W6: Efficacy of zanubrutinib in the treatment of Bing Neel syndrome

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Bing Neel syndrome (BNS) is a rare complication of Waldenström's macroglobulinemia (WM) characterized by clonal lymphoplasmacytic cell infiltration of the CNS, sometimes with cerebrospinal fluid (CSF) hyperglobulinemia[1]. Treatment approaches have been based on limited evidence[2].

A 75-year-old female was first diagnosed with WM in 2004 however did not require treatment until she presented in May 2014 with warm autoimmune hemolytic anemia. At that time, her serum IgM paraprotein was 23g/L with a bone marrow biopsy demonstrating effacement of normal hemopoiesis by lymphoplasmacytic lymphoma. She denied hyperviscosity, neurological or constitutional symptoms. The patient was treated initially with six cycles of rituximab, cyclophosphamide, vincristine and prednisone achieving a substantial reduction in paraprotein to 4 g/L and normalization of the hemoglobin. Vincristine-induced peripheral neuropathy in the fingers improved but persisted in the distal lower limbs bilaterally.

In May 2015, the patient presented with difficulty walking and was found on lower limb examination to have increased tone with extensor plantar responses and clonus. Power was moderately reduced, and pain, vibration and proprioception sensation were decreased distally. Brain and spine magnetic resonance imaging (MRI) revealed contrast-enhancing cervical and thoracic cord lesions consistent with intramedullary tumour infiltration and multiple enhancing lumbar nerve roots suggestive of intradural tumour infiltration (Fig 1A). CSF examination revealed lambda light chain restricted monoclonal B-cells (CD5-, CD10-, CD19+, CD20+, CD23-) and total protein of 0.86 g/L (normal 0.15-0.45 g/L). CSF electrophoresis revealed no M-spike; serum M-spike was relatively low at 4 g/L.

The patient was diagnosed with BNS and received 12 cycles of high-dose intravenous methotrexate (8 g/m^2), with partial symptomatic improvement in her gait but minimal change on MRI imaging. On treatment cessation, lower limb neurological function gradually deteriorated with increasing serum IgM paraprotein of 8 g/L. Bone marrow biopsy confirmed ongoing involvement with WM with molecular studies identifying *MYD88* L265P and *CXCR4* wild-type. In May 2017 she commenced zanubrutinib 160mg BD as part of a clinical trial resulting in significant improvement in lower limb weakness with an MRI scan (August 2017) demonstrating complete resolution of the cord lesions, and reduced intradural lumbar nerve root enhancement (Fig 1B). She has now been receiving zanubrutinib for over 12 months and remains well with an IgM paraprotein < 2 g/L.

While initial clinical trials of ibrutinib in WM excluded patients with BNS, there have been a number of reports of efficacy in relapsed/refractory[2,6,7] and untreated BNS[8],

and pharmacodynamic data confirm CSF drug diffusion[6]. Zanubrutinib is a second generation Bruton Tyrosine Kinase (BTK) inhibitor with greater selectivity for BTK versus off-target TEC- and HER-family kinases and better oral bioavailability compared to ibrutinib[9,10]. Zanubrutinib induces a higher major response rate (including very good partial responses) than ibrutinib in WM patients and has a favorable toxicity profile[11]. Further studies of zanubrutinib in BNS are warranted.

