Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome

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ABSTRACT

Bing Neel syndrome is a rare disease manifestation of Waldenström's macroglobulinemia that results from infiltration of the central nervous system by malignant lymphoplasmacytic cells. In this guideline we describe the clinical symptoms, as well as the appropriate laboratory and radiological studies, that can aid in the diagnosis. The presentation of Bing Neel syndrome may be very diverse, and includes headaches, cognitive deficits, paresis, and psychiatric symptoms. The syndrome can present in patients with known Waldenström's macroglobulinemia, even in the absence of systemic progression, but also in previously undiagnosed patients. Diagnostic work-up should include cerebral spinal fluid analysis with multiparameter flow cytometry to establish B-cell clonality, protein electrophoresis and immunofixation for the detection and classification of a monoclonal protein as well as molecular diagnostic testing for immunoglobulin gene rearrangement and mutated MYD88. MRI of the brain and spinal cord is also essential. The second challenge is to expand our knowledge of prognosis and treatment outcome. Prospective clinical trials on Bing Neel syndrome patients that employ uniform treatment along with appropriate laboratory cerebral spinal fluid assessments and standardized MRI protocols will be invaluable, constituting a significant step forward in delineating treatment outcome for this intriguing disease manifestation.

Introduction

Bing Neel syndrome (BNS) is a rare disease manifestation of Waldenström's macroglobulinemia (WM) that usually presents as a feature of relapsing disease, though it may also occur at first diagnosis of WM.[1] In BNS, malignant lymphoplasmacytic cells (LPC) invade the central nervous system (CNS). LPC may be detected in the cerebrospinal fluid (CSF), the meninges, and/or the cerebral parenchyma.

The syndrome is named after Jens Bing and Axel Valdemar von Neel; two physi-

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cians who described the first two patients with hyperglobulinemia and neurological symptoms in 1936.[2] The clinical symptoms of BNS may be very diverse, and include headaches, cognitive deficits, paresis, cranial nerve involvement, gait disorders, and psychiatric symptoms.[1]

Since the first case report by Bing and Neel, additional case reports of BNS have been published identifying at least 50 patients with this diagnosis. Two recent retrospective surveys added 44 and 34 patients, respectively, to this total.[3,4] A diagnostic work-up and a classification system for BNS were proposed by Hochberg and colleagues in 2009 and 2011.[5,6] However, 80 years following the first publication, no comprehensive guidelines exist for the diagnostic and therapeutic approach or response assessment of BNS. Therefore, during the 8th International Workshop on WM, a task force on BNS was established comprising hematologists, neurologists, immunologists and radiologists, with the aim of producing a practical guideline for the diagnosis and management of BNS. A comprehensive search was performed using the bibliographic database of PubMed up to February 2016. Both free text terms and MeSH terms were used as search terms. The terms used were; "Bing Neel" and "Waldenström's macroglobulinemia and central nervous system", and only English peer-reviewed publications were selected. In addition, all references of selected articles were searched for additional references. The draft of the manuscript was written by the first author and, in subsequent teleconferences, all items were discussed with a multidisciplinary team of international experts in WM.

Clinical picture

The clinical symptoms of BNS are diverse and reflect involvement of the CNS and, rarely, the peripheral nervous system (PNS). Importantly, there is no clinical picture or specific symptom(s) that can prove or exclude BNS. The symptoms are gradually progressive in nature, usually developing over the course of weeks or months. Of the symptoms described in literature, headache, nausea and vomiting, visual disturbances, hearing loss and cranial neuropathies, mostly of the facial or oculomotor nerves, usually accompany meningeal involvement. Seizures, cognitive decline, aphasia, psychiatric symptoms, cerebellar dysfunction, impairment of consciousness including coma, and paresis typically represent involvement of brain parenchyma or the spinal cord. Sensory symptoms - including paresthesias, pins and needles sensations, and pain - may represent involvement of brain parenchyma, spinal cord, cauda equine, and/or spinal nerve roots, depending on their anatomical distribution.

