bjh research paper

Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi-institutional retrospective study

Jorge J. Castillo,[1] Shirley D'Sa,[2] Michael P. Lunn,[2] Monique C. Minnema,[3] Alessandra Tedeschi,[4] Frederick Lansigan,[5] M. Lia Palomba,[6] Marzia Varettoni,[7] Ramon Garcia-Sanz,[8] Lakshmi Nayak,[1] Eudocia Q. Lee,[1] Mikael L. Rinne,[1] Andrew D. Norden,[1] Irene M. Ghobrial[1] and Steven P. Treon[1]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [2]University College London Hospitals, London, UK, [3]University Medical Centre Utrecht, Utrecht, the Netherlands, [4]Ospedale Niguarda Ca' Granda, Milano, Italy, [5]Dartmouth-Hitchcock Medical Center, Lebanon, NH, [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [7]Policlinico San Matteo, Pavia, Italy and [8]Hospital Universitario de Salamanca, Salamanca, Spain

Received 11 August 2015; accepted for publication 30 October 2015
Correspondence: Jorge J. Castillo, Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, 450 Brookline Ave, M221, Boston, MA 02215, USA.
E-mail: jorgej_castillo@dfci.harvard.edu

Summary

Bing-Neel syndrome (BNS) is a rare complication seen in patients with Waldenström macroglobulinaemia (WM), in which lymphoplasmacytic lymphoma cells colonize the central nervous system. In this retrospective multi-centre study, we present the clinicopathological features, imaging findings, therapy, response and outcomes of 34 patients with BNS. The median time from WM diagnosis to BNS diagnosis was 3 years, 15% of patients were diagnosed with BNS at the time of WM diagnosis, and 22% of patients developed BNS when responding to active treatment for WM. Patients with BNS presented with variable clinical features including limb motor deficits, change in mental status and cranial nerve palsies. The diagnosis was made using a combination of cerebrospinal fluid cytology, flow cytometry and detection of the *MYD88* L265 mutation, and magnetic resonance imaging. The estimated 3-year overall survival rate was 59%. Of the survivors, 40% have evidence of pathological and/or radiological persistence of disease. Age older than 65 years, platelet count lower than 100×10^9/l, and treatment for WM prior to BNS diagnosis were associated with worse outcome. Exposure to rituximab for treatment of BNS was associated with a better outcome. Multi-institutional collaboration is warranted to improve treatment and outcomes in patients with BNS.

Keywords: Bing-Neel syndrome, Waldenström macroglobulinaemia, lymphoplasmacytic lymphoma, central nervous system.

Waldenström macroglobulinaemia (WM) is a rare B-cell lymphoproliferative disorder that accounts for 1–2% of cases of non-Hodgkin lymphoma. WM is characterized by the malignant growth of IgM-secreting lymphoplasmacytic lymphoma (LPL) cells in the bone marrow and the presence of a monoclonal IgM paraprotein in the serum (Swerdlow *et al*, 2008). Patients with a diagnosis of WM can experience prolonged survival times, often measured in decades (Castillo *et al*, 2014, 2015).

Although WM is primarily located in the bone marrow space, up to 20% of patients with WM develop extramedullary disease during the course of their disease (Treon, 2015). Bing-Neel syndrome (BNS) is a rare complication seen in patients with WM, in which the malignant LPL cells gain access to the central nervous system (CNS). Given that literature on BNS is limited to case reports and small case series, the incidence of BNS is unknown, the diagnosis remains challenging, the treatment approaches are non-standardized and the prognosis is uncertain.

The objective of this multicentre retrospective study is to describe the characteristics as well as diagnostic and therapeutic approaches and outcomes in consecutive WM patients with pathological evidence of BNS.

Methods

We searched the database of our institutions for patients older than 18 years with a diagnosis of WM, based on current diagnostic criteria (Owen *et al*, 2003), and also clinical, radiological and pathological evidence of WM involvement

© 2015 John Wiley & Sons Ltd

First published online 21 December 2015
doi: 10.1111/bjh.13883

in the CNS. The presence of leptomeningeal enhancement by magnetic resonance imaging (MRI) and/or the presence of phenotypic malignant lymphoplasmacytoid cells in cerebrospinal fluid (CSF) cytology or clonal B-cells in the CSF flow cytometry were considered evidence of CNS involvement by WM. The Institutional Review Boards from all participating centres approved the present study. This study includes updated data from previously published cases (Varettoni *et al*, 2015; Vos *et al*, 2015).

Clinical [age at WM diagnosis, age at BNS diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, previous therapies, response to most recent therapy, presence of extramedullary involvement], laboratory (blood counts, immunoglobulin levels, albumin, beta-2-microglobulin) as well as diagnostic procedures (i.e. CSF and imaging studies) and therapies received by these patients (i.e. intrathecal and/or systemic) are presented descriptively. The International Prognostic Scoring System for Waldenström Macroglobulinaemia (IPSSWM) was calculated using established criteria (Morel *et al*, 2009). For the purpose of IPSSWM calculation in the present study, age and other parameters were collected at BNS diagnosis.

