Evaluation and Management of Bing–Neel Syndrome

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KEYWORDS

• Bing–Neel syndrome • Waldenström macroglobulinemia • Central nervous system • Cerebrospinal fluid • MRI

KEY POINTS

- Bing–Neel syndrome (BNS) is a rare manifestation of Waldenström macroglobulinemia (WM), which is caused by infiltration of lymphoplasmacytic lymphoma (LPL) cells in the central nervous system (CNS).
- Every WM patient with atypical or unexplained neurologic symptoms should be evaluated for BNS.
- Key in the diagnostic workup is an MRI of the brain and spine and cerebrospinal fluid (CSF) examination or (if possible) cerebral biopsy to confirm the presence of LPL cells in the CNS.
- Flow cytometry and molecular diagnostics aid in diagnosis by demonstrating a monoclonal B-cell population and the MYD88-mutation, respectively.
- The aim of the treatment is clinical improvement; BTK inhibitor ibrutinib is preferred as first-line therapy thanks to its high efficacy and limited toxicity.

INTRODUCTION

Bing–Neel syndrome (BNS) is an uncommon but serious manifestation of Waldenström macroglobulinemia (WM) caused by infiltration of the malignant lymphoplasmacytic cells in the central nervous system (CNS). The first report of this disorder dates to 1936, when the physicians Jens Bing and Axel Valdemar von Neel described two patients with hyperglobulinemia and subacute neurologic symptoms.[1] Remarkably, this was reported 8 years before Jan Waldenström described the disease we currently known as WM.[2] BNS represents an extramedullary presentation of WM, resulting in

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a diverse spectrum of neurologic symptoms, ranging from headaches or gait disorders to cognitive deficits and psychiatric symptoms.[3,4] Given this clinical heterogeneity and rarity of the disorder, the recognition and early diagnosis of BNS are challenging. This review aims to summarize the current knowledge and guidelines regarding the clinical presentation, diagnosis, and treatment of BNS.

EPIDEMIOLOGY

The exact incidence of BNS is unknown but is estimated to occur in about 1% of WM cases.[5] WM itself is a rare lymphoid malignancy with an incidence of about three patients per million persons per year.[6] The disease is caused by an immunoglobulin M (IgM)-producing monoclonal lymphoplasmacytic infiltration in the bone marrow. The clinical picture of WM is very heterogeneous, ranging from asymptomatic to constitutional symptoms, complaints secondary to the IgM paraprotein (such as hyperviscosity or peripheral neuropathy), or anemia because of bone marrow infiltration. BNS is a rare manifestation of WM, affecting the cerebrospinal fluid (CSF), the meninges, and/or the brain parenchyma.

BNS can occur at any moment in the disease course of WM. The median time between the diagnosis of WM and BNS is 3 to 4 years, but in about 15% to 26% BNS represents the first manifestation of the disease.[3,4] The median age is 63 years, and BNS is more often seen in males. Remarkably, occurrence of BNS is independent of the systemic activity of WM. In about one-third of patients with BNS, the syndrome occurred while they received active treatment for WM, most of them also showing responsive disease or even complete remission.[4]

CLINICAL PRESENTATION

The clinical presentation of BNS is very diverse, and there are no pathognomonic symptoms for the disease. Together with the rarity of the disorder, this often results in a significant diagnostic delay. The median time between first symptoms and diagnosis of BNS is 4 months, whereas in about 20% of cases, the diagnosis was made after 1 year.[3]

The signs of BNS reflect the involvement of the CNS and are usually progressive over weeks to months (**Fig. 1**). Most described (30%–50%) symptoms are balance and gait disturbances, cranial nerve involvement (mainly oculomotor and facial nerves) and cognitive dysfunction such as confusion, memory loss, or altered mental status.[3,4,7] Headache or limb pain, sensory deficits or paresthesias, and seizures are seen in approximately 20% to 30% of patients.[3,4,7] Finally, visual abnormalities, hearing loss, and psychiatric symptoms can also occur in 10% to 20% of patients.[3,4,7]

It is important to discriminate between the signs of BNS and other comorbidities associated with WM, such as IgM-related polyneuropathy (PNP) or hyperviscosity syndrome. The most important differences between BNS and IgM-related PNP are summarized in **Table 1**. IgM-related PNP is characterized by a symmetrical pattern, affecting the distal nerves first. There is primarily sensory loss, and symptoms are slowly progressive over months to years. Moreover, anti-myelin-associated glycoprotein (MAG) antibodies can be identified in most cases. Contrary to this, sensorimotor symptoms in BNS show an asymmetric radicular distribution with a predominance of motor deficits. The disease course is more rapidly progressive over weeks to months.

