

Title: Treatment With Iopofosine I 131 in a Patient With Bing-Neel Syndrome, A Rare Manifestation of Waldenström Macroglobulinemia: A Case Report

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Introduction: Bing-Neel syndrome (BNS) is a rare manifestation of Waldenström macroglobulinemia (WM) characterized by lymphoplasmacytic lymphoma (LPL) involvement of the central nervous system (CNS). We report the treatment of a patient with BNS who experienced severe complications with Bruton tyrosine kinase inhibitors (BTKis) and received iopofosine I 131, a radioconjugate therapy penetrating the blood-brain barrier and targeting overexpressed lipid rafts on tumor cells to induce apoptosis.

Case Presentation: The patient is a 69-year-old male diagnosed with WM based on bone marrow evaluation detecting 40% involvement by clonal B-cells, consistent with LPL. The patient developed slurred speech and erratic behavior; spinal and brain imaging showed diffuse leptomeningeal enhancement prominent in the cauda equina. He was diagnosed with BNS after polymerase chain reaction (PCR) testing and flow cytometry (FC) of the cerebrospinal fluid (CSF) detected an *MYD88* (L265P) mutation and clonal B-cells consistent with LPL, respectively. He received ibrutinib for 4 years, reducing immunoglobulin M (IgM) levels and improving the abnormal enhancement in the cauda equina, consistent with a partial response (PR). He discontinued therapy following a hemorrhagic pericardial effusion. At discontinuation, his IgM level was 136 mg/dL, indicating a very good partial response. One month later, he met disease progression and treatment criteria, with IgM levels of 1180 mg/dL, CSF analysis showing monoclonal B-cells, and debilitating fatigue. Bone marrow biopsy showed 40% involvement by LPL, with next-generation sequencing detecting *MYD88* (L265P) mutation. He participated in a study evaluating iopofosine I 131 in patients with previously treated WM. His baseline hemoglobin and IgM were 11.6 g/dL and 1900 mg/dL, respectively. One month after the second dose, he experienced a PR with IgM levels of 885 mg/dL. He had grade 1 anemia and grade 3 neutropenia and thrombocytopenia. After the fourth dose, administered 2 months after the first, his nadir IgM level was 609 mg/dL. He experienced expected grade 3 anemia, grade 4 neutropenia, and grade 4 thrombocytopenia, requiring granulocyte colony-stimulating factor (G-CSF), thrombopoietin agonists, and red blood cell transfusions. During treatment, he became transfusion- and G-CSF-dependent and experienced four pre-syncopal or syncopal episodes, with an unrevealing cardiopulmonary workup and etiology determined to be vasovagal. Follow-up evaluation after the cytopenias improved demonstrated 10%-15% LPL marrow involvement. CSF FC and PCR testing indicated partial response with no evidence of clonal B-cells or *MYD88*

(L265P) mutation. Immunoglobulin heavy chain testing remained positive. At the final visit, he had recovered from his cytopenias to grade 1 anemia and grade 2 thrombocytopenia, and he was no longer transfusion dependent. Despite laboratory response, his fatigue symptoms did not improve.

Conclusion: We detail a patient with BNS who experienced severe complications on BTKi and was treated with iopofosine I 131 in a clinical trial. While on treatment, he demonstrated partial BNS and WM responses with CSF clearance based on flow cytometry and *MYD88* testing. He experienced predictable and manageable cytopenic events consistent with prior experience with the drug. This case demonstrates encouraging evidence of targeted delivery of iopofosine I 131 to the CNS in a patient with BNS.

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