The differential diagnosis of BNS includes hyperviscosity syndrome (HVS) with neurological symptoms such as new-onset headaches, visual impairment, and spontaneous nosebleeds. Confirmation of HVS with appropriately increased IgM or serum viscosity measurements can aid in differentiating HVS related CNS symptoms from BNS.[7] Sensory symptoms of the legs due to nerve root/cauda equina involvement may be mistaken for neuropathy related to anti-myelin associated glycoprotein (MAG) antibodies produced in WM and IgM related disorders.[8] These patients mostly present with a sensory ataxia with impaired gait and mild to moderate distal muscle weakness which slowly develops over years.[9] Anti-MAG antibodies can be measured in the serum of these patients. Other types of lymphoma-like diffuse large B-cell lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia (CLL), Hodgkin Lymphoma, and NK/T-cell lymphomas, may also invade the CNS, and are sometimes difficult to differentiate from BNS without correct histology.[10]

Epidemiology

Due to the diversity of symptoms, and the rarity of BNS, there is often a considerable delay between the initial symptoms and the diagnosis. In a recent retrospective analysis, the median time between first symptoms and diagnosis of BNS was 4 months; but more than one year in 20% of patients.[3] It is possible that some patients succumb to BNS even before a correct diagnosis is made. The incidence of BNS is unknown, but in a retrospective cohort study of 1,523 WM patients, only 13 patients (0.8%) were diagnosed with BNS, suggesting a very low prevalence.[11] No risk factors were identified for BNS, other than the concurrent presence or history of WM. Most patients diagnosed with BNS were previously diagnosed with WM. It is important to recognize that BNS can occur despite WM being in remission with an M-protein level remaining stable or undetectable.[3]

In approximately 15% to 36% of patients, BNS was the presenting symptom with no previous history of WM.[3,4] These patients may have a better prognosis compared to patients with BNS and a previous history of WM.[4] The clinical suspicion of BNS in these patients with neurological symptoms was raised because of the presence of an IgM M-protein in the serum or the detection of a clonal B-cell population by multiparameter flow cytometry (MFC) in the cerebral spinal fluid (CSF). Solitary BNS without concurrent or past WM has also been reported.[12] Asymptomatic BNS may exist (personal observation), but the incidence is unknown since CSF examination is not routinely carried out in WM.

Diagnostic criteria and work up of BNS

Histology

The golden standard for the diagnosis of BNS is a histological biopsy of the cerebrum or meninges demonstrating a lymphoplasmacytic lymphoma, comprised of small lymphocytes in which there is morphological evidence of plasma cell differentiation. Immunochemistry is essential and, as in WM, the malignant cells are defined as monotypic B cells which express the pan B-cell antigens CD19, CD20, CD79a and CD79b and, in most cases, also the memory B-cell marker CD27 as well as CD52. CD5 and CD23 are expressed in a minority of cases only. Monotypic plasma cells may also be present, expressing CD138 and IgM.[13] Molecular testing is strongly advised and described in a separate section. Besides primary central nervous system lymphoma (PCNSL), also other systemic (indolent) lymphomas can be present in the CNS as well as transformation to high grade lymphoma and, therefore, biopsy remains an important diagnostic procedure.[10,14] Biopsy should be attempted prior to steroid administration, if possible, and the risks associated with this procedure should be carefully considered for each patient.

Table 1. Treatment regimens and response activity reported in BNS.

Therapy	Name of Drug	Outcome	Reference
Intrathecal or -ventricular (monotherapy)	methotrexate and/or (liposomal) cytarabine (7 patients)	3 CR 3 PR 1 PD	3, 17, 43, 62, 63
Systemic conventional	fluda/2-CDA ± rituximab (15 patients)	8 CR 4 PR 3 PD	1, 3, 4, 46, 52, 64
	bendamustine+ rituximab (9 pts)	2 CR 5 PR 2 SD	3, 4, 53
	DT-PACE /CVP/CD/ chlorambucil ± rituximab (14 patients)	5 CR (one with ASCT) 1 SD 8 PD	3, 37, 58
Systemic High Dose	BCNU based (1 patient)	1 PR	65
	HD-MTX based ± rituximab ± ASCT (48 patients)	15 CR 16 PR 9 SD 8 PD	1, 3, 4, 18, 36, 43, 44, 66-68
	HD-ARA-C based ± ASCT (12 patients)	8 CR 3 PR 1 SD	3, 4, 18, 21, 26, 48, 69
Novel	ibrutinib (5 patients)	2 CR 3 PR	4, 48, 55

Published treatment regiments and their outcome in BNS patients based upon response criteria provided in the publications. CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease. Fluda, Fludarabine; 2-CDA, Cladribine; BCNU, Carmustine; DT PACE, Dexamethasone, Thalidomide, Cisplatin, Doxoruucin, Cyclophosphamide, Etoposide. CVP: Cyclophosphamide, Vincristine, Prednisone; CD: Cyclophosphamide, Dexamethasone; HD-MTX: High Dose Methotrexate; HD- ARA-C: High Dose Cytarabine; ASCT: Autologous Stem Cell Transplantation.