Response to therapy in BNS has not been standardized, but we have defined complete response (CR) as resolution of symptoms as well as resolution of radiological and pathological abnormalities, independently of response of WM on bone marrow or protein level. Partial response (PR) was defined as improvement without complete resolution, or complete resolution of some but not all symptoms, radiological and/or pathological findings. Non-response was defined by persistence or worsening of symptoms, radiological or pathological findings.

We estimated the time from WM diagnosis to BNS diagnosis, and the time from BNS diagnosis to last follow-up or death [overall survival (OS)] using the Kaplan–Meier method for incomplete observations (Kaplan & Meier, 1958). OS comparisons between groups were performed using the log-rank test (Mantel, 1966). No multivariate analysis was attempted given the small sample size. *P*-values $< 0{\cdot}05$ were considered statistically significant. All graphs and calculations were performed using STATA/SE 13.1 (StataCorp, College Station, TX, USA).

Results

Patients' characteristics

A total of 34 patients with BNS from eight centres were included in our study. Twenty patients (59%) were from the US and 14 (41%) were from Europe. The male-to-female ratio was 1·3. The median time from WM diagnosis to BNS diagnosis was 3 years (range 0–16 years; Fig 1A). The most common symptoms at BNS diagnosis were motor deficits of the limbs (35%) and altered mental status (35%). The median ECOG performance status was 1 (range 0–3), 20 patients (59%) had history of extramedullary involvement and one patient (3%) presented with B symptoms. According to the IPSSWM, 15 patients (54%) were low, 10 (36%) were intermediate and 3 (10%) were high-risk for death. Selected clinical characteristics are shown in Table I.

Five patients (15%) were diagnosed with BNS at the time of WM diagnosis. In addition, five patients (15%) did not receive therapy for WM following WM diagnosis until the diagnosis of BNS. Twenty-four patients (70%) received treatment for WM before diagnosis of BNS. The median number of lines of therapy received by the 24 patients prior to BNS diagnosis was 1 (range 0–5). Twenty-four patients (100%) were previously exposed to rituximab, 19 (79%) to alkylating agents, 6 (25%) to proteasome inhibitors, 5 (21%) to nucleoside analogues, 2 (8%) to immunomodulators, 1 (4%) to everolimus and 1 (4%) to imatinib. At the time of BNS diagnosis, seven patients (29%) were actively receiving therapy, of which six (86%) were responding to their current therapy based on serum IgM level reduction.

Diagnostic workup

Leptomeningeal enhancement was seen on brain MRI in 20/34 (59%), and on spinal MRI in 15/24 (63%) of the patients tested. In total, 27 patients (79%) had abnormal MRI findings; 12 patients (44%) had findings in the brain only, 8 (30%) had brain and spine findings and 7 (26%) had findings in the spine only. Two cases showed the presence of a discrete intracranial mass along with leptomeningeal abnormalities. CSF cytology showed evidence of atypical lymphocytes with plasmacytoid differentiation in 28/34 (82%) and flow cytometry detected a monoclonal population of $CD19^+/CD20^+$ cells in 27/32 (84%) of the patients tested. Twenty-five patients (78%) showed evidence of BNS by CSF cytology and flow cytometry, four patients (13%) by CSF cytology only and three patients (10%) by CSF flow cytometry only. Representative cytology from a BNS patient is shown in Fig 2. CSF *IGH* gene rearrangement was detected by polymerase chain reaction (PCR) in 14/15 (94%) and the CSF *MYD88* L265P gene mutation was detected by PCR in 7/7 (100%) of the patients tested. All of the cases in which the *MYD88* L265P gene mutation was identified in the CSF showed the mutation in the bone marrow. Of the seven patients with no abnormal MRI findings, five had evidence of disease by CSF cytology and flow cytometry, one by cytology and one by flow cytometry.

Therapy for BNS

The median number of lines of therapy given for BNS was 1 (range 1–4). Of the 34 patients diagnosed with BNS, 32 (94%) received initial therapy for BNS. Of the 32 treated patients, 9 patients (28%) achieved CR, 12 (38%) PR and 11 (34%) did not respond to frontline therapy. After first line treatment, 15 patients did not receive additional treatment; 7 are alive without evidence of disease (AWOD), 5 died with disease, 2 died in CR and 1 is alive with evidence of disease