Typical complaints associated with hyperviscosity are spontaneous nose bleeds, progressive headaches, and visual disturbances, such as blurry vision. Moreover, the high level of the serum IgM protein (symptomatic hyperviscosity is uncommon

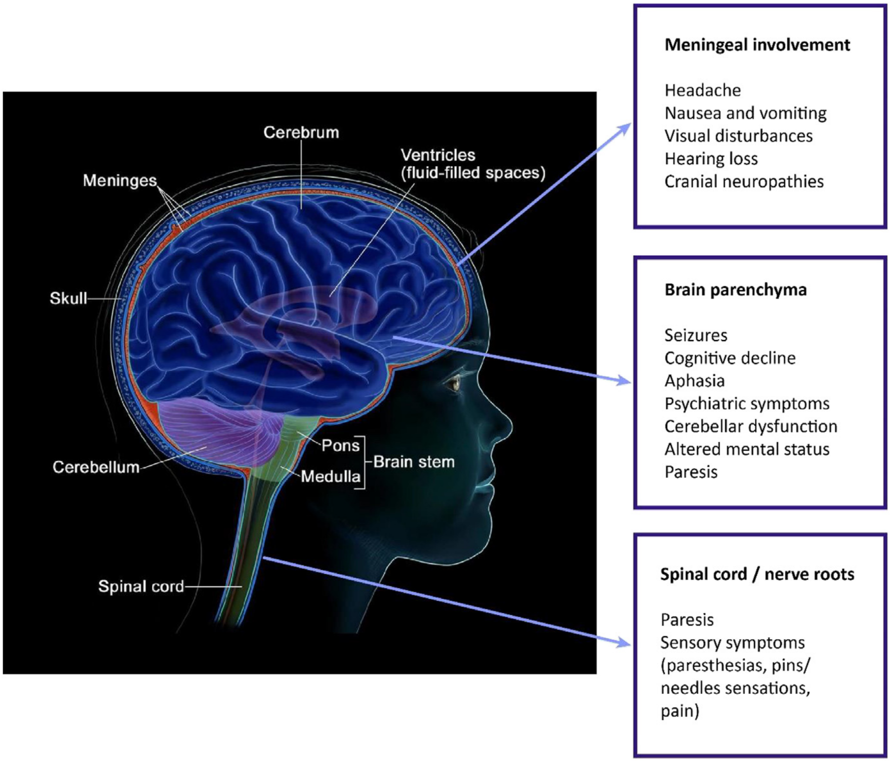

Fig. 1. Spectrum of clinical symptoms of Bing–Neel syndrome according to localization of CNS involvement.

with serum IgM levels <30 g/L) and typical findings by retinoscopy aid in differentiating between BNS and hyperviscosity syndrome.

DIAGNOSIS

Diagnosing BNS is challenging and requires a combination of clinical symptoms, blood and bone marrow examination, contrast-enhanced MRI of the brain and spine, and confirmation of the presence of lymphoplasmacytic lymphoma (LPL) cells in the CNS.

MRI of the brain and spinal cord is an important part of the diagnostic workup of BNS, both to support a diagnosis of BNS and exclude other causes and to identify

Table 1
Differences between immunoglobulin M-related polyneuropathy and Bing–Neel syndrome

	IgM PNP	Bing–Neel Syndrome
Pattern	Symmetrical Length-dependent (sock pattern) Mostly sensory loss	Asymmetrical Radicular distribution Mostly motor deficits
Disease course	Months to years	Weeks to months
Other	Anti-MAG positive EMG showing demyelination	

Abbreviations: Anti-MAG, anti-myelin associated glycoprotein; EMG, electromyography.

CNS tissue amenable to biopsy. MRI for fluid-attenuated inversion recovery (FLAIR) and T1-weighted sequences before and after gadolinium should be obtained to improve sensitivity. Moreover, radiological studies should be performed before lumbar puncture to prevent false-positive radiographic findings. The MRI abnormalities are seen in approximately 80% of patients; therefore, a normal scan does not rule out BNS.[3,4,8] In most cases (80%), MRI shows diffuse leptomeningeal enhancement, whereas in about 20%, tumoral masses are observed, usually located in periventricular/subependymal regions (**Fig. 2**).[8,9]

