

## Case Report

# A Case of Transformed Waldenström's Macroglobulinemia with Cerebral Affection Treated with Ibrutinib

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## Abstract

Waldenström's macroglobulinaemia (WM) is an indolent lymphoma characterized by bone marrow infiltration with lymphoplasmacytoid lymphocytes in conjunction with the production of monoclonal IgM. Cerebral affections of WM are a rare event but especially challenging and intensive regimen are primarily used for this difficult to treat condition

Ibrutinib inhibits Bruton's tyrosine kinase (BTK) which is essential in signal transduction of both normal and malignant B cells and has been recently introduced in the treatment of WM. Ibrutinib, in addition, has been shown to be of promising activity in CNS-lymphoma.

Here we report on the results of Ibrutinib treatment in a female patient with multiply relapsed WM with transformation and CNS involvement.

The patient was initially diagnosed with WM in 2006 at the age of 52 years and received 6 cycles of rituximab combined with cyclophosphamide, doxorubicine, vincristine and prednisone with the achievement of a complete remission in 2007. Until 2015 the patient experienced several relapses and underwent different therapy regimens including high dose therapy followed by autologous peripheral blood stem cell transplantation and radiotherapy.

In November 2015 the patient was admitted to the emergency unit with symptoms of increased intracranial pressure due to progressive lymphoma. Treatment with Ibrutinib was initiated and within a few days the patient's general condition improved substantially achieving almost normal quality of life. Two months later in January 2016 MRI of the brain showed a nearly complete remission which lasted for four months until the patient deceased.

To our knowledge – this is the first case reported of transformed WM with a substantial remission duration, which exceeded most responses observed in pCNS lymphoma.

## INTRODUCTION

Waldenström's macroglobulinaemia (WM) is an indolent lymphoma characterized by bone marrow infiltration with lymphoplasmacytoid lymphocytes in conjunction with the production of monoclonal IgM [1]. Approximately 50% of patients have additional manifestations as lymphadenopathy, splenomegaly or skin involvement. In general, WM is slowly progressive with a substantial number of patients not requiring treatment for a long period and remaining patients frequently respond well to chemotherapy and immunotherapy with Rituximab. Although the disease course is frequently indolent,

some patients experience transformation of their disease into a secondary aggressive lymphoma [2, 3]. If transformation occurs, regimens as R-CHOP are used [4] and in case of relapse thereafter salvage chemotherapy followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation (aPBSCT) are considered standard of care [5] with variable success [6]. Cerebral affections of WM are a rare event but especially challenging and intensive regimens like high dose methotrexate (MTX) are primarily used for this difficult to treat condition.

On a molecular level mutation L265P of MYD88 are present in almost all patients with WM, and alterations of CXCR4 are present

to a variable extent. Ibrutinib inhibits Bruton's tyrosine kinase (BTK) which is essential in signal transduction of both normal and malignant B cells [7,8] and has been recently introduced in the treatment of WM, and responses seem to correlate with the pattern of both MYD88 and CXCR mutations.

Ibrutinib, in addition, has activity in other lymphoma entities as mantle cell lymphoma and CLL, and interestingly has been shown to be of promising activity in CNS-lymphoma.

Here we report on the results of Ibrutinib treatment in a patient with multiply relapsed WM with transformation and CNS involvement [9-11].

## CASE REPORT

The female patient was initially diagnosed with WM in 2006 at the age of 52 years and received 6 cycles of rituximab combined with cyclophosphamide, doxorubicine, vincristine and prednisone (R-CHOP) with the achievement of a complete remission (CR) in 2007. In 2011 after symptomatic relapse she was treated with 6 cycles of bendamustine resulting in partial remission. In 2012 the patient presented at our department's outpatient clinic for the first time with a progressive tumor of the right lower leg and a pelvic mass. Biopsy proofed the diagnosis of diffuse large B-cell lymphoma (DLBCL), which was considered transformed WM.

One cycle of CD20-antibody rituximab combined with dexamethasone, cytarabine and cisplatin (R-DHAP) was administered as salvage treatment, which due to renal insufficiency was switched to one cycle of rituximab combined with dexamethasone, carmustine, etoposide, cytarabine, melphalan (R-Dexa-BEAM), followed by stem cell mobilization. Treatment resulted in PR and in March 2013 high dose therapy (BEAM) followed by autologous peripheral blood stem cell transplantation (PBSCT) was performed resulting in CR.

Four months later in July 2013 the patient presented with acute paresis of her right leg and left facial nerve paresis. Diagnostic evaluation revealed lymphoma manifestation in the basal ganglia, which was confirmed to be transformed lymphoma by stereotactic biopsy. Molecular diagnostics resulted in detection of the MYD88 mutation (L265P) which confirmed the relation to the initially diagnosed WM. However, paraprotein levels remained low.

Subsequently, the patient received treatment including rituximab combined with methotrexate and cytarabine, however disease progression was noted and therefore radiotherapy was applied resulting in disease stabilization with residual gait disturbance and ataxia.