© 2015 John Wiley & Sons Ltd

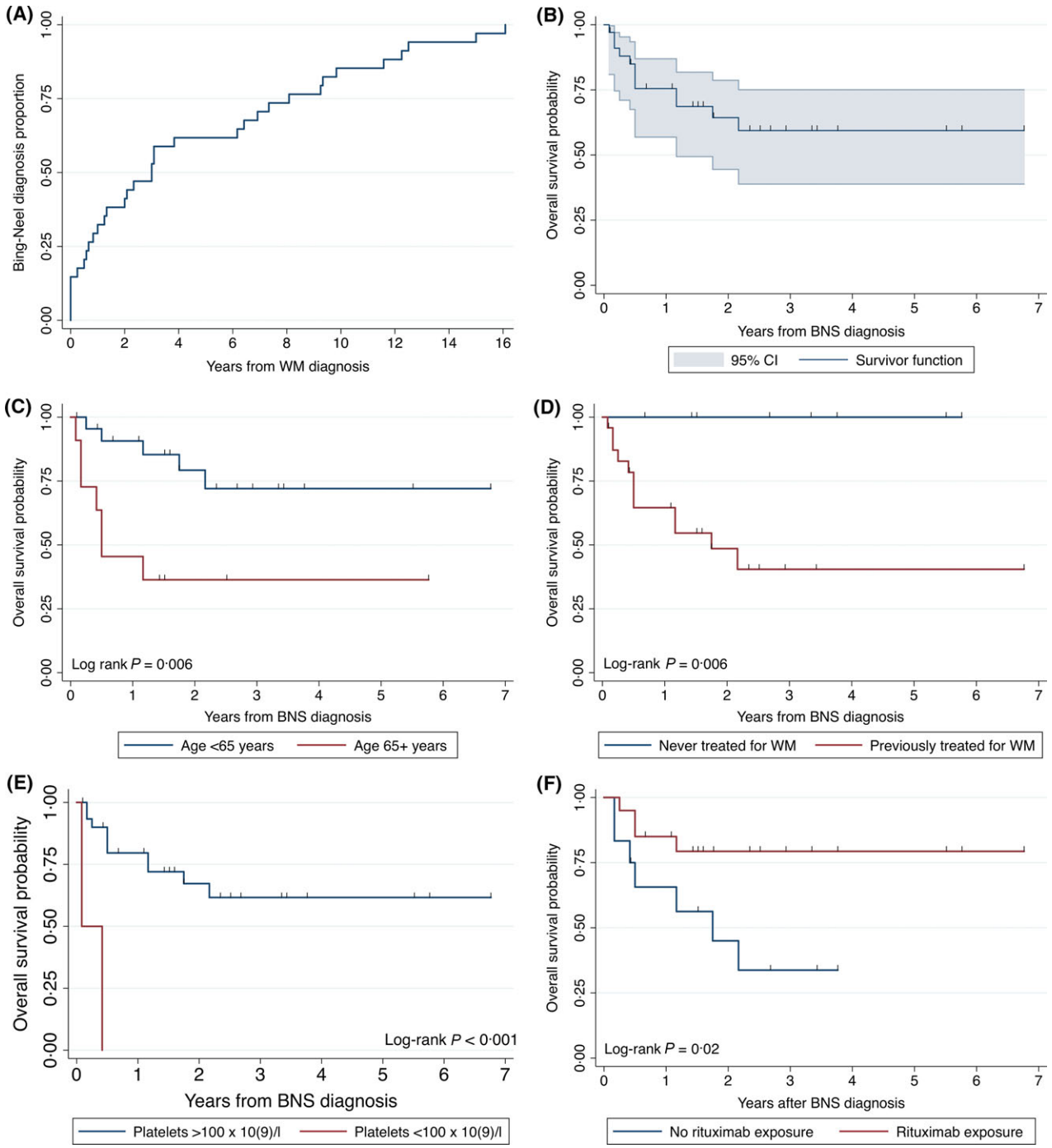

Fig 1. (A) Time in years from Waldenström macroglobulinaemia diagnosis to diagnosis of Bing-Neel syndrome (BNS), and overall survival estimates for (B) the whole cohort, and according to (C) age, (D) previous treatments for Waldenström macroglobulinaemia (WM), (E) platelet count, and (F) use of rituximab for BNS therapy. 95% CI, 95% confidence interval.

(AWD). Seventeen patients (53%) received second line therapy: 4 (24%) achieved CR, 4 (24%) PR and 9 (52%) did not respond to therapy. Of these patients, 9 did not receive additional treatment; 4 are AWD, 3 are AWOD and 2 died with disease. Eight patients (25%) received third line therapy; of those, 3 patients (38%) achieved CR, 3 (38%) PR and 2 (25%) did not respond. Of these, 7 patients did not receive additional treatment; 2 died with disease, 3 are AWD, 1 is AWOD and 1 died in CR. One patient has received fourth line therapy, and is currently in CR. A list of the regimens used to treat BNS and rates of response is shown in Table II. Three patients underwent autologous stem cell transplantation (SCT) for BNS; one achieved CR and is AWOD, one achieved CR but later progressed and died from BNS, and

© 2015 John Wiley & Sons Ltd

Table I. Selected clinical characteristics of 34 patients at the time of diagnosis of Bing-Neel syndrome.