Fintelmann *et al*. have proposed the terms type A and type B BNS.[5] Up to 75% of the patients were classified as type A, defined as patients in whom LPC could be demonstrated in the parenchyma, meninges, dura or CSF. Type B patients had very low (less than 5 cells/mm^3) counts of LPC in the CSF, and it was suggested that symptoms were caused by IgM deposits rather than by cellular infiltration of the CNS. However, the demonstration of M-protein deposition as a cause of BNS remains to be demonstrated.

Analysis of the CSF

When there is leptomeningeal involvement, the CSF may contain malignant LPC; it is therefore recommended to perform repeated CSF analysis and, if possible, to do so before MRI is performed to exclude non-specific meningeal enhancement that occurs after CSF sampling. The analysis of the CSF should include leukocyte cell count and differentiation, biochemistry, morphological analysis, MFC, and molecular testing to increase the sensitivity for the detection of malignant B cells. Also, replication of CSF analysis increases the diagnostic yield. CSF findings may include an elevated opening pressure, lymphocytosis, elevated total protein, and normal or decreased glucose.[1] It is important to recognize that other lymphomatous or infectious and inflammatory processes may present with CSF lymphocytosis, and should therefore be considered in the differential diagnosis and appropriately investigated. Morphology is the golden standard but may be difficult to interpret due to the cytospin technique; it also has a low diagnostic yield, as has also been demonstrated in PCNSL (Figure 1).[15,16] MFC analysis demonstrating B-cell or plasma-cell markers with light chain restriction is essential for establishing tumor clonality.[17,18] MFC should be performed as soon as possible because of the potential for rapid decay of viable cells in native CSF. A cell-stabilizing agent, such as TransFix, may enhance the detection of B-cell clones in the CSF by preventing cellular decay.[19] Clonal B cells in the CSF should have the same immunophenotypic features as those in bone marrow (BM). Since MFC is a sensitive method, caution should be taken to avoid blood contamination of the CSF.

Protein electrophoresis (PEP) and immunofixation (IF) for the detection and classification of an M-protein in the CSF can be used.[18,20,21] If there is no blood-brain barrier disruption, the presence of an IgM M-protein in the CSF with the same light chain restriction as the LPC in the BM and correlation with the serum M-protein may be indicative of the presence of LPC in the leptomeninges.[22] However, in the case of increased permeability of the blood-brain barrier, IgM proteins may diffuse from the blood into the CSF and do not reflect the presence of LPC in the CNS.[23] As before, caution should be taken to avoid blood contamination for laboratory studies aimed at identifying a monoclonal protein in the CSF.

Molecular testing in CNS biopsy and CSF

Immunoglobulin gene rearrangement analysis

Because of the complex process of VDJ rearrangement resulting in a unique B-cell receptor in each B lymphocyte, analysis of the immunoglobulin (Ig) gene rearrangement is an essential tool for establishing the clonal character of a lymphoid B-cell population.[24,25] In addition, Ig rearrangement testing can help establish the clonal relationship

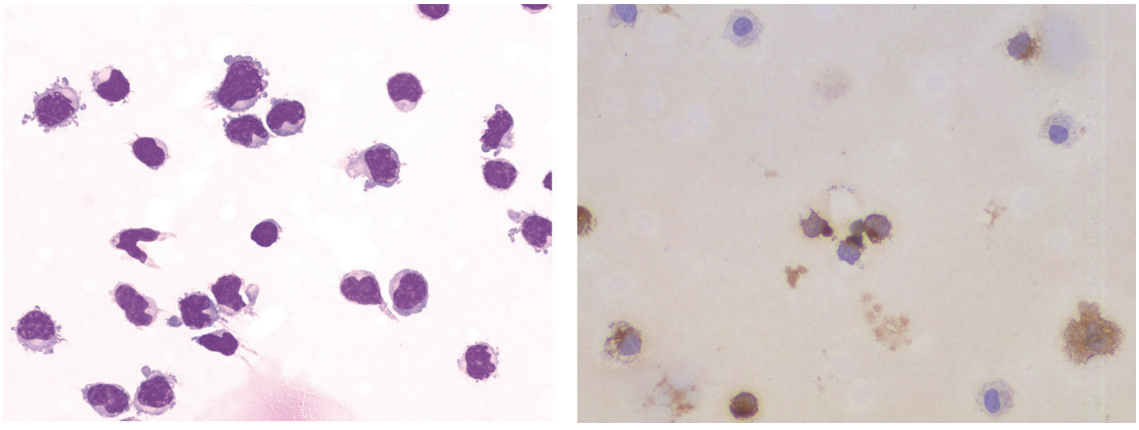

Figure 1. Morphology of CSF. Left panel; Giemsa stain of the CSF of a patient with BNS relapse after previous diagnosis of WM. Right panel; kappa immunohistochemistry positivity of the LPL cells which was concordant with LPL in bone marrow biopsy. *MYD88*^{L265P} mutation tested positive in the CSF. (*Courtesy of Mrs van Lom and Leguit*).

