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Pirtobrutinib as an effective salvage in relapsed Bing-Neel syndrome following ibrutinib therapy

Bing-Neel syndrome (BNS) is an uncommon but serious extramedullary complication of Waldenstrom Macroglobulinemia (WM) caused by infiltration of malignant lymphoplasmacytic cells in the central nervous system (CNS) including cerebral spinal fluid, meninges and brain parenchyma¹. Neurological symptoms in BNS can guide CNS localization: meningeal infiltration can result cranial palsies whilst brain parenchymal and spinal cord infiltration can result unified motor and sensory symptoms¹. BNS can occur independently to the systemic activity of WM and can manifest at any time of the course of the disease². Optimum CNS penetrating treatment for BNS has not yet been established but current practice favours using Bruton tyrosine kinase inhibitors (BTKi) over conventional chemotherapies^{3,4}. Covalent BTKi such as ibrutinib and zanubrutinib have been used, but this case highlights the challenges that can occur when treating BNS with ibrutinib. Subsequently the non-covalent BTKi- pirtobrutinib was introduced which is a highly selective potent reversible BTKi with limited off target toxicities⁵.

We describe a case of a 78 yrs old male who was diagnosed with WM in 2013. After a period of monitoring his disease progressed with anaemia, a rising IgM paraprotein of 27 g/L, lymphadenopathy and liver lesions. In 2016 he was treated with 6 cycles of rituximab, cyclophosphamide and dexamethasone(R-CD) achieving a good partial response (PR). Again in 2019 his disease was progressed and started on ibrutinib 420mg daily achieving a second PR. The dose of ibrutinib had to be reduced by 50% due to neutropenia but the patient maintained a response. In February 2026 he presented with B symptoms, new right proptosis and a right chest mass. MRI imaging confirmed bilateral intraorbital infiltrates. CSF analysis was not available as the patient declined a lumbar puncture. Tissue diagnosis from the orbital mass was not deemed feasible due to bleeding risks whilst on ibrutinib (the patient was unable to stop ibrutinib due to previous vigorous withdrawal symptoms). A biopsy of the chest wall mass showed lymphoplasmacytoid lymphoma in keeping with progressive WM. Since the right orbital progression was contemporaneous to the development of the chest wall deposit it was assumed that the orbital lesions represented

the same process. No clinically actionable variants in Tp53 gene and no amyloid depositions were detected. A staging FDG PET-CT scan showed that the progressive masses were mildly FDG avid, in keeping with a diagnosis of low-grade lymphoma. His bone marrow was involved by WM, 5.6% of MYD88 detected.

The patient received dexamethasone, radiotherapy to both orbits (4Gy in 2 fractions) and in April 2026 commenced pirtobrutinib 200mg daily via Lilly's Grant & Donation Medicine Scheme. He had a rapid, dramatic clinical improvement: within 2 weeks his right proptosis, double vision had improved, his anaemia resolved and his chest wall deposit was no longer detectable. The patient remains well and continues to tolerate pirtobrutinib without adverse effects.

On review of the literature, we found only a few case reports of successful treatment of BNS with pirtobrutinib^{6,7}. This case demonstrates the rapid efficacy of pirtobrutinib in a case resistant to a covalent BTKi.

Word – 500 (excluding references)

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