Characteristic	Median (range) or *N* positive/*N* tested (%)
Continuous variables	
Age at WM diagnosis (years)	56 (38–74)
Age at BNS diagnosis (years)	62 (39–76)
Immunoglobulin M (g/l)	13·1 (0·3–59·4)
Immunoglobulin G (g/l)	6·9 (2·2–15·5)
Immunoglobulin A (g/l)	0·6 (0·1–2·0)
Categorical variables	
Male sex	19/34 (56%)
Haemoglobin <115 g/l	12/33 (36%)
Platelet count <100 × 10^9/l	2/33 (6%)
Beta-2-microglobulin >3 mg/l	12/23 (52%)
Kappa light chain	22/34 (65%)
Lambda light chain	11/34 (32%)
No light chain	1/34 (3%)
Extramedullary involvement	
Lymphadenopathy	14/34 (41%)
Skeletal bone	3/34 (9%)
Eye and orbit	2/34 (6%)
Liver and spleen	2/34 (6%)
Ovary	1/34 (3%)
Para-spinal soft tissue	1/34 (3%)
Subcutaneous	1/34 (3%)
Symptoms at BNS diagnosis	
Limb motor deficits	12/34 (35%)
Altered mental status	12/34 (35%)
Cranial nerve symptoms	10/34 (29%)
Peripheral neuropathy	4/34 (12%)
Headaches	4/34 (12%)
Seizures	4/34 (12%)
Unsteady gait	4/34 (12%)
Limb pain	2/34 (6%)

WM, Waldenström macroglobulinaemia; BNS, Bing-Neel syndrome.

one did not respond but then achieved CR with high-dose methotrexate and rituximab followed by allogeneic SCT.

Survival analysis

After a median follow-up of 30 months, 13 patients (38%) had died and the estimated 3-year OS rate was 59% (95% CI 39–75%; Fig 1B). The most common cause of death was BNS progression in 10 patients (77%). At the time of this report, there were data on evidence of disease in 17 out of 21 of the survivors, of which 8 (47%) have clinical, radiological and/or pathological evidence of disease. In the univariate survival analysis, age ≥65 years, previous treatment for WM prior to BNS diagnosis, and platelet count <100 × 10^9/l were associated with worse OS. Kaplan–Meier OS estimates are shown in Fig 1C–E. Sex, other extramedullary disease, haemoglobin >115 g/l, beta-2-microglobulin >3 mg/l, ECOG performance status >1, light chain subtype and IPSSWM

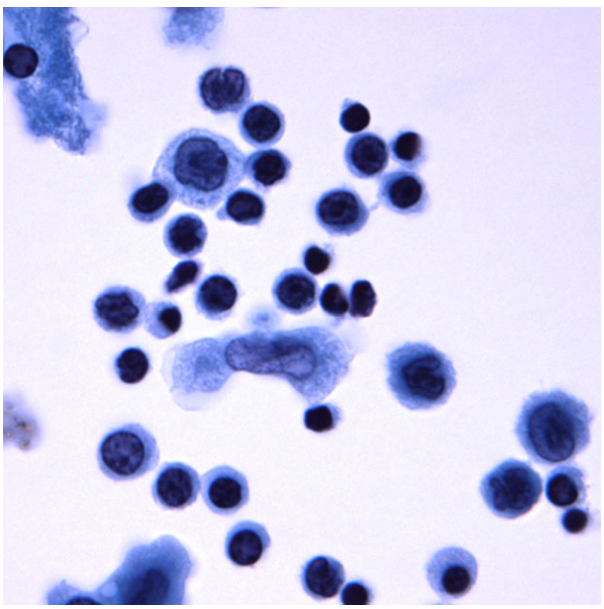

Fig 2. Cytological appearance of Waldenström macroglobulinaemia cells in the cerebrospinal fluid (400×).

Table II. Therapies and rates of response in patients with Bing-Neel syndrome.

Therapies	*N* (%)	CR (%)	PR (%)	NR (%)
First line (*n* = 32)				
HDMTX-based	13 (41)	2 (15)	6 (46)	5 (38)
Intrathecal-based	6 (19)	1 (17)	2 (33)	3 (50)
HDMTX+HIDAC-based	5 (16)	4 (80)		1 (20)
Fludarabine-based	3 (9)	1 (33)	2 (67)	
Bendamustine-based	2 (6)		2 (100)	
Other regimens*	3 (9)	1 (33)		2 (67)
Second line (*n* = 17)				
Intrathecal-based	6 (35)		3 (50)	3 (50)
HDMTX-based	2 (12)	1 (50)		1 (50)
HIDAC-based	2 (12)	1 (50)		1 (50)
Bendamustine-based	2 (12)		1 (50)	1 (50)
Fludarabine-based	1 (6)	1 (100)		
Other†	4 (24)			2 (100)
Third line (*n* = 8)				
Bendamustine	3 (38)	1 (33)	1 (33)	1 (33)
Fludarabine	2 (25)	1 (50)		1 (50)
Ibrutinib	2 (25)		2 (100)	
Other regimens‡	1 (13)	1 (100)		

CR, complete response; PR, partial response; NR, no response; HDMTX, high-dose methotrexate; HIDAC, high-dose cytarabine.
*Other regimens include: R-ICE (rituximab, ifosfamide, carboplatin, etoposide); R-DHAP (rituximab, cytarabine, cisplatin, dexamethasone); and radiotherapy only.
†Other regimens include: hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone); pemetrexed; dexamethasone and rituximab; and radiotherapy alone.
‡Other regimens include: radiotherapy alone.