The demonstration of LPL cells in the CNS by biopsy of the cerebrum or meninges is the gold standard for diagnosing BNS.[10] In case a biopsy is not possible, a CSF examination to test the presence of LPL cells must be performed. In both cases, biopsy and CSF examination, transformation to a high-grade lymphoma must be excluded.[10]

When performing lumbar puncture for CSF examination, an adequate volume should be obtained for leucocyte count and differentiation, biochemical analysis,

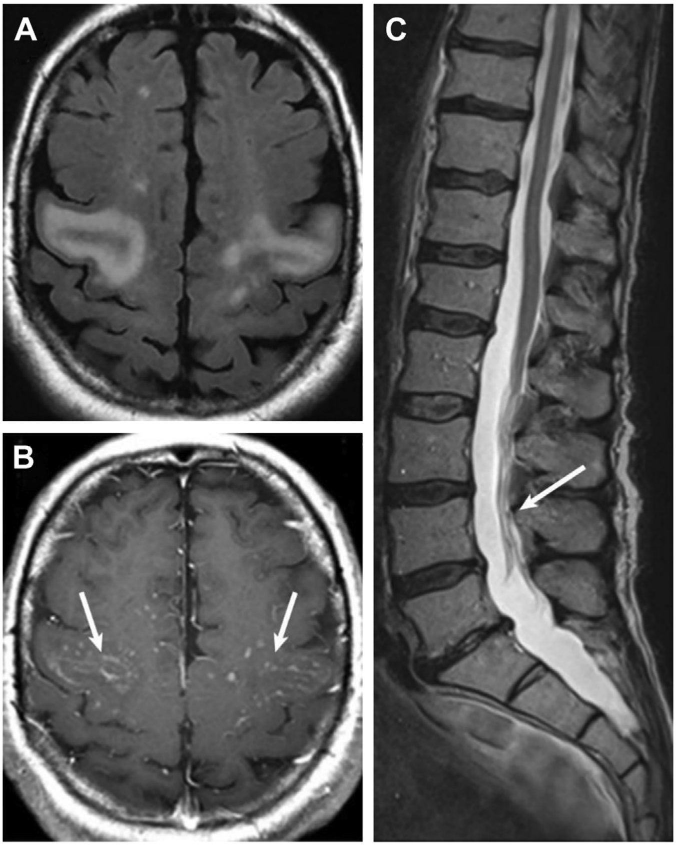

Fig. 2. MRI abnormalities in Bing–Neel syndrome. (*A*) Parenchymal involvement of the brain: Increased signal abnormalities in both precentral regions in axial FLAIR sequence. (*B*) Multiple nodular contrast enhancement in both precentral regions in axial T1 sequence after contrast media administration (see *arrows*). (*C*) Cauda equina thickening T2-sagittal sequence (see *arrow*). (Source (modified and re-used with permission): Minnema et al., Haematologica 2017.[10])

cytomorphology, flow cytometry, and molecular diagnostics.[10,11] The most frequent findings in the CSF are an elevated protein level and lymphocytic pleocytosis with cytomorphological atypical lymphocytes with a plasmacytic morphology (**Fig. 3**).[7] As these are all nonspecific findings, flow cytometry and molecular studies are essential in confirming BNS.

The role of flow cytometry is to demonstrate a clonal B-cell population. The flow cytometric profile of LPL is characterized by expression of the pan-B-cell markers CD19 and CD20, plasma cell markers CD138 and IgM, and restriction of the light chain.[12] Importantly, the immunophenotypic profile of the B-cell population in the CNS should be congruent with the malignant LPL cells in the bone marrow.

Molecular diagnostics detect Ig gene rearrangement or the presence of mutated MYD88 (L265P). Identifying a clonal relationship between Ig rearrangement of the LPL cells in the CNS and the bone marrow provides strong evidence supporting a diagnosis of BNS. The case series of Castillo and colleagues[4] demonstrated that an Ig rearrangement was observed in 94% of all cases. However, given the low cellular rate in the CSF, the sensitivity of this technique is limited. On the contrary, detection of the MYD88 L265P mutation by quantitative polymerase chain reaction (qPCR) is a very sensitive method and this mutation is seen in about 95% of all patients with BNS.[10] Given the high sensitivity of this method, caution must be taken to avoid blood contamination of the CSF to prevent false-positive results from LPL cells in the peripheral blood.[10] Blood contamination can be minimized by using the last diagnostic tube of CSF for this test. Finally, it should be noted that the MYD88-mutation is not specific to BNS, as it is also observed in primary CNS lymphoma (PCNSL) and rarely in other B-cell lymphomas.[13,14]

TREATMENT

Like WM, BNS is not curable, and treatment aims to improve the clinical symptoms and induce long progression-free survival.[10,11] Therapy is therefore only indicated in symptomatic patients with a definitive diagnosis of BNS. The complete eradication of all malignant cells in the CNS is not always possible and not necessary if patients have clinical benefit from the therapy similar to the treatment goals in WM and other indolent B-cell malignancies.

