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Ibrutinib as treatment for Bing–Neel syndrome reclassified as glioblastoma: a case report

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Abstract

Background Glioblastoma is a highly malignant disease with limited treatment options. Ibrutinib, a covalent Bruton tyrosine kinase inhibitor, is an oral agent with manageable side effects used for hematological diseases including Waldenström macroglobulinemia. We present the case of a 69-year-old Caucasian male patient treated with ibrutinib for suspected Bing–Neel syndrome (BNS), which following a biopsy, was reclassified as glioblastoma.

Case presentation In December 2018, a 69-year-old Caucasian male patient was diagnosed with Waldenström macroglobulinemia. As the patient was asymptomatic, without bone marrow failure or high M-component count, watchful waiting was initiated. Due to increasing neurological symptoms, the patient, based on magnetic resonance imaging, was diagnosed with Bing–Neel syndrome in May 2019. The patient received different treatments before starting ibrutinib monotherapy in August 2019 due to disease progression, both on magnetic resonance imaging and clinically. The patient remained clinically stable for 7 months. In March 2020, the patient developed headaches, and both magnetic resonance imaging and a biopsy revealed glioblastoma IDH-wildtype. Treatment was changed in line with the new diagnosis, but the patient died at the end of 2020.

Conclusion We present a case in which a patient with glioblastoma IDH-wildtype remained clinically stable for 7 months when treated with ibrutinib monotherapy, which is similar to what would be expected for the standard treatment for glioblastoma. To our knowledge, this is the first patient receiving ibrutinib for a glioblastoma IDH-wildtype with a meaningful clinical outcome. Our case may therefore support previous nonclinical findings, indicating a therapeutic value of ibrutinib in patients with glioblastoma and support for further investigation of ibrutinib as a possible treatment for glioblastoma.

Keywords Glioma, Glioblastoma, Bing–Neel syndrome, Ibrutinib, Case report

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Introduction

Glioblastoma IDH-wildtype (GBM) is a highly malignant World Health Organization (WHO) grade four brain tumor, with limited treatment options. Despite aggressive treatment, consisting of maximal safe surgery and radiotherapy with concomitant and adjuvant temozolomide (TMZ), prognosis remains poor [1]. Besides TMZ, only a few drugs have shown a clinical effect in either the primary or recurrent setting, primarily due to limited penetration of the blood–brain barrier. Here we present a case, with a patient treated with ibrutinib for suspected Bing–Neel syndrome (BNS), which following a biopsy, was reclassified as GBM.

Case

In December 2018, a 69-year-old Caucasian male patient was referred to the department of hematology from his general practitioner due to the abnormal presence of serum immunoglobulin (Ig) G lambda and IgM kappa M-component. According to the WHO classification, the patient was diagnosed with Waldenström macroglobulinemia (WM) after a bone morrow biopsy with 20% kappa-clonal lymphoplasmacytic cells and the presence of IgM M-components in the blood [2]. As the patient was asymptomatic, without bone marrow failure or high M-component count, watchful waiting was initiated [2].

In February 2019, the patient was admitted to the hospital with episodes of confusion, epigastric aura, and shivers. Several neurologic tests were conducted, including a head computed tomography (CT) and MRI. The CT scan showed nonspecific hypodense areas in the medial right temporal lobe with a suspicion of edema, while magnetic resonance imaging (MRI) found cerebral abnormalities in both temporal lobes. Several diagnoses, including gliomatosis cerebri and neoplasm, were possible based on the scans. Upon cytospin analysis and flow cytometry of the patient's cerebrospinal fluid, high levels of CD19 and CD20 kappa-clonal B-cells with lymphoplasmacytic morphology were found, leading to the diagnosis of WM involvement of the central nervous system, known as BNS. The patient immediately started treatment with ibrutinib. The first month of treatment resulted in a significant reduction of clonal B-cells in the spinal tap from 180 cells/ml to 100 cells/ml estimated by flowcytometry.

In May 2019, the patient experienced confusion and fatigue. A new spinal tap showed a minor reduction of clonal B-cells (75 cells/ml), and a brain MRI confirmed progression of the patient's disease. The treatment was changed to rituximab, methotrexate, procarbazine and vincristine (R-MPV). The patient had intolerable toxicity of R-MPV and ibrutinib was reintroduced in August 2019. The patients continued treatment with ibrutinib monotherapy and remained clinically stable for 7 months.