References

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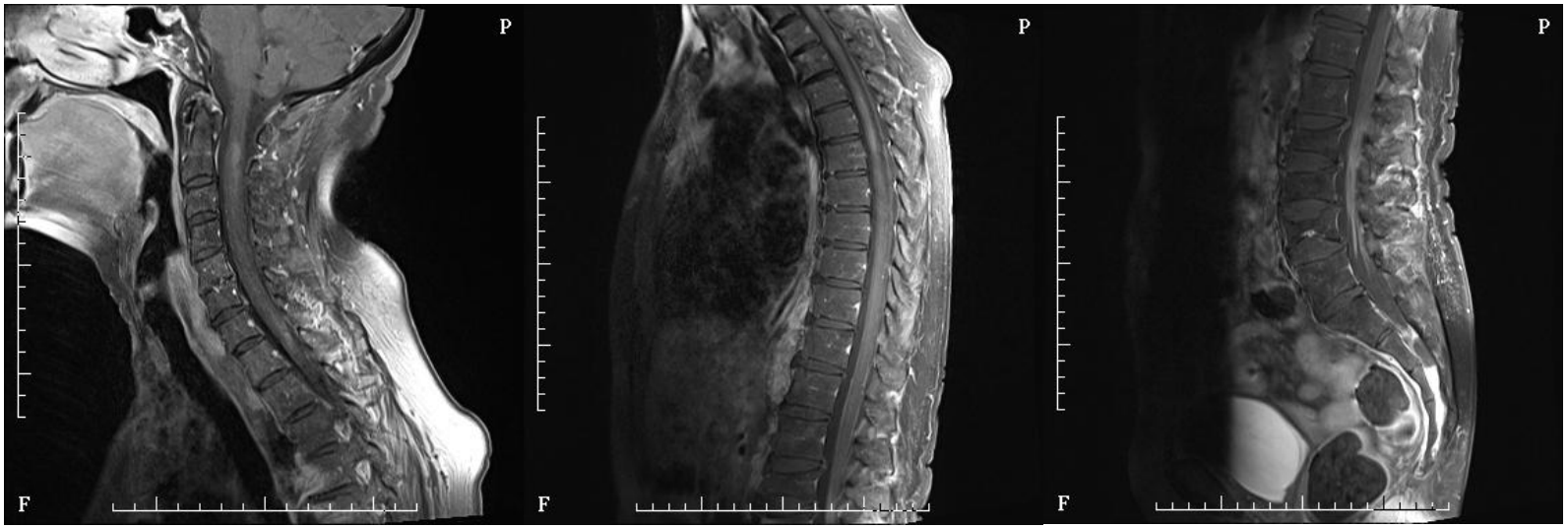
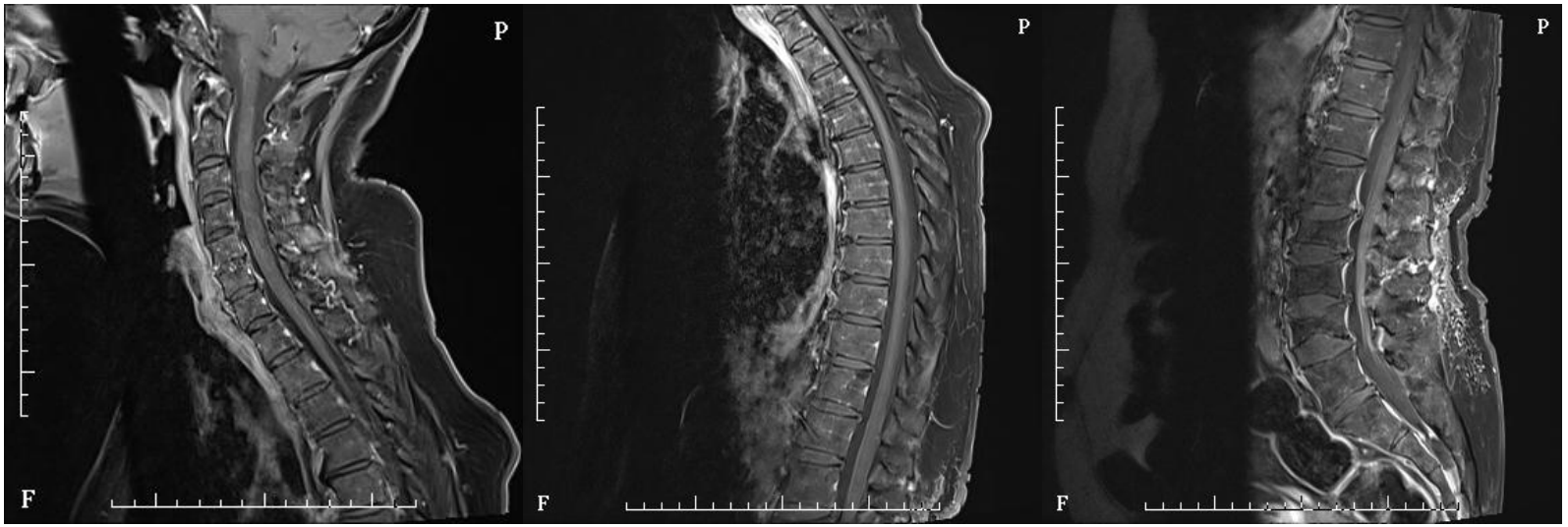
Figure 1

A – Pre-treatment



T1 sagittal post-contrast cervical spine T1 sagittal post-contrast thoracic spine T1 sagittal post-contrast lumbar spine

B – On zanubrutinib



T1 sagittal post-contrast cervical spine T1 sagittal post-contrast thoracic spine T1 sagittal post-contrast lumbar spine