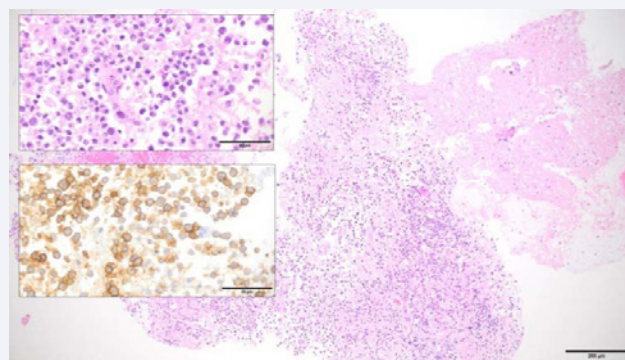
In November 2015 the patient was admitted to the emergency unit with symptoms of increased intracranial pressure (ICP) as nausea, vomiting and amentia. Emergency CT scan of the brain demonstrated progressive lymphoma located next to posterior horn of left lateral ventricle with massive perifocal oedema (Figure 1), lumbar puncture confirmed lymphomatous involvement of cerebrospinal fluid. Symptomatic treatment with high dose dexamethasone was initiated with moderate clinical benefit. Considering the prior therapy of this patient neither further chemotherapy nor was radiotherapy a doable option.

After Board recommendation and approval by the responsible health care provider treatment with Ibrutinib was initiated at a dose of 560mg once daily. Within a few days after initiation of treatment the patient's general condition improved substantially and the patient could rapidly be discharged from hospital with almost normal quality of life. Two months later in January 2016 MRI of the brain showed substantial reduction of the tumor mass with a minimal residual periventricular mass, consequently treatment was continued (Figure 2). Ibrutinib did not result in major side effects and QoL remained stable over time.

After additional 4 months and total treatment duration of 6 months condition of the patient deteriorated again despite of Ibrutinib treatment. With rapid progression being evident patient received palliative care support and subsequently deceased.

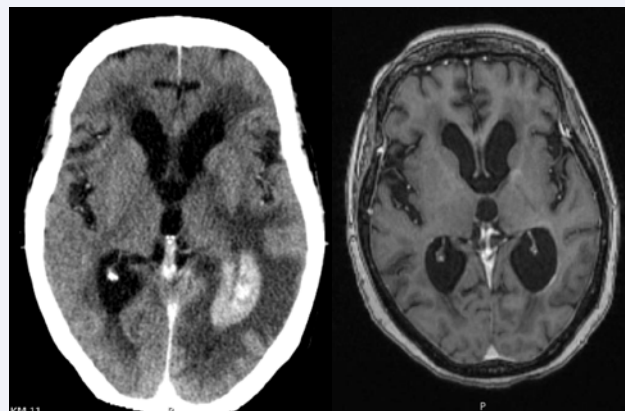
## DISCUSSION

Rare manifestation of WM in the CNS is known as Bing Neel



**Figure 1** CNS tissue biopsy with necrosis, haemorrhage and perivascular concentrated infiltrations (large image hematoxylin and eosin). Infiltration composed of blasts (upper insert, hematoxylin and eosin) expressing CD20 (lower insert, CD20). Size standards indicated.

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**Figure 2** CT in November 2015 and c MRI in January 2016 after 6 weeks treatment with Ibrutinib

(images by Department of Diagnostic and Interventional Radiology and Institute of Neuroradiology of University Medical Center of the Johannes Gutenberg-University Mainz)

syndrome [12]. Typically, on biopsy infiltrates of Waldenström like cells can be found which continue to show features of indolent lymphoma. In contrast, in the case presented here, transformation to aggressive lymphoma was evident. Relation to MW can be suspected by proof of MYD88 mutation, which is a hallmark of WM but not entirely pathognomonic. This mutation is present in a substantial proportion of patients with PCNSL, however its detection is rare in DLBCL.

As MYD88 mutations may be found either in WM or DLBCL, the concomitant development of two different lymphoma entities might alternatively be assumed. However due to the initial WM, the primary peripheral manifestation of a MYD88 positive lesion and the occurrence of a similar lesion we consider the different manifestations as related. Unfortunately we could not obtain sample material from the initial diagnoses for idiotype comparison, as this been collected at a different site.

Traditional approaches to treat primary and secondary CNS manifestations of malignant lymphomas are the use of methotrexate based regimen and the use of radiation therapy with variable results, which holds true for affection of the CNS by WM.

Recently, a variety of options has been evaluated for CNS lymphoma such as lenalidomide, PD1-antibodies or especially Ibrutinib, which is a first in class BTK-inhibitor. In primary CNS lymphoma – which commonly is of ABC-phenotype – responses to Ibrutinib are observed, however are frequently short lived. Anecdotaly, Bing Neels syndrome has been treated successfully with Ibrutinib [13], however – to our knowledge – this is the first case reported of transformed WM with a substantial remission duration, which exceeded most responses observed in pCNS lymphoma.

Ibrutinib is approved for therapy of pretreated WM based on the data of Treon et al. who showed overall response rates up to 100% in dependence of MYD88 and CXCR4 mutation status, estimated 2-year progression-free and overall survival rates among all patients were 69.1% and 95.2%, respectively [11]. BTK was identified as a downstream target of MYD88 signaling which makes it a possible target in WM patients [14].

There is further evidence that Ibrutinib can be an effective drug in treatment of DLBCL as shown by Wilson et al. in a phase1/2-trial with remission rates of nearly 40% or even higher depending by MYD88 or BCR status [15].

Ibrutinib alone or incorporated into a regime can be an efficient treatment of primary and refractory/relapsed CNS lymphoma as presented by Dunleavy et al 2015 [16]. In a small group of patients with CNS lymphoma Ibrutinib led to a partial remission in 7 of 8 patients, incorporated into a regime with conventional chemotherapeutics results were even better as 5 of 5 patients received a CR of their disease.

In conclusion this case highlights the potential of BTK-inhibition even in last line treatments.

Additional research is needed to identify the patients benefiting most like from this approach.

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