© 2015 John Wiley & Sons Ltd

were not associated with better or worse OS. With regard to therapy, the use of rituximab at any point during therapy for BNS was associated with better OS than not receiving rituximab (Fig 1F). Systemic methotrexate, systemic cytarabine, bendamustine, fludarabine, intrathecal chemotherapy and radiotherapy were not associated with OS (data not shown).

Discussion

Bing and Neel (1936) described two patients with a rapid neurological deterioration in the setting of macroglobulinaemia. Interestingly, these cases were reported 8 years before the seminal report by Jan Waldenström (1944). The data available have been limited to case reports and small case series (Grewal *et al*, 2009; Malkani *et al*, 2010; Abdallah *et al*, 2013; Poulain *et al*, 2014; Cuenca Hernandez *et al*, 2015; Vos *et al*, 2015), although a large case series has recently been published (Simon *et al*, 2015). A literature review found that several so-called BNS cases were actually cases of transformation to large cell lymphoma, hyperviscosity, peripheral neuropathy and/or cases of primary CNS lymphoma (PCNSL) (Fintelmann *et al*, 2009). Herein, we present the results of a multi-centre retrospective study aimed at describing the characteristics and outcomes of 34 patients with *bona fide* radiological and pathological evidence of CNS involvement by WM.

Our most salient results can be summarized as follows: (i) the median time from WM diagnosis to BNS diagnosis is 3 years, although in one quarter of the patients the diagnosis of BNS was made at the time of WM diagnosis; (ii) one-third of the patients were receiving and responding to active therapy for WM at the time of BNS diagnosis; (iii) most patients with BNS received therapy with combination of systemic and intrathecal chemotherapy, rituximab, novel agents and radiotherapy, although regimens were diverse, which is not unexpected given the lack of standardized treatment approaches for BNS; (iv) responses were seen with any line of therapy; (v) the 3-year OS rate was 59% with most deaths occurring within 2 years of BNS diagnosis; (vi) adverse prognostic factors were age >65 years, previous treatment for WM and platelet count $<100 \times 10^9$/l; and (vii) 40% of BNS survivors have evidence of persistent disease.

A recent French study presented data on 44 patients with BNS (Simon *et al*, 2015). Similarities between studies include a large proportion of patients with primary BNS (BNS detected at the time of WM diagnosis), diagnostic workup consisting of CSF cytology and flow cytometry as well as neuroimaging, the lack of uniformity on treatment approaches, most of the deaths occurred within 2 years of diagnosis and that there are a substantial proportion of BNS survivors. Our study provides additional insights on potential prognostic factors and persistence of disease in BNS survivors.

Bing-Neel syndrome is indeed a rare complication of WM that can be seen at any time during the course of the disease. Although half of the patients with WM developed BNS within 3 years of diagnosis, 18% of WM patients in our cohort developed BNS >10 years after WM diagnosis. Little is known about potential risk factors for the development of BNS. Given the probable low incidence, larger studies would need to be undertaken to evaluate risk factors in a reliable manner. Interestingly, some patients developed BNS while undergoing treatment for WM. This is not entirely unexpected given that most of the agents routinely used to treat WM might not achieve therapeutic levels in the CSF.

Patients with WM who develop BNS can have protean clinical presentations and, in this study, the most frequent reported symptoms were unexplained limb weakness, altered mental status and/or cranial nerve palsies. Diagnostic modalities in our cohort included brain and spinal MRI with gadolinium enhancement, and large volume lumbar puncture (i.e. 10–15 cc of CSF) for cytology, flow cytometry and molecular studies, including PCR assays for *IGH* gene rearrangement and *MYD88* L265P gene mutation. Approximately 90–95% of patients with WM carry the *MYD88* L265P gene mutation in the malignant cells, which can be detected using Sanger sequencing or allele-specific PCR assays (Treon *et al*, 2012). PCR assays can also be used to detect the presence of the mutation in the CSF of WM patients with suspected BNS (Poulain *et al*, 2014). In our cohort, the *MYD88* L265P mutation was detected in all the patients tested by PCR assay. However, it is possible that WM cells, being small lymphocytes, can gain access to the CNS without causing BNS. Therefore, whether neurologically asymptomatic WM patients carry low levels of the *MYD88* L265P mutation in the CSF is unknown at this time. Based on this, the presence of low levels of *MYD88* L265P mutation burden in the CSF should not be confirmatory of BNS in asymptomatic patients or with low suspicion of BNS. Although it is possible that the detection of low levels of *MYD88* mutation by PCR in the CSF could be a consequence of blood contamination, *MYD88* mutation is usually undetectable in the peripheral blood of WM patients who have been previously treated (Xu *et al*, 2014).

