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

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Background

Central nervous system involvement with Waldenstrom's Macroglobulinaemia (WM) or lymphoplasmacytic lymphoma (LPL) is termed Bing-Neel syndrome (BNS). An infrequent complication, it nevertheless causes significant morbidity. Optimum treatment sequencing remains to be established, with traditional CNS-penetrating chemotherapy agents and novel Bruton's Tyrosine Kinase inhibitors (BTKis) employed. We describe features and treatment outcomes at our WM centre.

Methods

A retrospective cohort analysis was undertaken using the UCLH WM patient registry.

Results

BNS was diagnosed in 59 patients between years 2012 and 2024; 46 had adequate data. Median follow up was 50 months (1-150m). Table 1 lists clinicopathological characteristics. Median duration from BNS symptom onset to diagnosis 5m (range 0-60m).

A preceding diagnosis of WM/LPL was present in 34/46 (73.9%) (WM in 31, IgG LPL 2, IgA LPL 1). Median time from WM diagnosis to BNS was 55m (0-265m). BNS occurred as part of systemic progression in 15 and CNS-only in 19. No prior history of WM/LPL in 12/46 (26.1%) cases; a systemic condition was established in 8 (5 LPL, 3 IgM MGUS) whereas isolated BNS occurred in 4 patients.

Diagnosis was made using brain biopsy in 2 and CSF studies in 44 (cytology 1, immunophenotyping 27, PCR 16). CSF $MYD88^{L265P}$ detected in 29/30 patients; 3 others had IgH rearrangements detected. Lack of surface immunoglobulin expression in 16 patients, but with PCR-proven clonality.

Prior treatment for WM had been given in 21/46 patients, median 1 prior line (range 0-4). Frontline (1L) therapy for BNS administered in 42/46 (95.6%), with high-dose methotrexate (MTX)-based regimens in 37 and BTKi in 5 (table 2). BCNU/Thiotepa autologous stem cell transplant (ASCT) consolidation in 3. Intrathecal-only chemotherapy was given in 2. Median post-treatment CSF WCC 4 (0-297) and protein 0.78 (0.34-6.03). Median 1L overall survival (OS) was not reached, 1- and 3-year rates 93% (84-100%).

Median 1L PFS 49m (26-63m), with 1-, 3-year and 5-year PFS 87% (76-100%), 56% (40-78%) and 30% (16-55%). Attainment of frontline negative CSF PCR for $MYD88^{L265}$ and/or IgH PCR occurred in 13/16 evaluable patients; none subsequently relapsed. Residual disease following MTX-based therapy present in 15/37 (40.6%), who initiated BTKi consolidation. PFS following 1L MTX-based therapy only 81.3% (64.2-100) at 1 year and 49.9% (29-85.7%) at 3 years; MTX-based therapy followed by BTKi consolidation 100% at 1- and 3 years; and BTKi-only therapy 100% at 1 year.

2L therapy was given in 23/46 (50%) patients, 21 with BTKi and 2 with chemoimmunotherapy. Median PFS following 2nd line BTKi therapy not reached, with 1- and 3-year PFS 89% (79-100%). Attainment of 2L CSF negativity by MYD88 or IgH PCR occurred in 6/9 evaluable patients, all on BTKis; none subsequently relapsed. 3L therapy was given in 3 patients.

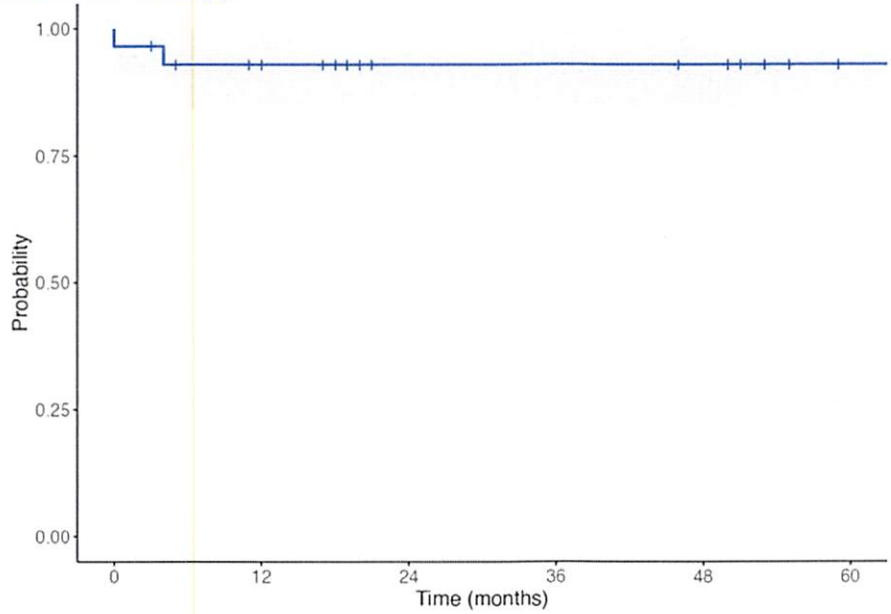
Conclusion

Symptoms of BNS are heterogenous. A quarter of patients have no history of LPL/WM when presenting with BNS. Over ½ cases with known WM occur as CNS-only progression. Isolated BNS is rarely seen. Patients who attained CSF $MYD88^{L265}$ or IgH PCR-negativity did not subsequently relapse from BNS. Regimens incorporating BTKi-based therapy result in excellent PFS rates.

