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【 EDITORIAL 】

The Impact of Tirabrutinib Monotherapy for Bing-Neel Syndrome in Waldenström's Macroglobulinemia

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Oyama et al. reported a case of successful treatment for Bing-Neel syndrome (BNS) in Waldenström's macroglobulinemia (WM) using tirabrutinib monotherapy (1), and this article carefully describes the so far unmet medical needs associated with the treatment of BNS in WM, for which there is still no consensus recommendation.

BNS was first described by Bing and Neel in 1936 (2) as a rare neurologic complication of WM, accompanied by various symptoms, including headache, cranial neuropathies, and seizures (3-5). It is caused by the involvement of the central nervous system (CNS) with neoplastic lymphocytes with plasma cell differentiation and usually lacks evidence of transformation to high grade B-cell lymphoma (3). It usually presents with a relapsed or refractory status, although it may also be evident at the initial diagnosis of WM (3-5).

Making an accurate diagnosis of BNS is challenging. The diagnosis can be made based on imaging findings, such as magnetic resonance imaging, biopsied histology, the leukocyte cell count and biochemistry, such as the protein level in the cerebrospinal fluid (CSF), cytology and flow cytometry (3). However, around 25% of cases have very low cell counts in the CSF (3, 4), and in such cases, the IgM level and immunofixation test in the CSF as well as the IgM index, calculated as "[CSF IgM (mg/L)/serum IgM (g/L)]/[CSF albumin (mg/L)/serum albumin (g/L)]" are reported to be useful (6). In addition, a molecular examination, including a *MYD88*^{L265P} mutation analysis, is also helpful (3).

Because of the rarity, no consensus recommendations have yet been made regarding therapy for BNS (3, 7). Therapeutic agents for BNS must have good penetration into the CNS, such as high-does methotrexate and cytarabine, although such conventional cytotoxic agents have been reported as being too toxic, especially for elderly patients (3, 7).

At present, ibrutinib, a Bruton's tyrosine kinase inhibitor (BTKi), is approved for treating WM in the US and Europe. Since BTKis have been proven to penetrate the CNS, they are considered promising agents with fewer toxicities than conventional cytotoxic agents (8, 9). In a multicenter retrospective analysis, Castillo et al. reported that ibrutinib had a rapid and durable response for BNS (8). However, because of its potential inhibition of off-target kinases effect (10), there are major concerns about adverse events with ibrutinib, such as atrial fibrillation, bleeding events and hypertension, which sometimes lead to treatment discontinuation (11, 12).

Second-generation BTKis, including tirabrutinib, with a high selectivity and few off-target effects have been developed to reduce those toxicities. In 2020, tirabrutinib was approved for untreated and previously treated WM (13) and relapsed/refractory primary CNS lymphoma (14) in Japan. A phase II study of tirabrutinib monotherapy for WM demonstrated durable efficacy with an acceptable safety profile (13, 15). Furthermore, reports by Oyama et al. (1) and Saburi et al. (16) have suggested that tirabrutinib monotherapy might be an effective treatment for BNS with low toxicity.

In summary, while no consensus treatment recommendation for BNS has yet been made, tirabrutinib monotherapy might be a reasonable therapeutic option for BNS in WM. Further studies are thus warranted.

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