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Bing-Neel Syndrome – A Case Series of 46 Patients from the United Kingdom

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Abstract:

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Data Sharing

Anonymised patient data is available by email request to the corresponding author.

Lymphoplasmacytic lymphoma (LPL), termed Waldenström's Macroglobulinaemia (WM) when associated with bone marrow infiltration and an IgM-paraprotein, is a low-grade non-Hodgkin's B-cell lymphoma characterised by the somatic mutation $MYD88^{L265P}$ in >90% of cases[1,2]. Central nervous system (CNS) involvement is termed Bing-Neel syndrome (BNS). Although an infrequent complication, it causes significant morbidity[3]. Optimum treatment remains to be established, with traditional CNS-penetrating chemotherapy agents employed, as well as Bruton's Tyrosine Kinase inhibitors (BTKis)[4]. There are limited but emerging data on treatment outcomes. A retrospective study of 28 patients reported an 80% 2-year progression-free survival (PFS) with ibrutinib for both treatment-naïve and relapsed/refractory patients[5]. A recent international series of 30 patients treated with Zanubrutinib reported >90% clinical and radiological response rates, with median PFS not reached at a median follow up of 13 months[6]. The Dana-Farber group reported successful outcomes with Zanubrutinib in nine patients[7].

We describe features and treatment outcomes using a retrospective cohort analysis from the UCLH WM patient registry. Overall survival (OS) was calculated from date of treatment initiation to death, PFS to progression, death or the initiation of next line of therapy using the Kaplan-Meier method, with censoring at last follow-up. Reverse Kaplan-Meier was used to calculate median follow-up. Progression was defined as per established consensus criteria[4].

A total of 474 patients with LPL/WM were registered and BNS was diagnosed in 59 cases (12%) between 2012-2024; 46 had adequate data and were included. Median duration from symptom onset to diagnosis was five months (range 0-60m). Median follow-up from diagnosis was 50m (range 1-150). A preceding WM/LPL diagnosis was present in 34/46 (74%): 31 WM, 3 non-IgM LPL. Median time from diagnosis to BNS was 55m (0-265). Table 1a lists full characteristics.

Leptomeningeal enhancement was present in 33/46 patients (72%), with additional parenchymal lesions in 12/46 (26%). No abnormalities were present on MRI in 7/46 (15%), despite subsequent CSF confirmation. Cerebrospinal fluid (CSF) involvement with LPL/WM was demonstrated in 44/46 (96%), using

immunophenotyping in 27, MYD88^{L265P} and/or immunoglobulin heavy chain (IgH) clonal rearrangements on allele specific (AS) polymerase chain reaction (PCR) in 16, and cytology alone in one case. Two (4%) cases required brain biopsy for BNS diagnosis.

CSF MYD88^{L265P} was detected in 29/30 tested patients; three others were not tested for MYD88^{L265P} but had IgH rearrangements. Lack of demonstrable surface immunoglobulin complicated confirmation of clonality 16 patients, but overcome with AS-PCR for MYD88^{L265} and/or IgH rearrangements.

BNS occurred with systemic progression in 15/46 (30%) patients, with rising paraprotein and/or evidence of radiological progression; 19/46 (41%) patients had CNS-only progression. There was no prior history of WM/LPL in 12/46 (26%) cases. BNS without systemic disease occurred in 4 patients, with no LPL on bone marrow biopsy and no lymphadenopathy on imaging. One such patient had an IgG kappa paraprotein (2g/L), whereas the remaining three had normal immunofixation. A systemic condition was established in the eight remaining patients, with clonal B-cells and MYD88^{L265P} on bone marrow aspirate. Prior treatment for systemic WM/LPL had been given in 21/46 (median of one line, range 0-4).