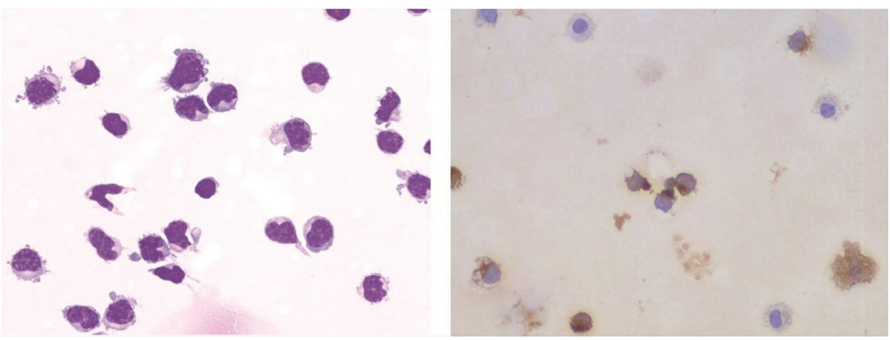

Fig. 3. Cytomorphology of cerebrospinal fluid (CSF) in Bing–Neel syndrome (BNS). Left: Giemsa stain of the CSF of a patient with BNS relapse after previous diagnosis of Waldenström macroglobulinemia. Right: kappa immunohistochemistry positivity of the lymphoplasmacytic lymphoma (LPL) cells, concordant with the LPL in bone marrow biopsy. (Source (reused with permission): Minnema et al., Haematologica 2017.[10])

As a result of the rarity of the disease, no randomized clinical trials have been performed and treatment advice is based on expert opinion and published case series. Earlier therapeutic options included chemotherapeutic agents with CNS penetration, intrathecal (IT) therapy, and radiotherapy (RT). The introduction of Bruton tyrosine kinase (BTK) inhibitors changed the treatment landscape of BNS (**Fig. 4**).[7,10,11]

Chemotherapy

Several chemotherapeutic options, with known or probable penetration of the blood–brain barrier, are suitable for treating BNS. Based on experiences treating PCNSL, one of the first therapies for BNS included high-dose methotrexate and high-dose cytarabine. Although effective, these treatments also carry high toxicity. Therefore, they should be reserved only for patients considered fit for intensive therapy. Other less toxic but effective treatment options include bendamustine or purine analogs such as fludarabine or cladribine.[15] Based on the two largest case series of BNS, the overall response rate of these agents was 70% with no differences between the various approaches.[3,4]

Bruton Tyrosine Kinase Inhibitors

The introduction of BTK inhibitors (BTKi) ibrutinib led to a breakthrough in treating BNS. After its demonstrated efficacy in WM, it was shown that ibrutinib penetrates the blood–brain barrier and is also effective in BNS.[16] Based on a retrospective case series of 28 patients, treatment with ibrutinib improved or resolved symptoms in 85% of patients.[17] Moreover, 83% had a decrease or resolution of radiologic abnormalities and in 47%, the disease was no longer detectable in the CSF.[17] The 2-year event-free survival was 80% and the 5-year survival rate 86%.[17] No differences were observed between the 420 and 560 mg doses and the toxicity was mild.[17]

Interesting in this regard is the introduction of the second-generation BTKi zanubrutinib, which bears higher selectivity for the BTK pathway and therefore has demonstrated fewer side effects. A randomized phase 3 trial in WM patients demonstrated that both zanubrutinib and ibrutinib are highly effective. Still, zanubrutinib was associated with less toxicity, particularly cardiovascular adverse events.[18] Experience with zanubrutinib in treating BNS is still limited, but the agent is already successfully used in a few cases.[19] Awaiting more results on the efficacy of zanubrutinib in BNS, it may have a role in treating BNS patients.

Role of Autologous and Allogeneic Stem Cell Transplantation

In patients with chemosensitive WM relapse, autologous stem cell transplantation (ASCT) is an effective therapeutic option.[20] Data regarding its role in BNS treatment are, however, limited. A retrospective case series by Simon and colleagues[20] describes 14 patients who underwent ASCT after induction treatment for BNS. The study cohort was very heterogeneous regarding treatment protocols used for induction and consolidation therapy.