between samples. Therefore, identifying the same clonal Ig heavy and/or light chain gene rearrangements in the LPC from a CNS biopsy or the CSF and BM can provide strong evidence in support of the diagnosis of BNS.[17,26] Due to the low rate of infiltration of cells in the CSF, it may be difficult to detect a clonal B-cell population in the CSF given the low sensitivity of this technique. Moreover, the possibility to perform several genetic tests may be limited with few malignant cells in the CSF.

MYD88^{L265P} *mutation*

Whole genome sequencing has shown mutations in *MYD88* to be highly prevalent in WM.[27] In the vast majority of patients, a point mutation at amino acid position 265 is found, resulting in a leucine to proline change (*MYD88*^{L265P}).[28] Using more sensitive diagnostic techniques, such as allele-specific PCR assay (AS-PCR), *MYD88*^{L265P} mutations are found in 93-97% of WM patients, whereas it is found only in a minority of other indolent lymphomas. Using a highly sensitive real time quantitative PCR (qPCR) technique, it has been demonstrated that *MYD88*^{L265P} can be detected in the CSF of BNS patients, and the mutation was also present in the CNS biopsy in one patient.[4,18,26] Moreover, disappearance of the *MYD88*^{L265P} by AS-PCR correlated with clinical and MRI response. Since the qPCR is a very sensitive technique, caution must be taken to avoid blood contamination of the CSF since *MYD88*^{L265P} can also be detected in peripheral blood.[29] It is therefore advised to use the last diagnostic tube of CSF for this test to decrease the likelihood of blood contamination and false detection of *MYD88*^{L265P}. The detection of the *MYD88*^{L265P} mutation in a CNS biopsy or CSF sample is not specific for BNS. In a recent study, *MYD88*^{L265P} was detected in brain biopsy material from 17/18 patients with PCNSL.[30] Other groups have also detected the *MYD88*^{L265P} mutation in high prevalence in PCNSL patients, and similarly in lymphomas presenting in other immune-privileged sites such as the testes.[31,32]

In WM patients, whole genome sequencing has also identified mutations in CXCR4, a cell surface receptor that binds to CXCL12 (SDF-1a) and promotes migration of LPC to the BM stroma.[33,34] Approximately 30-40% of WM patients harbor CXCR4 mutations.[35] Sanger sequencing of cells obtained from CSF and BM of 3 BNS patients did not identify CXCR4 mutations, though detection of these mutations by Sanger may have been outside the limits of detection.[18] Further studies, including the use of the more sensitive AS-PCR to detect nonsense mutations or high depth targeted re-sequencing may help identify CXCR4 mutations in LPC from CSF in WM patients with BNS.

Radiology

Magnetic resonance imaging (MRI) of the brain and spinal cord is essential for the diagnosis of CNS lymphomas, and this is also advised in cases of suspected BNS.[6,36] MRI abnormalities can be found in the majority of patients.[3,4] The goal of neuroimaging is not only to find supportive evidence for BNS, but also for the exclusion of differential diagnoses (infectious and others), and to select a possible site for biopsy. MRI should be performed prior to lumbar puncture to exclude focal mass effects and/or obstructive hydrocephalus as well as to avoid non-specific meningeal enhancement that occurs after CSF sampling. The MRI protocol must include fluid-attenuated inversion recovery and T1-weighted sequences before and after non-iodine gadolinium contrast injection. Due to the rarity of BNS, optimal imaging protocols have yet to be established.

Two categories of CNS involvement in BNS can be distinguished by MRI imaging: the diffuse form, and the tumoral form.[37] The diffuse form corresponds to lymphoid cell infiltration in the leptomeningeal sheaths and the perivascular spaces, and usually presents with contrast enhancement and/or thickening of meningeal sheaths; best evaluated in T1 WI after gadolinium administration (Figure 2A&B). In contrast, the tumoral form can be unifocal or multifocal, and is usually located in the deep subcortical hemispheric regions, well-demonstrated in T1 WI and FLAIR sequences as well as in T1 WI after gadolinium administration (figure 2A&B).[38] Other characteristic findings of leptomeningeal lymphoma can include abnormal contrast enhancement of cranial and spinal nerves as well as thickening and enhancement of the *cauda equina* (Figure 2C). Increased parenchymal signal intensity can be identified in T2 and in FLAIR images corresponding either to the tumoral form of the disease or to vasogeneic edema (figure

