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LETTER TO THE EDITOR

# Standard Dose of Ibrutinib is Effective in the Treatment of Bing-Neel Syndrome

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Dear Editor,

The direct involvement of the central nervous system by malignant B-cells is a rare complication in Waldenström Macrglobulinaemia (WM), called Bing-Neel syndrome (BNS). The diagnosis is often delayed because of the rarity of the condition, the heterogeneous clinical presentation and the occurrence of BNS independently of systemic disease progression [1]. Most of the patients are treated according to protocols consisting of high dose methotrexate (HD-MTX) and intrathecal chemotherapy. Although the overall response rates to first line therapy are only 64–70% [1, 2], the BNS shows sometimes an indolent clinical course, because responses can be seen with any line of therapy and 40% of survivors have signs of persistent disease [2].

Ibrutinib, a small molecular inhibitor of Bruton tyrosine kinase (BTK), was proved to be highly active in relapsed WM [3]. Ibrutinib is able to penetrate through the blood-brain barrier and can induce responses in mantle cell lymphoma with central nervous system relapse [4]. Until now, three cases of relapsed BNS treated with ibrutinib were reported. Mason et al. applied 560 mg/die, while Cabannes-Hamy et al. 420 mg/die, but the concentrations of Ibrutinib were similar in the cerebrospinal fluid (CSF); 2,2–3,5 or 1–7% CSF/plasma ratio, respectively and over the 50% inhibitory concentration ($IC_{50}$) for BTK (0,5 nmol/l) [5, 6]. Very recently, a case successfully treated with the combination of Ibrutinib 420 mg/day, first-line and prednisone was published [7].

Here we report two cases with relapsed BNS successfully treated with Ibrutinib.

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Patient 1. The 53-year-old man was diagnosed with WM in 2010. Due to the high disease burden he received rituximab, cyclophosphamide, vincristine, doxorubicine and prednisolon (RCHOP). Eighteen months later a rapid progression of WM was treated with rituximab, cisplatine, cytarabine and dexamethasone (RDHAP). The autologous stem cell transplantation (ASCT) was not feasible because of severe infectious complications as lung abscess. In the second relapse the patient received idelalisib and rituximab in a clinical trial and achieved a sustained partial response for 26 months until the termination of the study. In 5 months (August of 2016), he was hospitalized due to anaemia, generalized lymphadenomegaly, visual disturbances, dizziness and hearing loss. Trephine biopsy showed massive bone marrow infiltration of LPL with MYD88 L265P gene mutation and wt CXCR4. Serum IgM was 27.7 g/l, brain MRI revealed optic nerves thickening with contrast enhancement and a tumor in the left parietal lobe (Fig. 1a). CSF total protein was 0,7 g/l, but cytology and flow cytometry didn't detect abnormal B-cells. A stereotactic brain biopsy was attempted unsuccessfully from the tumor, but was not repeated due to the quick deterioration in the patient's performance status. Standard dose of Ibrutinib (420 mg/day) was initiated. In 4 weeks his neurological symptoms resolved completely, blood counts improved, serum IgM decreased to 5.1 g/l. The brain MRI confirmed the regression of the tumor in the parietal area and the disappearance of the infiltration around the optic nerve (Fig. 1b). At 24 months' follow-up, the asymptomatic patient has a stable disease in partial remission.

Patient 2. The 52-year-old man was diagnosed with WM from an epidural mass biopsy in 2005. Initially, he was treated with RCHOP, then 7 years later, in the first relapse with RDHAP, consolidated with ASCT. During the second course of chemoterapy hepatitis B virus (HBV) reactivation occurred and was treated with Entecavir. Twelve

