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Zanubrutinib is effective in the treatment of patients with Waldenström's macroglobulinemia and Bing-Neel syndrome: a retrospective multicenter study.

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Introduction: Bing-Neel syndrome (BNS) affects 1% of patients diagnosed with Waldenström Macroglobulinemia (WM) and consists of infiltration of the central nervous system by lymphoplasmacytic lymphocytes (LPLs). Overall survival (OS) is highly variable, and treatment is not standardized.
There are no studies with zanubrutinib (a new generation Bruton tyrosine kinase inhibitor) in this setting.

Objectives: to evaluate the efficacy of zanubrutinib in BNS considering clinical presentation, biological (cerebrospinal fluid (CSF) infiltration) analysis, radiological findings and their response parameters. As a secondary objective, we analyzed the toxicity of the drug, time of exposure and survival outcomes.

Methods: retrospective study of eleven patients from ten spanish centers who received zanubrutinib as WM treatment with BNS between 2022-2024. All patients who had received at least one cycle were considered evaluable for response and toxicity.

Results: The characteristics of the series are described in figure 1. Six patients were male. The median age at WM diagnosis was 72 years (range 47-84). According to the ISSWM risk scale, 4 had low, 4 intermediate and 3 high risk. The MYD88L265p mutation was detected in 9 patients.
The median age at BNS diagnosis was 75 years (range 61-85). The clinical, biological and radiographic features of BNS are described in figure 2. Sensory deficits and visual abnormalities were most observed. CSF flow cytometry was performed in all patients with a median B clonal infiltration of 33% (range 13-80). The median IgM monoclonal component in blood was 0.8 g/dl (0.5-3). MRI was normal in six patients, three had diffuse leptomeningeal enhancement and two had tumoral form.
Nine patients received zanubrutinib as first-line BNS treatment. BNS was the initial WM feature in six patients, and in five was diagnosed on the setting of WM with a mean time of 8.2 years (0.1-22). These last group received a median of 2 lines of treatment (range 1-3) including immunotherapy in all cases, ASTC (1) and ibrutinib (1).

The median time of exposure to zanubrutinib was 7 months (range 1.5-15).
Zanubrutinib was used at a dose of 160 mg/12h in seven patients and as single dose of 320mg daily in four.
No patient required dose adjustment and one discontinued treatment due to non-response.
Only two patients developed neutropenia (one grade 3, one grade 2) during treatment.
Two patients died within one month of treatment: one due to disease progression and other due to neutropenic septic shock and CMV disease.
Clinical response was observed in 8 (73%) patients: two complete responses (CR) and six partial. In two patients with clinical CR, infiltration persisted in MRI and CSF although to a lesser degree.
At last follow-up, 7 patients are alive (four with BNS as the initial presenting feature of WM and three on the setting of Waldenström's evolution). With a median follow-up of seven months (range 1-39), OS was 82%.

Conclusions: zanubrutinib is effective and safe for WM with CNS infiltration, achieving 73% overall responses. Therefore, it can be considered a treatment option in BNS both in first line and in advanced stages of the disease.

VARIABLES	
Gender	
Male, n (%)	6 (6%)
Female, n (%)	5 (5%)
Age at WM diagnosis (years), median (IQR)	72 (47-84)
Laboratory findings at WM diagnosis:	
Hemoglobin (gr/dL), median (IQR)	11,8 (6,4-13,8)
Platelets (x 10^3/μL), median (IQR)	233 (31-447)
LDH (U/l), median (IQR)	139 (103-357)
B2MG (mg/L), median (IQR)	4,27 (2-10)
Hyperviscosity syndrome, n (%)	1 (9%)
Constitutional symptoms, n (%)	5 (45%)
ISSWM	
Low risk, n (%)	4 (36,5%)
Intermediate risk, n (%)	4 (36,5%)
High risk, n (%)	3 (27%)
Bone marrow mutations:	
MYD 88, n (%)	10 (91%)
CXCR4:	
Mutated, n (%)	1 (9%)
Wt, n (%)	4 (36%)
Not assesed, n (%)	6 (55%)

Figure 1. Patient's characteristics at Waldenström diagnosis.