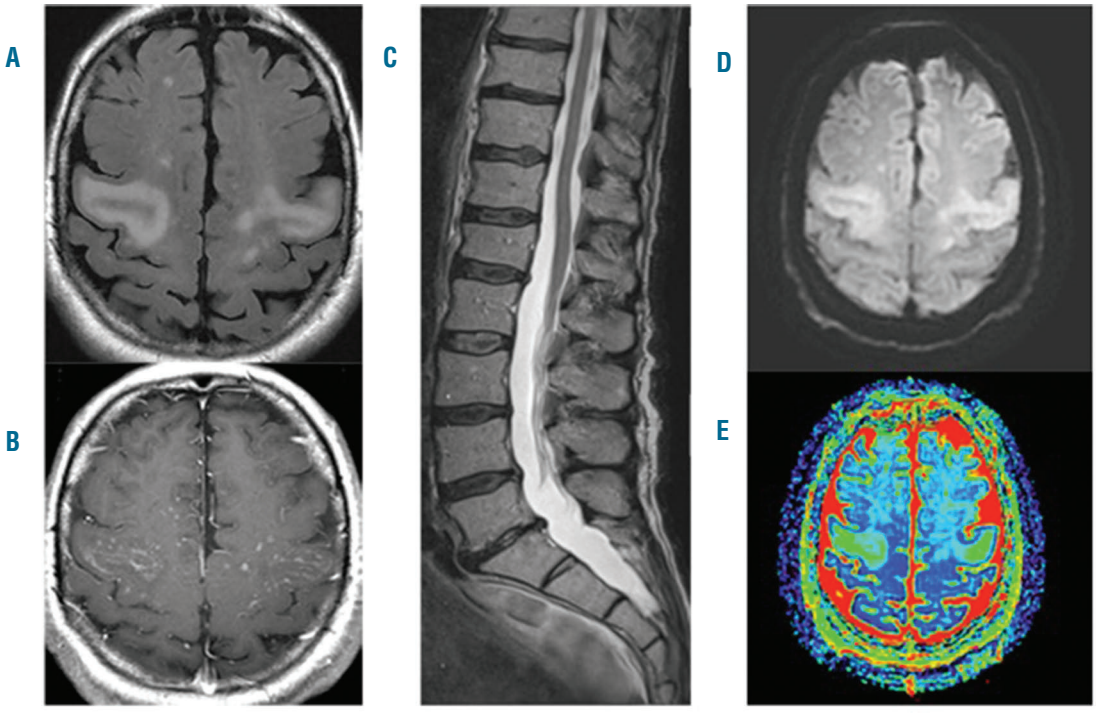

Figure 2. MRI abnormalities in BNS. A. Parenchymal involvement of the brain, increased signal abnormalities in both pre-central regions in axial FLAIR sequence. B. Brain parenchymal involvement, multiple nodular contrast enhancement in both pre-central regions in axial T1 sequence after contrast media administration. C. Cauda equina thickening T2 sagittal sequence D. Positive diffusion showing high signal in both pre-central regions. E. ADC map reconstruction showing high signal in both pre-central regions.

2A).[39,40] In diffusion weight imaging (DWI) images, increased signal intensity with elevated or normal (isointense) apparent diffusion coefficient (ADC) values , suggestive of vasogenic edema, can be caused by a malignant cell infiltration in the perivascular spaces damaging this blood-brain barrier (figure 2D&E).[38,39] In contrast, a restriction of diffusion due to vascular infarcts may be related to HVS and, therefore, DWI can help in the differential diagnosis of BNS.

Although MRI is a very sensitive technique for the detection of malignant infiltration of the CNS, it cannot differentiate between the different histological entities of CNS lymphoma, nor does it obviate the need for CSF or tissue sampling. Absence of MRI findings should not be considered a basis to exclude the diagnosis of BNS.[21]

Blood analysis

Because BNS is mainly diagnosed concurrently with or following a prior diagnosis of WM, the blood work-up should include at least a full blood count, serum viscosity, serum PEP, serum IF, and quantification of serum IgM, IgG and IgA levels, β2 microglobulin, and cryoglobulins. When systemic WM is present, the IPSSWM score at diagnosis may help with risk assessment for systemic disease, though it is not a prognostic marker for BNS.[41,42]

Ocular assessment

Involvement of the eye is rarely described in WM, besides the changes in the retina in HVS, but may occur in BNS.[43,44] It is advised to consult an ophthalmologist for extended eye examination in patients with new complaints of the eyes and/or sight where no abnormality is evident from direct ophthalmoscopy.