In March 2020 the patient developed persistent headache, and a brain MRI was performed, revealing increasing contrast enhancement in the right hemisphere (see Fig. 1). As the parenchymatic changes did not resemble those normally associated with BNS, a biopsy was performed. Surprisingly, the histology was glioblastoma, IDH wild-type, MGMT methylated. The patient was referred to the department of oncology for further treatment. Due to extensive tumor distribution in both hemispheres, radiotherapy was refrained, and the patient started treatment with TMZ as monotherapy. The patient remained clinically and radiologically stable for 6 months. In October 2020 the MRI showed mixed response, and different treatment strategies were discussed with the patient and his relatives, including continuing TMZ, starting lomustin, or awaiting the result of a new scan after a few weeks. The shared decision was to reevaluate with a new MRI after 4 weeks. Within the next month the patient had considerable symptomatic progression, which was in accordance with the follow-up MRI that showed severe progression. Due to the patient's rapidly declining condition, further treatment was abandoned. The patient died shortly after.

Discussion

BNS is a rare complication of WM, characterized by clonal lymphoplasmacytic cells infiltrating the central nervous system. Patients often exhibit neurological symptoms, including balance disorders, gait abnormalities, cranial nerve deficits, cognitive impairment, and headaches [3], resembling symptoms seen in patients with GBM [4]. BNS is seen in 1–2% of patients with WM, and it is associated with great morbidity and mortality [3, 5, 6]. In addition to imaging, the gold standard for diagnosis of BNS is a spinal tap with WM cells or a brain tissue biopsy in cases where the diagnosis is uncertain [7, 8]. As our patient presented with high levels of B-cells in the cerebrospinal fluid, and responded to the initial treatment, a biopsy was not indicated.

GBM is a highly aggressive disease with a median overall survival of around 15 months [9, 10] despite multimodal treatment. It is well known that one of the treatment obstacles is the presence of the blood–brain barrier, allowing only a few small lipid soluble drugs to enter the brain parenchyma [11]. Due to the small molecular weight, ibrutinib, a covalent Bruton tyrosine kinase (BTK) inhibitor that reduces the NF-κB pathway activity, possesses the ability to pass the blood–brain barrier [8, 12, 13]. It has been widely investigated in hematological cancers and is currently recommended as first-line treatment in patients with BNS [2, 8, 14].