The treatment for BNS in our cohort was not uniform, which is a reflection of the lack of standardization. It is difficult to recommend one therapy over another based on the limitations of our study. High-dose methotrexate has been the standard of care for patients with PCNSL (Rubenstein *et al*, 2013), but has been associated with high rates of toxicity and, in our cohort, did not seem to provide benefit in response or survival. Cytarabine can also cross the blood-brain barrier although, when used at high doses, it can induce incompletely reversible neurological deficits (Baker *et al*, 1991). There is evidence that nucleoside analogues can penetrate into the CNS (Cheson *et al*, 1994). Fludarabine, when given systemically, has shown efficacy in patients with CNS involvement by chronic lymphocytic leukaemia (Elliott *et al*, 1999; Knop *et al*, 2005), and a recent report has shown a high rate of response in patients with BNS (Vos *et al*, 2015). Similarly, bendamustine has shown CNS penetration in animal models, and has shown activity in patients with PCNSL (Cheson & Rummel, 2009; Chamberlain, 2014). A

© 2015 John Wiley & Sons Ltd

recent case report showed response to bendamustine in a patient with BNS (Varettoni *et al*, 2015). Also, there is evidence that ibrutinib can cross into the CNS (Bernard *et al*, 2014); this drug induced a response in two patients treated in our cohort. Finally, rituximab might be of benefit in patients with BNS. Although rituximab has a large molecular size and questionable brain penetration, it has demonstrated benefit in combination with other agents in newly diagnosed PCNSL in a randomized trial (Ferreri *et al*, 2015), and also as single agent and in combination in recurrent PCNSL (Chamberlain & Johnston, 2010; Batchelor *et al*, 2011; Nayak *et al*, 2013). In addition, intrathecal administration of rituximab is feasible, with proved efficacy in selected cases (Rubenstein *et al*, 2007). Based on our limited experience, agents such as bendamustine, fludarabine and ibrutinib have shown glimpses of efficacy. Indeed, prospective studies are needed to identify safe and effective therapies, which will be difficult to pursue given the rarity of BNS.

The survival analysis shows that all deaths occurred within 2 years of BNS diagnosis but follow-up continues. Also, 40% of the survivors showed persistence of disease. In all, this finding potentially suggests two distinct biological behaviours. On one hand, some BNS patients would have an aggressive disease that will result in their demise. On the other hand, some patients might have indolent disease that will not cause death but will persist. Adverse prognostic factors in BNS include older age, thrombocytopenia and previous therapy for WM. Additional studies are needed to confirm these findings.

Our study carries a series of weaknesses. This is a retrospective study, which can suffer from selection bias although the included patients were consecutive. Given the small sample, there might be a high rate of false positive and falsely negative results. There was some degree of missing data, which is common in this type of study, however the missing data appeared random. Additionally, defined response criteria have not yet been developed for this disease, and we used a combination of radiographic, pathological and clinical findings to assess response. Finally, although no strong recommendations can be made at this time regarding best therapy, let our study be an effort to bring BNS to the attention of practitioners and scientists.

Conclusion

Bing-Neel syndrome is a rare complication of WM that can occur at any time during the course of the disease and even in patients who are responding to systemic therapy. The treatment of BNS has not been standardized and prospective studies are warranted. Most of the deaths due to BNS progression occur within 2 years of BNS diagnosis, and many of the survivors show persistence of disease. Multi-institutional collaboration could be the answer to improving outcomes in patients with BNS.

Acknowledgements

Portions of this research have been presented at the 2014 American Society of Hematology Annual Meeting, in San Francisco, CA, and at the 2015 International Conference on Malignant Lymphoma, in Lugano, Switzerland.

Author contributions

JJC, SPT designed the study. All the authors provided the subjects for the study, analysed the data and approved the final manuscript.

Conflicts of interest

JJC: Advisory Board: Gilead Sciences. Consultancy: Biogen Idec, Otsuka Pharmaceuticals. Research funding: Gilead Sciences, Millennium Pharmaceuticals, Pharmacyclics. SD: Honoraria: Janssen. MPL: Advisory Board: CSL Behring, Baxter Pharmaceuticals. Research funding: CSL Behring. Speaker: CSL Behring, Grifols, Kedrion. Honoraria: CSL Behring, Grifols. MCM: Consultancy: Amgen, Celgene, Janssen Cilag. AT: No conflict of interest to disclose. FL: Research funding: Teva Pharmaceuticals. MLP: No conflict of interest to disclose. MV: No conflict of interest to disclose. RGS: Honoraria: Novartis, Amgen, Millennium Pharmaceuticals. Research funding: Novartis. Advisory Board: Amgen. SW: No conflict of interest to disclose. LN: No conflict of interest to disclose. EQL: Consultancy: Genentech. MLR: Consultancy: N-Of-One Therapeutics. ADN: No conflict of interest to disclose. IMG: Advisory Board: Bristol-Myers-Squibb, Celgene, Novartis, Takeda. SPT: Research funding, consulting fees, and/or speaking honoraria from Janssen, Onyx, Pharmacyclics, Gilead Sciences.

References

Abdallah, A.O., Atrash, S., Muzaffar, J., Abdallah, M., Kumar, M., Van Rhee, F. & Barlogie, B. (2013) Successful treatment of Bing-Neel syndrome using intrathecal chemotherapy and systemic combination chemotherapy followed by BEAM auto-transplant: a case report and review of literature. *Clinical Lymphoma, Myeloma & Leukemia*, **13**, 502–506.