Recommendations

The task force recommends that definitive histological evidence should be sought to establish the diagnosis of BNS. Weighing the risks *versus* benefits of this procedure may be accomplished as follows:

I) A direct biopsy of the affected CNS tissue demonstrating lymphoplasmacytic lymphoma.

or

II) CSF analysis demonstrating cytological detail supportive of lymphoplasmacytic lymphoma without evidence of clinical transformed disease, and the presence of monoclonal B cells evidenced by MFC or molecular technique such as Ig rearrangement analysis or MYD88^{L265P} mutation.

Abnormal brain and/or spinal MRI imaging demonstrating leptomeningeal or parenchymal disease is supportive but not sufficient for the diagnosis of BNS. Absence of abnormal MRI findings does not exclude the diagnosis of BNS.

In all other circumstances, BNS may be suspected without definitive evidence for diagnosis, and further diagnostic testing is advised.

Prognosis

WM is an indolent lymphoma with an estimated median survival of 7-12 years.[45] Treatment for WM is initiated when symptomatic disease is present, and current prognostic criteria are not useful in either determining start of treatment nor in choosing which treatment type to use. For BNS, there are no established prognostic factors, and in most case reports only a short follow-up is available. However, long-term survival for more than 10 years after successful treatment has been described.[46] Simon *et al.*

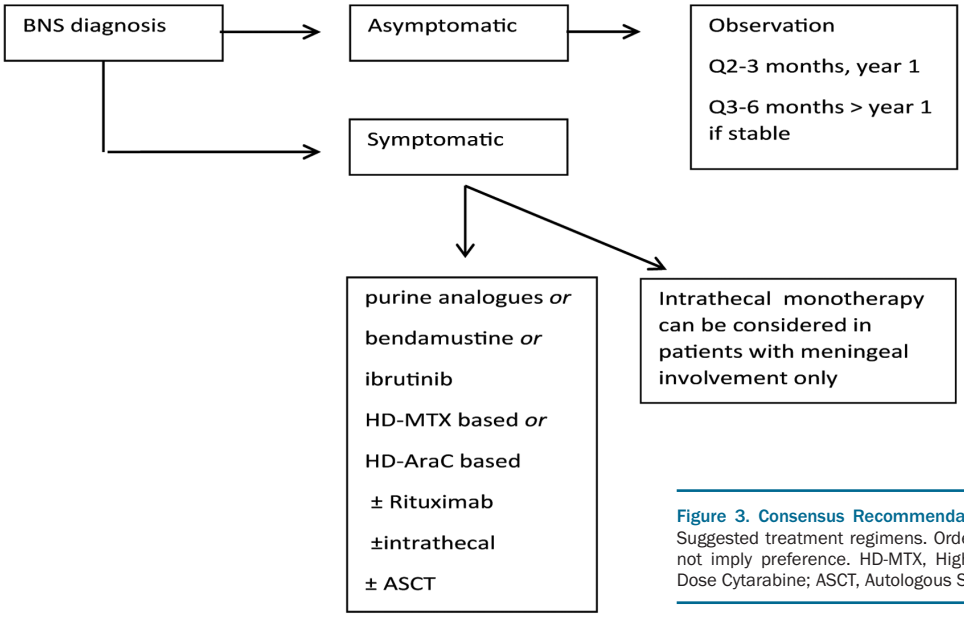

Figure 3. Consensus Recommendations for Treatment Approach of BNS. Suggested treatment regimens. Order of regimens is alphabetical and does not imply preference. HD-MTX, High Dose Methotrexate; HD- ARA-C, High Dose Cytarabine; ASCT, Autologous Stem Cell Transplantation.

described a survival rate of 71% at 5 years and 59% at 10 years in a retrospective cohort of 44 patients with BNS.[3] In a cohort of 34 patients, Castillo *et al*. estimated the 3 years overall survival rate to be 59% and identified, in univariate analysis, age above 65 years, previous treatment for WM, and platelet count <100 x 10^9/L as adverse prognostic factors.[4]

