 4-6 years and the 5-year OS rate from BNS diagnosis was 70%. Most of the deaths occurred within 2 years of BNS diagnosis and two thirds of the causes of death were related to BNS or BNS treatment. The median PFS after the first line treatment for BNS was 26 months. In the study by Castillo *et al.* (2016), the median follow-up time was 30 months, and the 3-year OS rate from BNS diagnosis was 60%. Most deaths occurred within the first two years after BNS diagnosis, and 75% of patients died of BNS progression. BNS patients who were previously untreated for their WM had better outcomes with 3-year OS rate of 100% vs. 40% in patients who were previously treated for their WM prior to BNS diagnosis. Patients younger than 65 years and with platelet counts $\geq 100 \times 10^9/l$ at BNS diagnosis also had better outcomes than patients older than 65 years and platelet counts $< 100 \times 10^9/l$, respectively. It is important to note that, in these two studies, BNS patients were treated with heterogeneous treatments, and the survival rates presented above do not represent the outcomes expected with one specific treatment modality.

In a study on 28 BNS patients treated with ibrutinib, the estimated 2-year survival rate from ibrutinib initiation was 81%, and the 5-year survival rate from BNS diagnosis was 86% (Castillo *et al.*, 2019). There were no detectable differences between patients who were previously treated or untreated for their BNS, or between patients who received an ibrutinib dose of 560 mg or 420 mg daily, with regard to survival from ibrutinib initiation or survival from BNS diagnosis.

What is exciting on the future treatment of patients with BNS?

As previously mentioned, the treatment options for BNS patients are restricted to agents with CNS penetration. A number of novel agents with CNS penetration are in clinical development for the treatment of haematological malignancies, such as multiple myeloma, CLL and WM, and could positively impact the treatment of patients with BNS. A few examples include marizomib, zanubrutinib, venetoclax and dasatinib.

Proteasome inhibitors have been shown to be safe and effective in patients with systemic WM (Treon *et al.*, 2009; Ghobrial *et al.*, 2010; Dimopoulos *et al.*, 2013; Treon *et al.*, 2014; Castillo *et al.*, 2018a). However, these agents are well known for not crossing the blood-brain barrier, and therefore are not treatment options in BNS. The novel

proteasome inhibitor, marizomib, is under clinical development for the treatment of multiple myeloma (Harrison *et al.*, 2016; Richardson *et al.*, 2016; Spencer *et al.*, 2018). Marizomib has shown CNS penetration properties in glioma preclinical animal models, in which marizomib distributed into brain tissue at 30% of blood levels in rats and significantly inhibited proteasome activity in brain tissue of cynomolgus monkeys (Di *et al.*, 2016). Clinically, Badros *et al.* (2017) reported on two patients with CNS relapse of multiple myeloma following allogeneic stem cell transplantation who experienced short-lived clinical benefit from marizomib therapy (Badros *et al.*, 2017).

Several novel BTK inhibitors are undergoing clinical development. Zanubrutinib, specifically, is an irreversible oral BTK inhibitor with greater selectivity for the BTK pathway, which was shown to be safe and effective for the treatment of WM (Trotman *et al.*, 2018). A recent report suggested activity of zanubrutinib in BNS as well (Wong *et al.*, 2018). A 75-year-old woman was diagnosed with BNS and was initially treated with high-dose methotrexate. However, symptoms reappeared and progressed upon cessation of therapy. The patient was treated with zanubrutinib 160 mg by mouth twice daily with symptomatic improvement and resolution of radiological abnormalities within 3 months of therapy.

The oral BCL2 antagonist, venetoclax, is approved by the United States Food and Drug Administration for the treatment of CLL and acute myeloid leukaemia. Venetoclax was also shown to be safe and effective in patients with previously treated WM (Castillo *et al.*, 2018b). A recent report demonstrated CNS penetration of venetoclax in a patient with relapsed CLL (Reda *et al.*, 2019). The patient was treated with venetoclax and intrathecal chemotherapy, obtaining clinical improvement within one month of therapy. Three months into venetoclax therapy, CSF and plasma levels of venetoclax were measured. The percentage of CSF to plasma concentration was 0.1% with a trough CSF level of 1.5 ng/ml, which was close to the IC50 for BCL2 inhibition.

Conclusion

Bing-Neel Syndrome is a rare complication of WM and is associated with significant morbidity and mortality. It is important that the care of these patients is shared between haematologists, neurologists and neurooncologists. BNS patients could be referred to centres with experience of managing these challenging cases. The establishment of diagnostic and response criteria certainly has moved the field forward to unify clinical and research efforts. There appears to be an increasing number of safe and effective treatment options for BNS patients. However, the treatment of BNS remains non-standardized. BNS patients are typically excluded from prospective clinical trials and given the rarity of BNS, prospective therapeutic studies will only be possible through multi-institutional efforts.

Authorship contribution

JJC and SPT designed the structure of the review. JJC performed the literature search and wrote the initial draft. SPT critically reviewed the manuscript. Both authors approved the final manuscript.

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