Id	Age	Clinical presentation	MRI findings	CSF analysis	CSF Flow cytometry	MYD 88	Management	Response	Evaluation criteria	2nd Line
1	76	Hemisphere syndrome, motor deficits	Localized tumor	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation (CD19 34%)	No	Zanubrutinib	NE	Clinical, CSF, MRI	NO
2	72	Sensory abnormalities lenguage disorder	Leptomeningeal enhancement	N/A	Clonal lymphocytic proliferation (CD19 80%)	No	Zanubrutinib	CR	Clinical, LCR	NO
3	78	Sensory abnormalities headache	Normal	Elevated protein	Clonal lymphocytic proliferation (CD19 36%)	No	R/HD-MTX/ PROCAR-BAZINE	NR	Clinica, MRI	Yes, Zanubrutinib
4	76	Lenguage disorder, visual abnormalities	Leptomeningeal enhancement.	Acelular	Clonal lymphocytic proliferation (CD19 27%)	MUT	Ibrutinib	PR	Clinical	Yes, Zanubrutinib
5	72	Sensory abnormalities	Normal	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation	No	Zanubrutinib	PR	Clinical	NO
6	69	Sensory abnormalities	Normal	N/A	Clonal lymphocytic proliferation (CD19 20%)	No	Zanubrutinib	PR	CSF	NO
7	84	Visual symptoms	Normal.	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation (CD19 20%)	No	Zanubrutinib	PR	Clinical	NO
8	69	Confusion	Leptomeningeal enhancement	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation (CD19 40%)	MUT	Zanubrutinib	PR	Clinical	NO
9	61	Sensory abnormalities, visual symptoms, headache	Normal	Normal	Clonal lymphocytic proliferation (CD19 33%)	MUT	Zanubrutinib	CR	Clinical	NO
10	84	Pseudobulbar palsy, sensory abnormalities	Localized tumor	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation (CD19 13%)	No	Zanubrutinib	PR	Clinical	NO
11	75	Lenguage disorder, confusion	Normal	Lymphocytic pleocytosis, elevated protein	Clonal lymphocytic proliferation (CD19 54%)	No	Zanubrutinib	NE	NE	NO

Figure 2. Clinical, radiological and CSF findings at Bing-Neel Sydrom diagnosis. Fist line treatment and response achieved. MUT: mutated; R: Rituximab; HD-MTX: high dose Metotrexate; NE: not evaluated; CR: Complete response; PR: Partial response; NR: Not response.

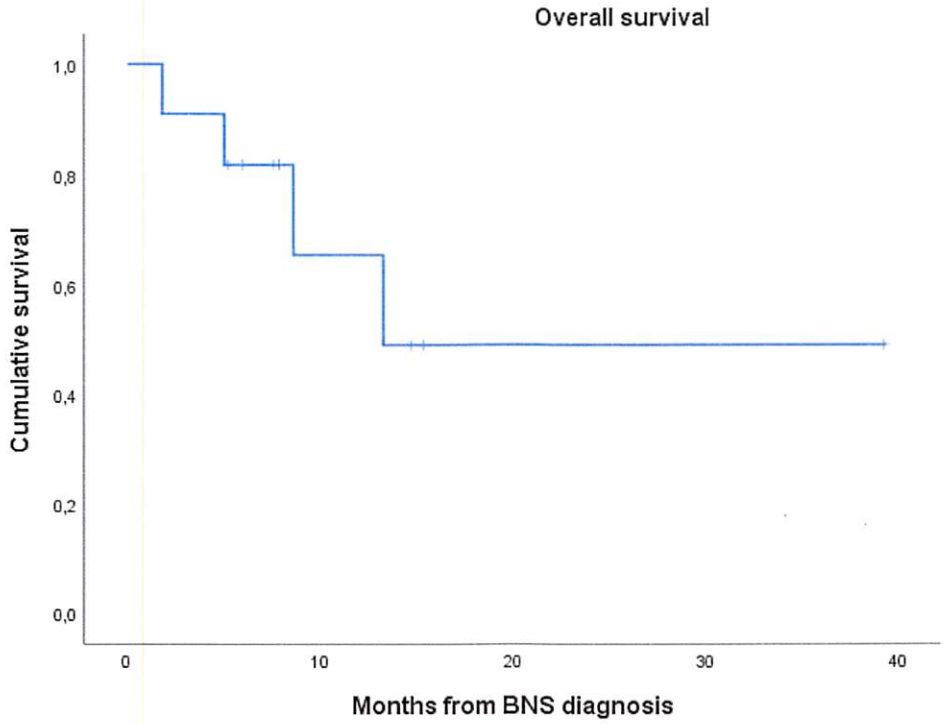

Figure 3. Overall survival since Bing-Neel Syndrome diagnosis. With a median follow up of seven months, more than 50% of the series is still alive.