Efficacy of Zanubrutinib in the Treatment of Bing–Neel Syndrome

Jonathan Wong1,2, Lawrence Cher3, James Griffiths1, Aileen Cohen4, Jane Huang4, Lai Wang4, Gareth Gregory1,2, Stephen Opat1,2

Correspondence: Jonathan Wong (e-mail: jonathan.wong@monashhealth.org).

Bing–Neel syndrome (BNS) is a rare complication of Waldenström’s macroglobulinemia (WM) characterized by clonal lymphoplasmacytic cell infiltration of the CNS, sometimes in association with CSF hyperglobulinemia.1 Treatment approaches have been based on limited evidence such as case reports and series.2 Herein, we report on a patient with BNS who responded to zanubrutinib, a second-generation Bruton tyrosine kinase (BTK) inhibitor.

A 75-year-old female was first diagnosed with asymptomatic WM in 2004 following an incidental finding of IgM lambda paraproteinemia measuring 11g/L. She did not require treatment until she presented in May 2014 with warm autoimmune hemolytic anemia requiring immunosuppression and red cell transfusion. At that time, her serum IgM paraprotein had reached 23g/L. Bone marrow biopsy demonstrated effacement of normal hemopoiesis by lymphoplasmacytic lymphoma (comprising 40% of bone marrow cellularity). She denied any hyperviscosity, neurological, or constitutional symptoms.

The patient was initially treated with 6 cycles of rituximab, cyclophosphamide, vincristine, and prednisone in 2014. She achieved a substantial reduction in the paraprotein to 4g/L and normalization of the hemoglobin, consistent with a partial response (PR) according to modified 6th IWWM response criteria. During chemotherapy she developed paresthesia and pain in the fingers and distal lower limbs bilaterally, consistent with vincristine-induced peripheral neuropathy. Although the hand symptoms improved shortly after completion of treatment, mild sensory symptoms persisted in her distal lower limbs.

In May 2015, the patient presented with progressive difficulty in walking. There were no cranial nerve or upper limb neurological deficits. In the lower limbs, tone was increased with bilateral extensor plantar responses and clonus, power was moderately reduced, and pain, vibration and proprioception sensation were decreased distally. Her gait was impaired with a positive Romberg’s sign. Brain and spine MRI revealed multiple contrast-enhancing lesions in the cervical and thoracic cord consistent with intramedullary tumor infiltration and multiple enhancing nerve roots in the lumbar subarachnoid space suggestive of intradural tumor infiltration (Fig. 1). CSF examination revealed a total protein of 0.86g/L (normal 0.15–0.45g/L) and lambda light chain restricted monoclonal B-cells (CD3–, CD10–, CD19+, CD20+, CD23–). CSF electrophoresis revealed no M-spike; serum IgM M-spike was still relatively low at 4g/L.

The patient was diagnosed with BNS and received 12 cycles of high-dose intravenous methotrexate (8g/m2) administered monthly. Treatment was well-tolerated and there was partial symptomatic improvement in her gait, but MRI of the central nervous system did not show any change compared with pretreatment imaging. On cessation of methotrexate therapy, lower limb neurological function gradually deteriorated with increasing serum IgM paraprotein to 8g/L. Bone marrow biopsy confirmed ongoing involvement with WM (lymphoplasmacytic lymphoma cells comprising 30% of bone marrow cellularity) with molecular studies identifying MYD88 L265P and CXCR4 wild-type.

In May 2017 she commenced zanubrutinib (BGB-3111) 160 mg twice daily on a clinical trial, resulting in significant improvement in lower limb weakness bilaterally. She has had improvement in hip flexion power from MRC 3/5 bilaterally to 5/5 bilaterally, and a measurable improvement in timed vibration sense. Although there is ongoing spasticity, she is now able to walk 200 m, a marked improvement compared to a distance of only 20 m before commencement of zanubrutinib. MRI in August 2017 demonstrated complete resolution of the contrast-enhancing lesions in the cervical and thoracic cord, and reduced contrast enhancement in the intradural lumbar nerve roots (Fig. 2). The patient has been receiving zanubrutinib

Funding/support: None.

Disclosures: Dr Cohen, Dr Huang and Dr Wang are employees of BeiGene and own stocks in BeiGene.

The other authors declare no conflicts of interest.

Off label use: Zanubrutinib (BGB-3111) is not licensed for treatment of B-cell malignancies.

Author contributions: Jonathan Wong wrote the manuscript.

Lawrence Cher, James Griffiths, Aileen Cohen, Jane Huang, Lai Wang, Gareth Gregory, and Stephen Opat performed critical revision of manuscript for intellectual content.

1 Department of Hematology, Monash Health, Clayton, Victoria, Australia
2 Monash University, Clayton, Victoria, Australia
3 Olivia Newton John Cancer & Wellness Centre, Austin Health, Heidelberg, Melbourne, Australia
4 BeiGene Company Ltd, San Mateo, CA, USA

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

HemaSphere (2018) 2:81–155
Received: 6 August 2018 / Accepted: 3 October 2018

Citation: Wong J, Cher L, Griffiths J, Cohen A, Huang J, Wang L, Gregory G, Opat S. Efficacy of Zanubrutinib in the Treatment of Bing–Neel Syndrome. HemaSphere, 2018/2/8. http://dx.doi.org/10.1097/HSS.0000000000000155
for 15 months and, as of the date of this report, has maintained an IgM paraprotein below 2 g/L, consistent with a very good partial response.