In nearly all cases, BNS induction therapy consisted of systemic and IT therapy, often with the addition of rituximab. None of the patients was treated with ibrutinib. For the conditioning scheme, BEAM (carmustine, etoposide, cytarabine, and melphalan) or a thiotepa-based regimen was applied. All patients had chemosensitive disease before ASCT. With a median follow-up of 35 months, the overall response rate was 92% and only one patient relapsed. Five-year overall survival was 84%. Although these results of ASCT seem promising, the heterogeneity in treatment protocols (without incorporation of ibrutinib) and short follow-up make it difficult to determine

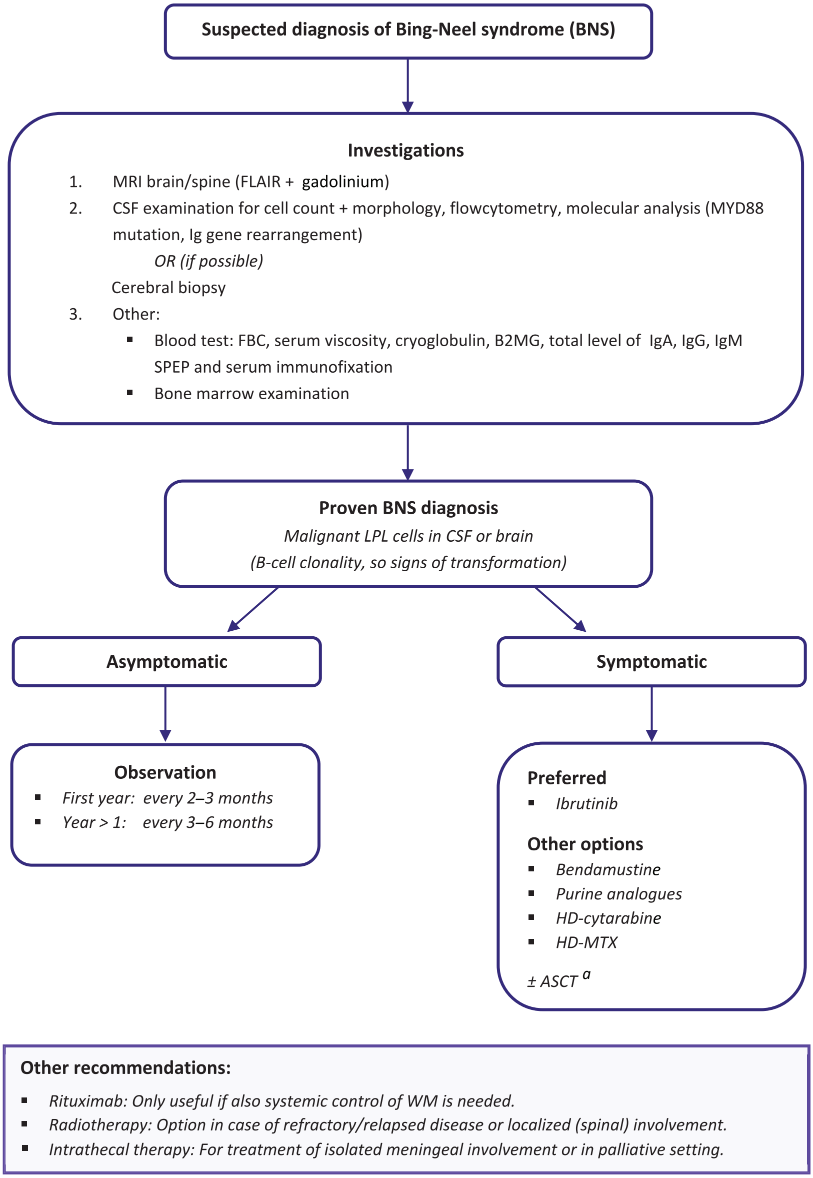

Fig. 4. Diagnostic workup and treatment of Bing–Neel syndrome (BNS). ASCT, autologous stem cell transplantation; B2MG, beta-2 microglobulin; CSF, cerebrospinal fluid; FBC, full blood count; FLAIR, fluid-attenuated inversion recovery; HD, high-dose; Ig, immunoglobulin; LPL, lymphoplasmacytic lymphoma; MTX, methotrexate; SPEP, serum protein electrophoresis. [a]ASCT can be considered in fit patients with relapsed disease showing chemosensitive disease. (Analogues to Minnema et al., Haematologica 2017, with permisson.[10])

the exact role and optimal timing for this relatively toxic treatment. It could, however, be considered in fit patients with relapsed disease.