Treatment Goals

Treatment should be offered to symptomatic patients in whom a definitive diagnosis of BNS has been established. The aim of treatment of BNS is to reverse the clinical symptoms and induce long progression-free survival (PFS). As in WM, which is an indolent, non-curative disease, the current goal of treatment does not necessitate the complete eradication of all malignant cells, but the improvement of outcome for patients. Some patients may continue to have CSF detectable disease, for example with sensitive *MYD88*^{L265P} AS-PCR testing, following treatment despite becoming asymptomatic.[4] Currently, there is not enough information to support continuous treatment in these patients. Moreover, radiological findings may lag behind clinical improvement or resolution of symptoms. Also, while gadolinium-enhancing lesions are expected to regress with successful therapy, residual lesions on T2 or FLAIR images may persist, representing gliosis or demyelination rather than residual LPC; these T2/FLAIR lesions alone do not necessarily constitute persisting disease. As such, treatment should be guided by clearance of the patient's symptoms. On the other hand, it is also important to realize that some clinical symptoms or signs may not be reversible due to the lower regenerative capacity of the CNS and PNS. These sequelae should therefore not be interpreted as treatment failure, and treatment may be stopped when the best clinical result is accomplished. Since the used treatment regimens can also induce brain damage, the possibility of clinical decline induced by the brain penetrating treatment regimens should be excluded as much as possible when considering progression of relapse.[47]

Response Criteria

Besides the clinical response, ongoing response, as well as progression or relapse, can be monitored by way of serial MRI imaging and/or examination of the CSF. The CSF response can be monitored during and after treatment, and normalization of the CSF may indicate an adequate anti-tumor strategy. Serial quantitative measurement of the CSF cellular compartment for *MYD88*^{L265P} mutation by qPCR has not been examined, but may represent a promising technology given its ability to detect changes in systemic WM disease.[18,48]

The task force therefore proposes the following response criteria:

Complete Remission (CR); resolution of all reversible clinical symptoms with normalization of cerebrospinal fluid (CSF) and magnetic resonance imaging (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 CR attainment.

Partial response (PR); 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 MFC, and/or molecular techniques of BNS disease; or progression or new findings attributed to BNS by MRI examination of the brain and/or spine.

Evaluation of response should be considered once during treatment, and then at the end of treatment. With continuous treatment, testing can be done after 3-4 months and then yearly, but only in those patients in which a neurological improvement is seen. Evaluation should be performed earlier if there is a lack of clinical response, and also at the moment of progressive neurological disease.

The above criteria for BNS assessment should be

applied independently of the evaluation of systemic WM disease.

Treatment Strategy

General

In the recent retrospective surveys with response data of 44 and 34 BNS patients, respectively, the overall response rate was 70% to first line therapy, and no differences according to type of treatment could be made.[3,4] Therefore, the choice for the type of systemic treatment should be made on an individual basis, considering the patient condition, medical history, preference and experience of the physician.

BNS can exist with or without concurrent WM. It is not known if the occurrence of both disease presentations influence one another. Furthermore, there are no data to suggest that effective treatment of the systemic WM component may beneficially influence the outcome of the BNS treatment. On the other hand, many of the treatments used for BNS, such as fludarabine, cladribine, bendamustine, and ibrutinib, clearly have systemic effects and therefore a positive effect of adequate systemic treatment cannot be ruled out. However, the indication for treatment for the systemic WM component should be made on its own merits according to the published guidelines for definition of symptomatic WM.[13]

Steroid therapy

Evidence from PCNSL cases indicates sensitivity to steroid therapy, with prompt clinical improvement and radiological resolution within 48 hours.[49] However, this response is short-lived, with disease recurrence occurring soon after steroid cessation. Steroid treatment should therefore not be thought of as long-lasting effective therapy in BNS, and should, if possible, be avoided before tissue biopsy and CSF investigation to assure optimal histopathological assessment.

Chemotherapy

Several treatment options can be considered. These options include intrathecal, intraventricular, and systemic chemotherapy with known or probable penetration of the blood-brain barrier. Most series that have reported on the outcome of treatment for BNS are retrospective, with only one small series reported on the treatment of four serial consecutive patients.[46] Chemotherapy regimens commonly used for the treatment for BNS are mainly adapted from treatment schedules used in the treatment of PCNSL. These treatments include high dose methotrexate (MTX) and high dose cytarabine (Ara-C) for several cycles.[50] This may be an appropriate treatment for patients considered fit for intensive therapy. However, with standard dosed fludarabine, cladribine, and bendamustine, responses have been achieved, and these drugs can also be used in the front-line setting.[3,4,51-53] Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has recently been improved for the treatment of WM, dosed 420 mg once daily. Recent reports suggest that both this dose, as well as the 560 dosing as used in Mantle cell lymphoma, is effective and capable of passing the blood-brain barrier.[48,54,55]

Intrathecal treatment may be combined with systemic treatment to treat meningeal involvement of BNS since monotherapy with intrathecal drugs rarely induces long-lasting responses.[17]

Anti-CD20 therapy

Rituximab is mostly given systemically and combined with chemotherapy. Monotherapy is not advised due to uncertainty of blood-brain barrier passage. In PCNSL, intrathecally administered rituximab therapy has been described as efficacious, but serious side effects have also been reported with this type of administration and is, therefore, not advised as first-line treatment.[56, 57]