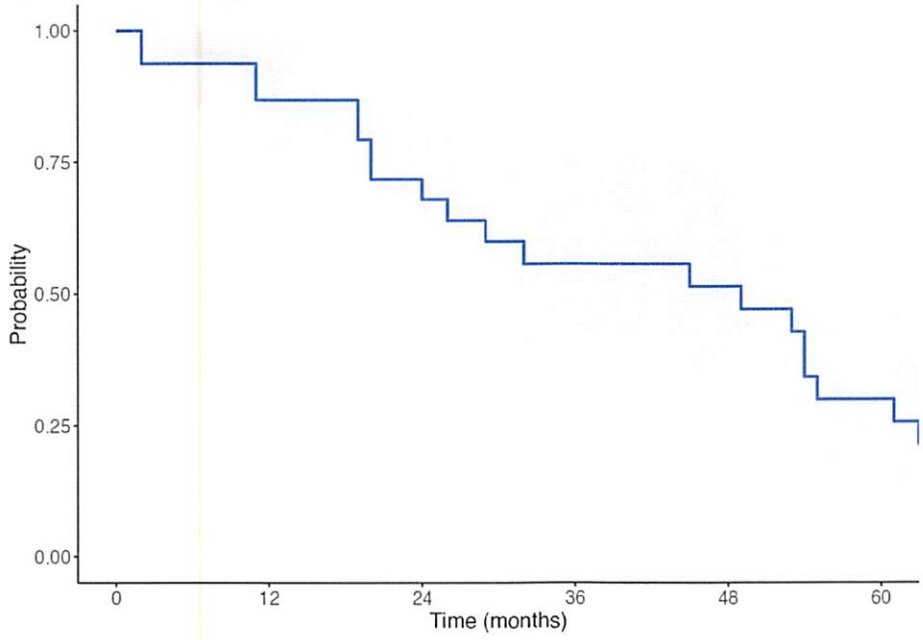
Table 1 – Clinicopathological Characteristics of Patients with Bing-Neel Syndrome	
Demographics	n = 46
Age, median (range)	66.5 (48-85)
Male	26 (52.5%)
WM Disease Characteristics	
Extramedullary disease	14/46 (30.4%)
Bone marrow infiltration, median (range)	20% (0-80%)
Bone marrow $MYD88^{L265}$	27/28 (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, median (range)	15.5 (1-153)
CSF protein, median (range)	1.40 (0.25-4.69)
CSF IgM, 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 findings	7 (15.2%)

Table 2 – Bing-Neel Syndrome Treatment Regimens	
Frontline (1L) Treatment Regimen	n = 44/46 (95.7%)
Rituximab-Cytarabine-MTX	16 (36.4%)
MATRix (MTX-Cytarabine-Thiotepa-Rituximab)	15 (34.1%)
R-IDARAM (Rituximab-MTX-Cytarabine-Idarubicin)	5 (11.4%)
R-ESHAP/MTX(Rituximab-Etoposide-Methylprednisolone-Cytarabine-Cisplatin)	1 (2.3%)
Zanubrutinib	4
Ibrutinib	1
MTX Intrathecal	1
MTX/Cytarabine/Hydrocortisone Intrathecal	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

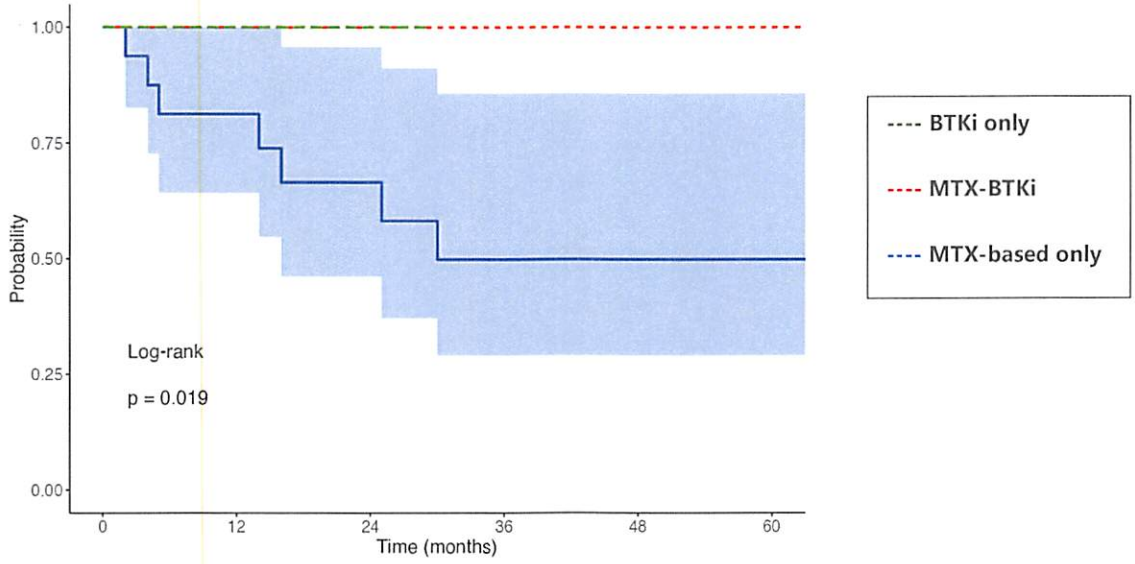
1L OS All Therapy



1L PFS All Therapy



1L PFS MTX-Chemo vs BTKi vs BTKi consolidation



2L BTKi PFS