To our knowledge, allogeneic stem cell transplantation (SCT) has not been used in BNS. In WM, the role of allogeneic SCT is very limited given the high non-relapse-associated mortality and the relatively low probability of long-term remission, rendering the newer, less toxic treatment options preferable.[21]

Other Treatment Options

Rituximab monotherapy is not recommended for treating BNS due to poor CNS penetration. Adding rituximab to other therapies, such as ibrutinib or chemotherapy, can be useful when systemic disease control is also needed. Experience with IT rituximab in BNS is limited. In other B-cell lymphomas involving the CNS, IT rituximab appeared effective but was also associated with serious toxicity. Therefore, its use is not advised as a first-line treatment.[22,23]

Other treatment options for BNS include IT chemotherapy and RT.[10,11] Monotherapy with IT drugs has been associated with short-lived responses. Therefore, if used, it is advised in combination with systemic therapy to treat meningeal involvement or in the palliative setting.

BNS is sensitive to RT, and effective use of RT is described in several case reports.[10,24] The downside of this therapeutic modality is the risk of neurotoxicity, especially the occurrence of late neurocognitive effects. For this reason, RT is not recommended as a first-line option but should be reserved for patients in the refractory of relapsed setting or in case of localized involvement of the CNS, such as exclusive cauda equina involvement in which toxicity is limited.[10,11]

TREATMENT OF OCULAR BING–NEEL SYNDROME

Although rare, involvement of the eye and surrounding structures may occur in BNS, requiring specific attention. Patients with new complaints of the eyes and/or sight should be evaluated by an ophthalmologist for an extended eye examination. A biopsy should be performed to confirm ocular involvement. For lesions in a surgically inaccessible site, conjunctival biopsy (or CSF examination) could be used as a surrogate.

Only a few cases of ocular BNS have been described in the literature and, in each case, a different treatment strategy was applied.[25–29] Most patients received a combination of intravenous (IV) and IT chemotherapy. In two of six patients, RT was also used. Treatment resulted in (at least) partial response in five patients, whereas one patient showed no improvement in vision despite aggressive treatment with IV high-dose methotrexate, IT cytarabine, and radiotherapy.[26]

PROGNOSIS

There are limited data on the prognosis of BNS and results are quite variable. The case series of Simon and colleagues[3] showed a 5-year survival rate of 71% and a 10-year survival rate of 59%, whereas in the cohort of Castillo and colleagues,[4] 3-year survival was 59%. For comparison, the median overall survival in WM is 9.2 years with a 10-year survival rate ranging from 84% in the very low-risk group to 9% in the very high-risk group.[30] The median progression-free survival after first-line treatment of BNS was 26 months.[3] Most deaths occur within 2 years of diagnosis, in 70% secondary to the progression of BNS or toxicity of treatment. There are no established prognostic factors, but no previous treatment for WM (3-year survival 100% vs 40%), age less than 65 years and platelet count greater than 100×10^9/L all seem to be associated with a favorable prognosis.[4]

It should be noted that in the abovementioned studies, the treatment was heterogeneous, and the results predate the introduction of ibrutinib. Based on a retrospective case series, 5-year survival in patients treated with ibrutinib was 86%.[17] As such, it is expected that the prognosis of BNS nowadays might be more favorable than described above.

SUMMARY

All WM patients with unexplained neurologic symptoms must be evaluated for the presence of BNS to prevent diagnostic delay and the risk of permanent neurologic damage. Essential in the diagnostic workup is an MRI of the brain and spine and a CSF examination or cerebral biopsy to demonstrate the presence of LPL cells. As BNS is a non-curable disease, treatment should be aimed at improving symptoms. Several chemotherapeutic agents with good CNS penetration have proven efficacy in this syndrome. The introduction of ibrutinib has provided a breakthrough in treating BNS because of its high efficacy and is therefore preferred as the first-line therapy.

DISCLOSURE

S.J. Schep: nothing to disclose. M.C. Minnema: Speakers Bureau Janssen-Cilag, WebMD Global, Consultancy Janssen-Cilag, CDR-life, BMS, GSK, research funding; BeiGene; all honoraria are institutional. J.M.I. Vos: consultancy and advisory board (Sanofi), research funding (BeiGene, China & Abbvie, United States/Genmab), Speakers bureau and conference support (BMS); all honoraria are institutional.

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