Treatment of Relapsed BNS

Relapse treatment is feasible in BNS patients. In a retrospective analysis, 53% of the initial 34 patients were re-treated, and 48% responded to this treatment.[4] In this setting, factors to be considered are the depth of response and duration of response to previous treatment. The role of autologous stem cell transplantation (ASCT) is unclear but can be considered in young patients with aggressive disease behavior.[3,4,58] The optimum conditioning therapy has not been clarified, but in patients with PCNSL, BCNU/thiotepa conditioning is recommended over BEAM (BCNU, etoposide, cytarabine and melphalan) by the European Association for Neuro-Oncology.[50]

The toxicity of standard chemotherapy treatment is well known to oncologists and hematologists but it must be realized that applying blood-brain barrier penetrating chemotherapy may induce more unknown central nervous system toxicity like dizziness, confusion and changes in mental status. These side effects must be distinguished from disease progression.[47] In Table 1, all chemotherapy regimens published in English peer reviewed journals are listed with information on treatment outcome.

Radiation Therapy

BNS is sensitive to radiotherapy (RT). The effective use of RT has been described in many case reports, both as first-line and as rescue therapy.[12,59,60] Localized RT to affected lesions at a dose of 30 to 40 Gy may be preferable to whole brain radiation to limit toxicity; this may fail to address widespread deposits that are not apparent on imaging. In general, cerebral RT, even when localized (stereotactic techniques), is associated with enhanced neurotoxicity, especially the occurrence of late neurocognitive effects in elderly patients which can affect up to 80% of patients.[61] Therefore, first-line use of RT is not recommended and should be reserved for patients failing other treatment options. However, RT may be considered in BNS patients with localized spinal involvement in whom toxicity can be limited.

Treatment Algorithm

Although limited data are available, a treatment algorithm is proposed for the treatment of *de novo* BNS patients (Figure 3). Since anecdotal information confirms that patients can be asymptomatic and that clinical improvement is the most important treatment goal, asymptomatic patients may be observed without initial treatment. When patients have BNS with a tumoral presentation localized in deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum), systemic therapy is advised; in some patients with only meningeal involvement, use of monotherapy with intrathecal treatment may be an option. However, most of

the responses with only intrathecal chemotherapy are not long-lasting. Other factors to be considered are prior therapy for WM with persisting or possible long-term side effects. For example, repeated use of purine analogues may compromise stem cell collection in the future and may increase the risk of disease transformation. Intensive chemotherapy with high dose chemotherapy increases the occurrence of side effects in patients. In the relapse setting, factors to be considered are the response and duration of response to previous treatment. The use of blood-brain barrier passing chemotherapy in patients that were previously treated with RT is not advised due to the increased neurotoxicity if used in this order.

Proposed Clinical Trials

The task force recognizes that there is a need for prospective clinical trials that will incorporate a uniformly diagnosed patient group with BNS, treated with a standardized treatment protocol. Moreover, incorporating the novel diagnostic CSF techniques both for diagnosis and follow up will aid in the understanding of this rare disease manifestation. Since BNS patients are often elderly, these treatments should be as toxicity-sparing as possible. Both fludarabine and BTK inhibitors may be particularly attractive candidates for a prospective study given their CNS drug penetrance and efficacy in BNS.

Conclusions

BNS is a rare disease manifestation of WM. The first challenge is to increase physician awareness of the existence of this syndrome and of the performance of the appropriate tests in the right clinical setting to establish the diagnosis. In this guideline, we describe the clinical symptoms as well as the appropriate laboratory and radiological studies that can aid in the diagnosis of BNS. It is important to realize that BNS can present in patients with known WM even in the absence of systemic progression. In a substantial portion of WM patients, BNS can also be the presenting symptom in previously undiagnosed WM. Like other CNS lymphomas, it is important to perform a brain biopsy whenever possible and to expand CSF analysis to include MFC testing; if possible M protein screening as well as molecular diagnostic testing for immunoglobulin gene rearrangement and *MYD88*. MRI of the brain and spinal cord is essential.

The second challenge is to expand our knowledge of the prognosis and treatment outcome of BNS. It should be possible to improve the prognosis for these patients if better treatment strategies are employed and backed up by a commonality of aims and the use of uniform diagnostic and response criteria. Prospective clinical trials in BNS patients that employ uniform treatment along with appropriate laboratory CSF assessments and standardized MRI protocols will be invaluable, and will constitute a significant step forward in delineating treatment outcome for this intriguing disease manifestation.

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