Systemic therapy for BNS was administered in 42/46 cases (95.6%), with high-dose methotrexate (MTX)-based regimens in 37 (80%) and BTKi in five cases (11%) (Zanubrutinib in four, Ibrutinib in one) (table 1b). BCNU/Thiotepa-conditioned autologous stem cell transplant consolidation was performed in 3/46 cases. Intrathecal-only chemotherapy was given in 2/46 cases. Median pre- and post-treatment CSF white cell count was 15.5/mm^3 (1-153) and 4/mm^3 (0-297). Median pre- and post-treatment CSF protein was 1.40g/L (0.25-4.69) and 0.78 g/L (0.34-6.03).

Complete resolution of neurological symptoms occurred frontline in 10/44 patients, partial resolution in 24/44, no response in 7/44, and progressive symptoms in 1/44; two patients died prior to assessment.

Frontline median OS was not reached; OS at 2- and 4-years were both 93% (95% CI 84-100%). Median PFS was 89m (70-89m), with 1-, 3-year and 5-year PFS 85% (68-93%), 72% (52-86%) and 72% (52-86%) respectively. PFS following frontline methotrexate-based therapy was 78% (51-91%) at 1 year and 48% (22-71%) at 3 years. Symptomatic residual disease was present in 15/37 (40.6%) patients, who initiated BTKi consolidation. For these patients, PFS was 100% at 1 and 3 years. Compared to patients who commenced BTKi without preceding chemoimmunotherapy for BNS, PFS was also 100% at 1 year (p=0.009), but is limited by smaller patient numbers (n=5).

Attainment of frontline negative CSF MYD88^{L265} AS-PCR occurred in 13/16 evaluable patients, none of whom subsequently relapsed; nine had been treated with MTX-based therapy, two with intrathecal, and two with Zanubrutinib.

Second-line therapy for BNS was required in 23/46 (50%) patients, due to progressive disease in eight and symptomatic residual disease in 15. A BTKi was employed in 21 patients: Ibrutinib in 15 and Zanubrutinib in six. The remaining two patients received R-Bendamustine and R-Cladribine. Median time to second-line therapy was 4m (range 2-111). Median PFS following second-line BTKi therapy was not reached, with 1- and 3-year PFS both 95% (69-100%) Attainment of second-line CSF-negativity by MYD88 or IgH AS-PCR occurred in 6/9 evaluable patients, all treated with BTKis. Again, none of these six patients relapsed. Third-line therapy for BNS was given in 3 patients.

Zanubrutinib was administered at 320mg daily in 9/10, with one dose reduction due to febrile neutropaenia. Ibrutinib was administered at 420mg daily in all 16 patients.

Our series of 46 patients with BNS is the largest published to date. The prevalence of BNS in our registry was 12%. Presenting symptoms are heterogenous and although most cases occurred in patients with a known WM/LPL diagnosis, a quarter were not previously diagnosed. Four cases were limited to the CNS. This series reinforces that BNS can occur without systemic progression, necessitating the evaluation of

neurological symptoms in otherwise stable patients. CSF MYD88^{L265P} was detected in 97% patients with BNS.

Although methotrexate-based therapies have historically been employed for BNS, the PFS in this cohort is disappointing with residual disease in half. Frontline PFS was 78% at 12m, whereas it was 100% with BKTi. BTKi resulted in an excellent PFS both front- and second line, although is limited by shorter follow-up. Significant use of high-dose therapy in this cohort reflects practices borrowed from high-grade CNS lymphoma, the aim to obtain rapid disease control in patients with neurological compromise, the pre-BTKi era, and the current unavailability of publicly funded BTKis frontline in England. This analysis adds weight to emerging data in favour of BTKis in BNS[5]. Our study is limited by its retrospective nature and potentially differing characteristics in the chemoimmunotherapy and BTKi cohorts.

Patients initially positive for MYD88^{L265} and/or IgH rearrangements on CSF using AS-PCR, but negative on post-treatment testing did not subsequently relapse from BNS. Requiring further study, this finding has the potential to guide follow-up, the need for routine disease re-evaluation, and may be a useful surrogate marker for PFS in studies.