Current consensus recommendations for the treatment of BNS include purine analogues, bendamustine, high-dose methotrexate, cytarabine-based regimens or ibrutinib. Ibrutinib was the first BTK inhibitor approved by the USFDA and the EMA for treatment of WM, following a prospective multicenter study which reported an overall response rate (ORR) of 91% and 2-year progression-free survival (PFS) rate of 69% in previously treated patients. In this study, MYD88 and CXCR4 genotype status was found to have an effect on systemic responses to ibrutinib. There were no major responses in previously treated patients with MYD88WT disease, and the presence of concurrent CXCR4MUT disease conferred longer time to major response and median time to progression, as well as reduced ORR, major response rate (MRR), and very good partial response (VGPR) rates. A subsequent prospective study in 30 previously untreated patients with MYD88MUT disease demonstrated an ORR of 100% and 18-month estimated PFS rate of 92%. Higher MRR and VGPR rates and shorter time to major responses were seen in patients with CXCR4WT versus CXCR4MUT. In a phase III trial of ibrutinib and rituximab versus placebo and rituximab in treatment-naïve and previously treated patients with WM, ibrutinib–rituximab induced a higher MRR than placebo–rituximab (72% vs 32%) and improved PFS rate at 30 months (82% vs 28%). The benefit in this trial was independent of MYD88 or CXCR4 genotype. In a study of 31 patients with rituximab-refractory disease, ibrutinib monotherapy induced an ORR of 90% and an MRR of 71%. Patients with MYD88MUT and CXCR4MUT were slower to respond compared to those with CXCR4WT. Patients with BNS were excluded from these trials.

Ibrutinib has been shown to penetrate the blood–brain barrier and induce response in CNS-infiltrating non-Hodgkin lymphoma, and there have been a number of reports of efficacy in both relapsed/refractory and previously untreated BNS, with pharmacodynamic data confirming drug diffusion in CSF.
To the best of our knowledge, this is the first report to describe effective treatment of BNS with a second-generation BTK inhibitor. Zanubrutinib (BGB-3111), an investigational drug product, is a potent, highly specific and irreversible BTK inhibitor, which has shown greater selectivity for BTK versus other off-target TEC- and HER-family kinases, and more favorable oral bioavailability compared to ibrutinib in *in vitro* cell-based assays.\(^\text{12,13}\) In a phase I study of patients with WM, zanubrutinib induced an ORR of 92% and MRR of 83% (including VGPR in 33%), with a favorable toxicity profile.\(^\text{14}\) A phase III study comparing zanubrutinib and ibrutinib is ongoing (Clinicaltrial.gov identifier NCT03053440). Our report supports the efficacy of BTK inhibitors in the treatment of BNS but further studies of zanubrutinib in BNS are warranted.

**Acknowledgment**

The authors acknowledge the editorial support of BeiGene.

**References**

1. Bing J, Neel AV. Two cases of hyperglobulinaemia with affection of the central nervous system on a toxic-infectious basis. *Acta Med Scand.* 1936;88:492–506.
2. Castillo JJ, D’Sa S, Lunn MP, et al. Central nervous system involvement by Waldenström macroglobulinaemia (Bing-Neel syndrome): a multi–institutional retrospective study. *Br J Haematol.* 2015;172:709–715.
3. Minnema MC, Kimby E, D’Sa S, et al. Guideline for the diagnosis, treatment and response criteria for Bing-Neel syndrome. *Haematologica.* 2016;102:43–51.
4. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström’s macroglobulinemia. *N Engl J Med.* 2015;372:1430–1440.
5. Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naïve patients with Waldenström macroglobulinemia. *J Clin Oncol.* 2018;36:2755–2761.
6. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström’s macroglobulinemia. *N Engl J Med.* 2018;378:2399–2410.
7. Dimopoulos MA, Trotman J, Tedeschi A, et al. Ibrutinib for patients with rituximab-refractory Waldenström’s macroglobulinaemia (INNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. *Lancet Oncol.* 2017;18:241–250.
8. Bernard S, Goldwirt L, Amorim S, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. *Blood.* 2015;126:1695–1698.
9. Mason C, Savona S, Rini JN, et al. Ibrutinib penetrates the blood brain barrier and shows efficacy in the therapy of Bing Neel syndrome. *Br J Haematol.* 2016;179:339–341.
10. Cabannes-Hamy A, Lemal R, Goldwirt L, et al. Efficacy of ibrutinib in the treatment of Bing-Neel syndrome. *Am J Hematol.* 2016;91:E17–E19.
11. Boudin L, Patient M, Roméo E, et al. Efficacy of ibrutinib as first-line treatment of tumoral Bing–Neel syndrome. *Leuk Lymphoma.* 2018;1–3. DOI: 10.1080/10428194.2018.1441409. Epub ahead of print.
12. Li N, Sun Z, Liu Y, et al. Abstract 2597: BGB-3111 is a novel and highly selective Bruton’s tyrosine kinase (BTK) inhibitor. *Cancer Res.* 2015;75 (15 suppl):Abstract 2597.
13. Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a phase 1 first-in-human trial. *Blood.* 2015;126:Abstract 832.
14. Tam CS, Trotman J, Opat S, et al. High major response rate, including very good partial responses (VGPR), in patients (pts) with Waldenstrom macroglobulinina (WM) treated with the highly specific BTK inhibitor Bgb-3111: expansion phase results from an ongoing phase I study. *Blood.* 2016;128:Abstract 1216.