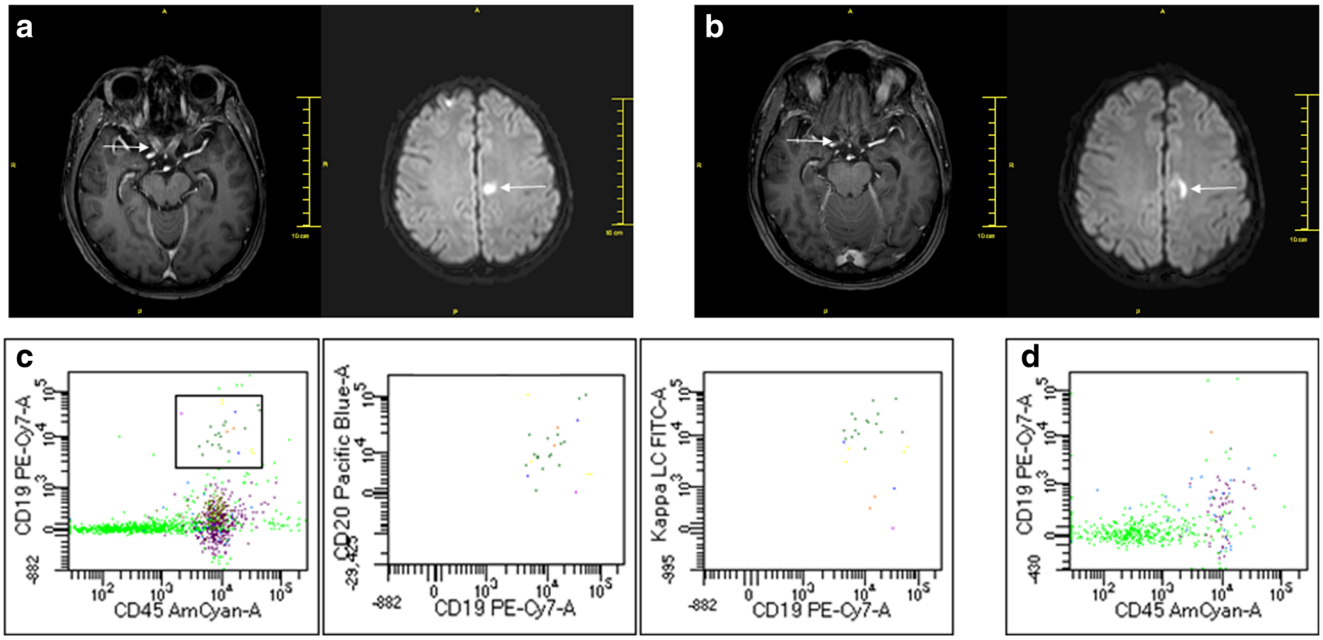


**Fig. 1** **a** Patient 1 pre-treatment axial contrast-enhanced T1-weighted MRI image about the infiltration of the optic nerve and diffusion weighted MRI image of the tumor in the parietal lobe. **b** post treatment MRI images. **c** Patient 2 Mature (CD19, CD20, CD45 positive), Kappa LC monoclonal B cell population at diagnosis. **d** B-cells are not detectable 3 months after the initiation of ibrutinib treatment. Measurements were performed by FACSCanto II flow-cytometer and analysed by FACS Diva software

months later, he presented with progressing paresthesia and pain in the extremities. The diagnostic work-up found 4,4 g/l IgM in the serum, no lymphadenomegaly, no abnormality in the brain MRI, but in the CSF monoclonal, mature B-cells were shown by flow-cytometry. Because of the active HBV hepatitis he received only intrathecal therapy consisting of methotrexate, cytarabine, dexamethasone and rituximab. The intrathecal therapy induced arachnoiditis with transient worsening of the pain and weakness of the extremities, but achieved a long-lasting remission. Three years later, neurological symptoms as paresthesia and dizziness progressed again. CSF analysis revealed elevated protein 0,82 g/l and low count (14/mm$^3$) of monoclonal B-cells (Fig. 1c). The brain MRI didn't display any abnormality. Monoclonal IgM can be detected only with immunofixation in his serum and blood counts were normal. The patient rejected the repeat of intrathecal or systemic chemotherapy and Ibrutinib 420 mg/day was started. His symptoms improved in 2 weeks and in the CSF the monoclonal B cell population could not be detected in 3 months (Fig. 1d). At 12 months of Ibrutinib, the patient is still in complete remission.

These cases confirm that 420 mg/day dose of ibrutinib is effective in Bing-Neel sy also in heavily pretreated population and no additional drug e.g. corticosteroid is required. The response was rapid and the remission is long-lasting in both cases.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflict of interest.

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