We consider a BTKi the therapy of choice for BNS, considering this comparison and other series with encouraging outcomes[6,7]. Chemoimmunotherapy still has a role in patients with suspected or proven transformation or potentially in those who are particularly symptomatic disease requiring rapid disease control, but a high proportion require further therapy with a BTKi thereafter. Ultimately, international multi-centre prospective trials are required to inform optimum treatment approach for BNS but will be challenging in a rare disorder.

Table 1a – Clinicopathological Characteristics of Patients with Bing-Neel Syndrome	
Demographics	n = 46
Age, median (range)	66.5 (48-85)
Male	26 (52.5%)
WM Disease Characteristics	
Extramedullary disease	14/46 (30.4%)
Bone marrow infiltration, median (range)	20% (0-80%)
Bone marrow $MYD88^{L265}$	27/28 (96.4%)
Bone marrow $CXCR4^{WHIM}$	1/6 (16.7%)
Symptoms	
Sensory and/or motor deficits	21 (45.7%)
Cognitive change or confusion	8 (17.4%)
Cranial nerve	5 (10.9%)
Headaches	4 (8.7%)
Seizures	3 (6.5%)
Hearing loss	3 (6.5%)
Ocular/orbital	2 (4.3%)
CSF Findings	
CSF leucocyte count (/mm^3) median (range)	15.5 (1-153)
CSF protein, median (g/L) (range)	1.40 (0.25-4.69)
CSF IgM (g/L), median (range)	4.13 (0.147-475)
CSF $MYD88^{L265P}$	29/30 (96.7%)
Imaging Findings	
Parenchymal lesions	12 (26.1%)
Leptomeningeal enhancement	33 (71.7%)
Intracranial	24 (52.2%)
Spinal/cauda equina	27 (58.7%)
No MRI findings but positive CSF-studies	7 (15.2%)

Table 1b – Bing-Neel Syndrome Treatment Regimens	
Frontline (1L) Treatment Regimen	n = 44/46 (95.7%)
Rituximab-Cytarabine-Methotrexate	16 (36.4%)
MATRix (Methotrexate-Cytarabine-Thiotepa-Rituximab)	15 (34.1%)
R-IDARAM (Rituximab-Methotrexate-Cytarabine-Idarubicin)	5 (11.4%)
R-ESHAP/Methotrexate (Rituximab-Etoposide-Methylprednisolone-Cytarabine-Cisplatin)	1 (2.3%)
Zanubrutinib	4
Ibrutinib	1
Intrathecal Methotrexate	1
Intrathecal MTX/Cytarabine/Hydrocortisone	1
+BCNU/Thiotepa ASCT consolidation	3
+BTKi consolidation	15
Second Line (2L) Treatment Regimen	n = 23/46 (50%)
Ibrutinib	15 (65.2%)
Zanubrutinib	6 (26.1%)
R-Bendamustine	1 (4.3%)
R-Cladribine	1 (4.3%)
Third Line (3L) Treatment Regimens	n= 3/46 (6.5%)
MATRix+ASCT	1
R-ICE +ASCT	1
R-Bendamustine	1

Author Contribution

OT conceived the study, collected data, performed analyses and wrote the draft letter. SD supervised the study. All authors critically appraised the study and contributed to the final letter.

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Disclosures

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Table 1. Baseline clinicopathological characteristics of patients diagnosed with Bing-Neel syndrome (1a); details of therapy delivered (1b).

Figure 1. Frontline overall survival (1a) and progression-free survival (PFS) (1b) with all therapies; frontline PFS by therapy type (1c); second-line PFS with Bruton's Tyrosine Kinase Inhibitor therapy.