Baker, W.J., Royer, Jr, G.L. & Weiss, R.B. (1991) Cytarabine and neurologic toxicity. *Journal of Clinical Oncology*, **9**, 679–693.

Batchelor, T.T., Grossman, S.A., Mikkelsen, T., Ye, X., Desideri, S. & Lesser, G.J. (2011) Rituximab monotherapy for patients with recurrent primary CNS lymphoma. *Neurology*, **76**, 929–930.

Bernard, S., Goldwirt, L., Amorim, S., Brice, P., Briere, J., Sauvageon, H. & Thieblemont, C. (2014) Promising results of ibrutinib in three patients with secondary central nervous system mantle cell lymphoma. *Blood (ASH Annual Meeting Abstracts)*, **124**, 3105.

© 2015 John Wiley & Sons Ltd

Bing, J. & Neel, A. (1936) Two cases of hyperglobulinemia with affection of the central nervous system on a toxi-infectious basis. *Acta Medica Scandinavica*, **LXXXVIII, V-VI**, 492–506.

Castillo, J.J., Olszewski, A.J., Cronin, A.M., Hunter, Z.R. & Treon, S.P. (2014) Survival trends in Waldenstrom macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database. *Blood*, **123**, 3999–4000.

Castillo, J.J., Olszewski, A.J., Kanan, S., Meid, K., Hunter, Z.R. & Treon, S.P. (2015) Overall survival and competing risks of death in patients with Waldenstrom macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. *British Journal of Haematology*, **169**, 81–89.

Chamberlain, M.C. (2014) Salvage therapy with bendamustine for methotrexate refractory recurrent primary CNS lymphoma: a retrospective case series. *Journal of Neuro-oncology*, **118**, 155–162.

Chamberlain, M.C. & Johnston, S.K. (2010) High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. *Neuro-oncology*, **12**, 736–744.

Cheson, B.D. & Rummel, M.J. (2009) Bendamustine: rebirth of an old drug. *Journal of Clinical Oncology*, **27**, 1492–1501.

Cheson, B.D., Vena, D.A., Foss, F.M. & Sorensen, J.M. (1994) Neurotoxicity of purine analogs: a review. *Journal of Clinical Oncology*, **12**, 2216–2228.

Cuenca Hernandez, R., Guzman de Villoria Lebiedziejewski, J.A., Roa Martinez, E. & Menarguez Diaz, J. (2015) Bing-Neel syndrome as an initial sign of Waldenstrom macroglobulinaemia associated with orbital infiltration. *Neurologia*, **30**, 252–255.

Elliott, M.A., Letendre, L., Li, C.Y., Hoyer, J.D. & Hammack, J.E. (1999) Chronic lymphocytic leukaemia with symptomatic diffuse central nervous system infiltration responding to therapy with systemic fludarabine. *British Journal of Haematology*, **104**, 689–694.

Ferreri, A., Cwynarski, K., Pulczynski, E., Ponzoni, M., Deckert, M., Politi, L., Fox, C., La Rosee, P., Ambrosetti, A., Roth, A., Hemmaway, C., Ilariucci, F., Linton, K., Soffietti, R., Pukrop, T., Binder, M., Balzarotti, M., Fabbri, A., Schorb, E., Johnson, P., Sonderskov Gorlov, J., Cavalli, F., Reni, M., Zucca, E. & Ilerhaus, G. (2015) Addition of thiotepa and rituximab to antimetabolites significantly improves outcome in primary CNS lymphoma: first randomization of the IELSG32 trial. *Hematological Oncology*, **33**, 103–104.

Fintelmann, F., Forghani, R., Schaefer, P.W., Hochberg, E.P. & Hochberg, F.H. (2009) Bing-Neel Syndrome revisited. *Clinical Lymphoma & Myeloma*, **9**, 104–106.

Grewal, J.S., Brar, P.K., Sahijdak, W.M., Tworek, J.A. & Chottiner, E.G. (2009) Bing-Neel syndrome: a case report and systematic review of clinical manifestations, diagnosis, and treatment options. *Clinical Lymphoma & Myeloma*, **9**, 462–466.

Kaplan, E.L. & Meier, P. (1958) Nonparametric estimation from incomplete observations. *Journal of American Statistical Association*, **53**, 457–481.

Knop, S., Herrlinger, U., Ernemann, U., Kanz, L. & Hebart, H. (2005) Fludarabine may induce durable remission in patients with leptomeningeal involvement of chronic lymphocytic leukemia. *Leukaemia & Lymphoma*, **46**, 1593–1598.

Malkani, R.G., Tallman, M., Gottardi-Littell, N., Karpus, W., Marszalek, L., Variakojis, D., Kaden, B., Walker, M., Levy, R.M. & Raizer, J.J. (2010) Bing-Neel syndrome: an illustrative case and a comprehensive review of the published literature. *Journal of Neuro-oncology*, **96**, 301–312.

