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A challenging case of Bing Neel Syndrome (BNS) treated with zanubrutinib, followed by BCNU-Thiotepa conditioned autologous stem cell transplant (ASCT).

Bing Neel Syndrome (BNS) is a rare manifestation of Waldenstrom's Macroglobinaemia with central nervous system (CNS) involvement, seen in approximately 1% of patients. Treatment is not standardized and based on limited evidence but includes chemo-immunotherapy regimens given for systemic disease, such as rituximab–bendamustine, or for high-grade CNS disease[1]. BTK inhibitors can penetrate the CNS; Ibrutinib was effective in treating BNS in a multicenter study[2] . Only 2 reports have described the use of zanubrutinib in BNS[3,4].

We report a challenging case treated with zanubrutinib. A 44-year-old gentleman presented with history of back pain and unilateral lower limb paresthesia in 2018; MRI of spine revealed the L4-S1 lesion causing nerve root compression. Blood tests revealed IgM kappa paraprotein of 4.4 g/L. CT guided biopsy of the lesion showed lymphoplasmacytic lymphoma with MYD88 p(Leu265Pro) variant. Bone marrow was morphologically normal; immunophenotyping showed a small population of sIgM bright B-cells, without obvious clonality.

He initially received radiotherapy (24Gy in 12 fractions) to the involved site achieving partial response (PR) but, due to ongoing neurological symptoms, he subsequently underwent 6 cycles of R-CVP which led to further radiological improvement and clinical remission.

In March 2023, he presented with B symptoms, back pain, collapse, left sided sensory disturbance and vomiting. MRIs revealed extensive leptomeningeal enhancement surrounding the medulla oblongata and the entire spinal cord and developing hydrocephalus. PET scan showed mild FDG avid leptomeningeal disease with no disease outside the CNS; bone marrow was not involved. Traces of IgM paraprotein were detectable on serum electrophoresis. Immunophenotyping on cerebrospinal fluid demonstrated a B-cell clone of small to medium sized cells, with MYD88 p(Leu265Pro) variant. A diagnosis of BNS was made and he received one cycle of dose modified MATRix owing to the significant disease burden in the CSF, but this was complicated by significant transaminitis and only marginal improvement of hydrocephalus.

A second opinion was sought and, in July 2023, the patient commenced zanubrutinib which led to radiological PR and remarkable clinical improvement at 3 months. He successfully collected 6.57 x10^6/kg CD34+ peripheral blood stem cells (PBSC) with Plerixafor + G-CSF priming, 5 months into zanubrutinib therapy, without break in administration. Serial MRIs showed gradual resolution of all abnormalities, especially around the lumbar spine. His paraprotein became undetectable and by January 2024 he achieved a very good partial response (VGPR). Nevertheless, he developed side effects such "brain fog" and arthralgia. After discussing whether to continue zanubrutinib at reduced doses, to ameliorate side effects, or to consolidate the response with a BCNU-Thiotepa conditioned ASCT, the patient opted for the ASCT. He continued zanubrutinib until the day before conditioning in March 2024, to avoid disease flare. MRI at 3 months post autograft confirmed sustained VGPR.

This case highlights the efficacy of zanubrutinib in BNS, albeit following one cycle of MATRIx and, as far as we are aware, demonstrates for the first time that continuous treatment with zanubrutinib does not impair collection of CD34+ PBSCs. Based on this experience, ASCT appears to be a feasible consolidation option.

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To whom it may concern,

I hereby confirm Dr Medha Ratnayake is a Doctor in Haematology Training (ST4) in Wales, United Kingdom and currently employed in University Hospital of Wales.

Please feel free to contact me if you have any concerns.

Yours Faithfully,

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