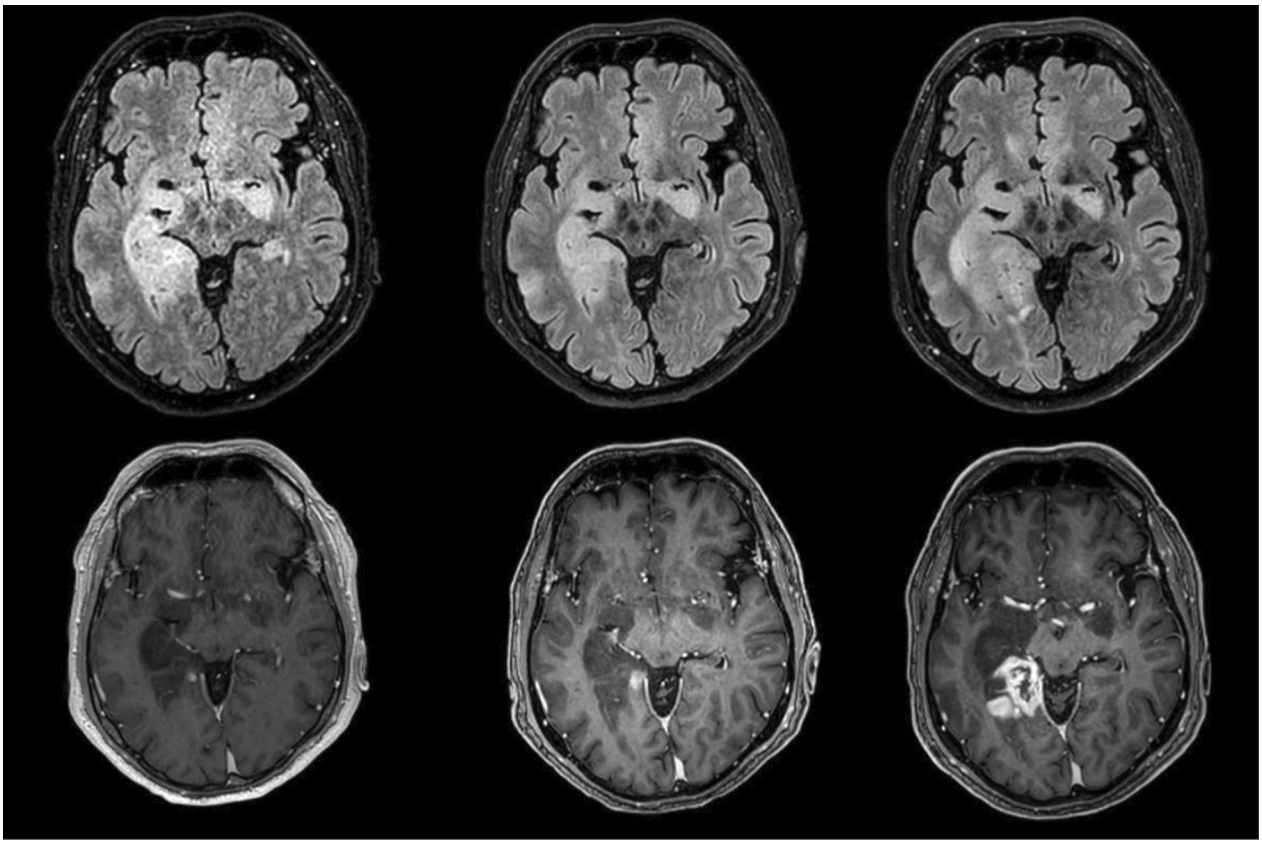

Fig. 1 From left to right, each column illustrating the patient's magnetic resonance imaging showing T2 weighted and T1 with gadolinium from May 2019, August 2019, and March 2020, respectively

Due to the ability of penetrating the blood–brain barrier, the antitumoral effect of ibrutinib in glioblastomas was investigated in a laboratory setting, revealing a profound antitumor effect and induction of autophagy in GBM cells [15]. Shi *et al*. [16] demonstrated suppression of GBM tumor growth due to the inactivation of bone marrow and X-linked non-receptor tyrosine kinase caused by ibrutinib. To our knowledge, information on other patients with GBM treated with ibrutinib monotherapy has not been published previously. However, in the study by Lewis *et al*. [17], three patients developed GBM after treatment for IgM paraproteinaemic neuropathy. We are not able to evaluate whether there was a connection between development of WM and GBM in our case.

In the present case, the patient remained clinically stable for 12 months when treated with ibrutinib and R-MPV. This is unusually long for a patient with GBM, as it is a very aggressive tumor, with survival rates of only approximately 3–6 months without relevant treatment [1]. For the first 5 months, the patient received treatment with ibrutinib or R-MPV. Although procarbazine is part of the procarbazine, lomustine, vincristine (PCV) regimen often used as adjuvant treatment in patients with oligodendrogliomas, the effect in patients with GBM has been limited [18]. Therefore, we do not expect that this treatment contributed significantly to the outcome for our patient. Interestingly, the patient remained clinically stable for 7 months when ibrutinib was reintroduced. This is in line with median progression-free survival reported for patients with GBM treated with surgery, radiotherapy, and chemotherapy [1]. Therefore, this case could support the need for clinical trials for treatment with ibrutinib for patients with GBM. Currently, a study for pediatric patients with brain cancer is recruiting. [19].

We acknowledge that regular MRIs are usually used to evaluate response in patients with GBM and that an earlier MRI may have revealed progression before the patient experienced clinical worsening. As the patient did not present with symptoms, and the main goal was to keep the patient clinically stable, scans were not indicated. This was in line with the treatment and assessment strategy presented by Castillo and Treon [3].

Currently, the most clinical use of tyrosine kinase inhibitors in patients with GBM has been in a recurrent

setting and with limited success [20]. Intriguingly, Wei *et al.* [21] investigated ibrutinib in combination with TMZ for GBM using a patient-derived xenograft mouse model, reporting that the anti-tumorigenic effect increased with a combination of ibrutinib and TMZ. A recent phase 1 study reported that daily ibrutinib in combination with TMZ and radiation is safe and feasible, indicating a clinical effect of ibrutinib, as seen in our case [22].

Conclusion

To our knowledge, this is the first patient to receive ibrutinib for GBM with a meaningful clinical outcome. Our case may support previous preclinical findings showing a therapeutic value in patients with GBM. Furthermore, as ibrutinib is an oral agent with manageable side effects, the use in an out-patient setting seems beneficial. However, no recommendations regarding ibrutinib as treatment for GBM in general can be made without further studies, including animal tests and functional studies, to reveal the true clinical effect.

Abbreviations

GBM	Glioblastoma IDH-wildtype
WHO	World Health Organization
TMZ	Temozolomide
BNS	Bing–Neel syndrome
WM	Waldenström macroglobulinemia
R-MPV	Rituximab, Methotrexate, Procarbazine and Vincristine
BTK	Bruton tyrosine kinase

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Author contributions

CDG was primary manuscript author and general editor; IC was primary editor of sections regarding hematology; IBK was primary editor of sections regarding hematology and provided relevant citations; MBJ was editor with neurosurgical perspective; FSGH was editor with radiology perspective and provided images; and RHD was primary editor of sections regarding oncology and provided relevant citations. All authors approved final version of manuscript.

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Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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