Mantel, N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports. Part 1*, **50**, 163–170.

Morel, P., Duhamel, A., Gobbi, P., Dimopoulos, M.A., Dhodapkar, M.V., McCoy, J., Crowley, J., Ocio, E.M., Garcia-Sanz, R., Treon, S.P., Leblond, V., Kyle, R.A., Barlogie, B. & Merlini, G. (2009) International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*, **113**, 4163–4170.

Nayak, L., Abrey, L.E., Drappatz, J., Gilbert, M.R., Reardon, D.A., Wen, P.Y., Prados, M., Deangelis, L.M. & Omuro, A.; North American Brain Tumor Consortium. (2013) Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. *Leukaemia & Lymphoma*, **54**, 58–61.

Owen, R.G., Treon, S.P., Al-Katib, A., Fonseca, R., Greipp, P.R., McMaster, M.L., Morra, E., Pangalis, G.A., San Miguel, J.F., Branagan, A.R. & Dimopoulos, M.A. (2003) Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Seminars in Oncology*, **30**, 110–115.

Poulain, S., Boyle, E.M., Roumier, C., Demarquette, H., Wemeau, M., Geffroy, S., Herbaux, C., Bertrand, E., Hivert, B., Terriou, L., Verrier, A., Pollet, J.P., Maurage, C.A., Onraed, B., Morschhauser, F., Quesnel, B., Duthilleul, P., Preudhomme, C. & Leleu, X. (2014) MYD88 L265P mutation contributes to the diagnosis of Bing Neel syndrome. *British Journal of Haematology*, **167**, 506–513.

Rubenstein, J.L., Fridlyand, J., Abrey, L., Shen, A., Karch, J., Wang, E., Issa, S., Damon, L., Prados, M., McDermott, M., O'Brien, J., Haqq, C. & Shuman, M. (2007) Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. *Journal of Clinical Oncology*, **25**, 1350–1356.

Rubenstein, J.L., Gupta, N.K., Mannis, G.N., Lamarre, A.K. & Treseler, P. (2013) How I treat CNS lymphomas. *Blood*, **122**, 2318–2330.

Simon, L., Fitsiori, A., Lemal, R., Dupuis, J., Carpentier, B., Boudin, L., Corby, A., Aurran-Schleinitz, T., Gastaud, L., Talbot, A., Lepretre, S., Mahe, B., Payet, C., Soussain, C., Bonnet, C., Vincent, L., Lissandre, S., Herbrecht, R., Kremer, S., Leblond, V. & Fornecker, L.M. (2015) Bing-Neel syndrome, a rare complication of Waldenstrom's macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO). *Haematologica*, doi:10.3324/haematol.2015.133744 [Epub ahead of print].

Swerdlow, S., Berger, F., Pileri, S., Harris, N., Jaffe, E. & Stein, H. (2008) Lymphoplasmacytic lymphoma. In: WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues (ed. by S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele & J.W. Vardiman), pp. 194–195. IARC, Lyon.

Treon, S.P. (2015) How I treat Waldenstrom macroglobulinemia. *Blood*, **126**, 721–732.

Treon, S.P., Xu, L., Yang, G., Zhou, Y., Liu, X., Cao, Y., Sheehy, P., Manning, R.J., Patterson, C.J., Tripsas, C., Arcaini, L., Pinkus, G.S., Rodig, S.J., Sohani, A.R., Harris, N.L., Laramie, J.M., Skifter, D.A., Lincoln, S.E. & Hunter, Z.R. (2012) MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *New England Journal of Medicine*, **367**, 826–833.

Varettoni, M., Marchioni, E., Bonfichi, M., Picchiecchio, A., Arcaini, L., Arbasino, C., Gotti, M., Da Via, M., Delmonte, M., Sciarra, R. & Cazzola, M. (2015) Successful treatment with Rituximab and Bendamustine in a patient with newly diagnosed Waldenstrom's Macroglobulinemia complicated by Bing-Neel syndrome. *American Journal of Hematology*, **90**, E152–E153.

Vos, J.M., Kersten, M.J., Kraan, W., Groeneveld, O.N., Linn, C., Pals, S.T. & Minnema, M.C. (2015) Effective treatment of Bing-Neel Syndrome with oral fludarabine: a case series of four consecutive patients. *British Journal of Haematology*, doi:10.1111/bjh.13483 [Epub ahead of print].

Waldenström, J. (1944) Incipient myelomatosis or 'essential' hyperglobulinemia with fibrinogenopenia a new syndrome? *Acta Medica Scandinavica*, **CXVII**, 217–246.

Xu, L., Hunter, Z.R., Yang, G., Cao, Y., Liu, X., Manning, R., Tripsas, C., Chen, J., Patterson, C.J., Kluk, M., Kanan, S., Castillo, J., Lindeman, N. & Treon, S.P. (2014) Detection of MYD88 L265P in peripheral blood of patients with Waldenstrom's Macroglobulinemia and IgM monoclonal gammopathy of undetermined significance. *Leukemia*, **28**, 1698–1704.

© 2015 John Wiley & Sons Ltd