Figure 1

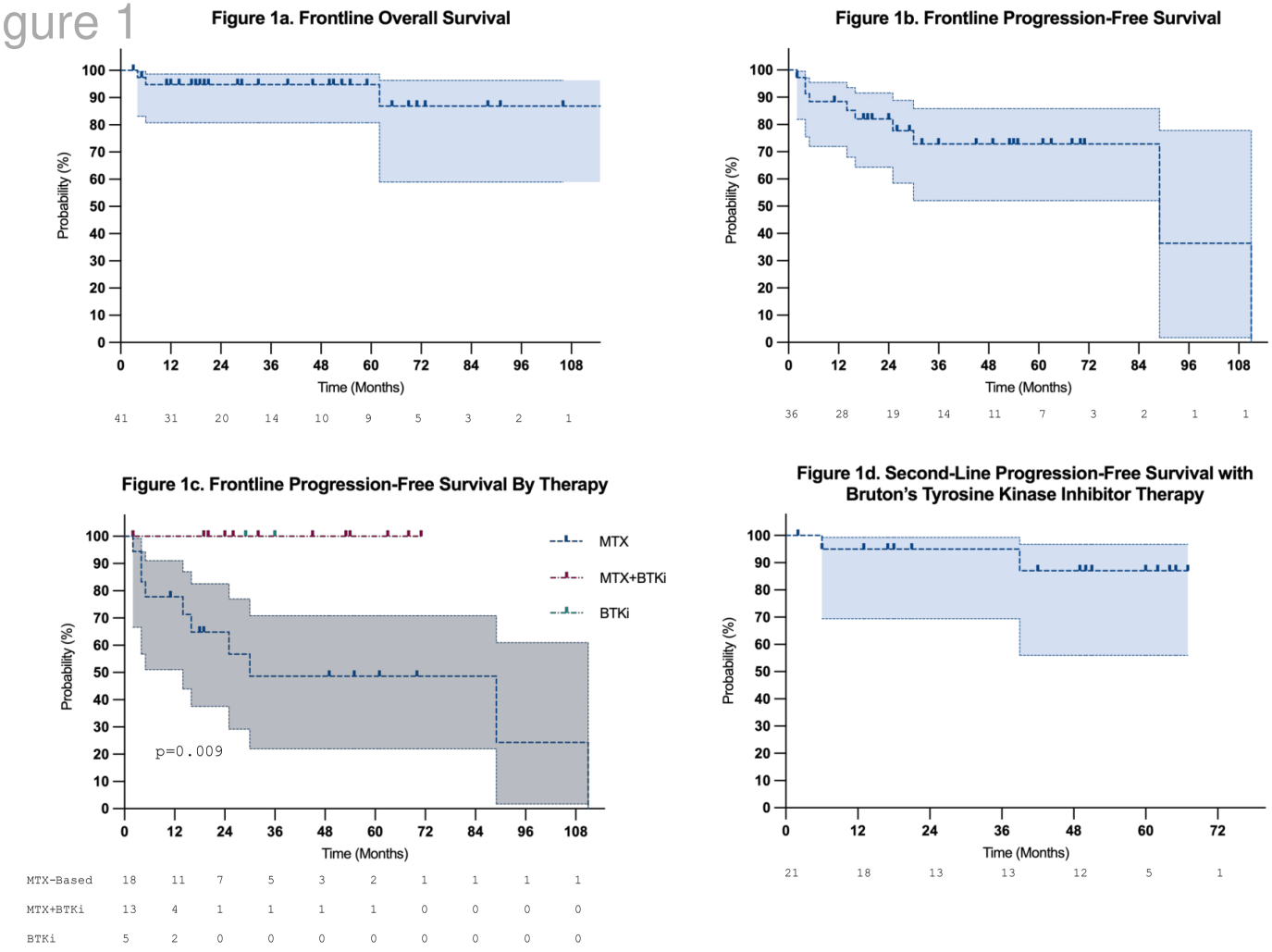

Figure 1. Frontline overall survival (1a) and progression-free survival (PFS) (1b) with all therapies; frontline PFS by therapy type (1c); second-line PFS with Bruton's Tyrosine Kinase Inhibitor therapy.