Received: 16 October 2019 | Revised: 2 January 2020 | Accepted: 6 January 2020

DOI: 10.1111/ejh.13382

CASE REPORT

European Journal of Haematology WILEY

Obinutuzumab and venetoclax induced complete remission in a patient with ibrutinib-resistant non-nodal leukemic mantle cell lymphoma

Xiang Zhou[1] | Maximilian Johannes Steinhardt[1] | Johannes Düll[1] | Franziska Krummenast[1] | Sophia Danhof[1] | Katharina Meckel[1] | Katharina Nickel[1] | Denise Grathwohl[1] | Hans-Benno Leicht[1] | Andreas Rosenwald[2] | Hermann Einsele[1] | Leo Rasche[1] | Martin Kortüm[1]

[1]Department of Internal Medicine II, Würzburg University Hospital, University of Würzburg, Würzburg, Germany

[2]Department of Pathology, Würzburg University Hospital, Würzburg, Germany

Correspondence
Xiang Zhou and Martin Kortüm, Department of Internal Medicine II, Würzburg University Hospital, Oberdürrbacher Street 6, D-97080 Würzburg, Germany.
Emails: zhou8285@126.com; kortuem_m@ukw.de

Abstract

We herein report the case of a 73-year-old male patient who was diagnosed with leukemic non-nodal MCL. This patient had received six cycles of bendamustine, which resulted in a transient remission, and a second-line therapy with ibrutinib, which unfortunately failed to induce remission. We started a treatment with single-agent obinutuzumab at a dose of 20 mg on day 1, 50 mg on day 2-4, 330 mg on day 5, and 1000 mg on day 6. The laboratory analysis showed a rapid decrease of leukocyte count. Four weeks later, we repeated the treatment with obinutuzumab at a dose of 1000 mg q4w and started a therapy with venetoclax at a dose of 400 mg qd, which could be increased to 800 mg qd from the third cycle. This combination therapy was well tolerated. The patient achieved a complete remission (CR) after three cycles of obinutuzumab and venetoclax. To date, the patient has a progression-free survival of 17 months under ongoing obinutuzumab maintenance q4w. This is the first report about obinutuzumab and venetoclax induced CR in rituximab-intolerant patient with an ibrutinib-resistant MCL. This case suggests that obinutuzumab- and venetoclax-based combination therapy might be salvage therapy in patients with ibrutinib-resistant MCL.

KEYWORDS

mantle cell lymphoma, obinutuzumab, venetoclax

1 | INTRODUCTION

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin's lymphoma (NHL) characterized by diffuse lymphadenopathy, bone marrow involvement and splenomegaly.[1] Leukemic non-nodal MCL with extensive leukocytosis presents a variant of this disease, and high leukocyte count indicates a poor survival outcome according to MIPI (MCL international prognostic index).[2,3] In recent years, novel agents have been evaluated in patients with relapsed or refractory (RR) MCL.[1] For instance, ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, has shown its single-agent

efficacy with an overall response rate (ORR) of 68% (21% complete remission [CR]).[4] Moreover, Morschhauser et al[5] observed that RRMCL patients treated with obinutuzumab, a third-generation, humanized anti-CD20 monoclonal antibody, had an ORR of 27%. Venetoclax is a novel selective B-cell leukemia/lymphoma-2 (BCL-2) inhibitor.[6] In a phase 1 trial of venetoclax monotherapy in patients with RRMCL, Davids et al observed an ORR of 75%, which was obviously higher than that in patients treated with temsirolimus (ORR 22%) or lenamidomide (ORR 28%), and venetoclax was generally well tolerated.[7-9] However, experience with the combination of venetoclax and obinutuzumab in patients with RRMCL is limited. Here, we present a case of a male patient with ibrutinib-resistant leukemic non-nodal MCL that was successfully treated with obinutuzumab and venetoclax.

Novelty Statement

1. What is the NEW aspect of your work? (ONE sentence)

- This is the first report about obinutuzumab and venetoclax induced CR in rituximab-intolerant patient with an ibrutinib-resistant MCL.

2. What is the CENTRAL finding of your work? (ONE sentence)

- We observed the efficacy and safety of obinutuzumab and venetoclax in ibrutinib-resistant MCL.

3. What is (or could be) the SPECIFIC clinical relevance of your work? (ONE sentence)

- Obinutuzumab and venetoclax based combination therapy might be salvage therapy in patients with ibrutinib-resistant MCL.

2 | CASE PRESENTATION

A 73-year-old male patient had been diagnosed as leukemic non-nodal MCL with asymptomatic leukocytosis in July 2017. At diagnosis, leukocyte count in peripheral blood was highly elevated with 379 460/μL with 95% lymphocytes and 1.1% neutrophils. The patient showed mild anemia and thrombocytopenia with hemoglobin value of 9.4 g/dL and platelet count of 116 000/μL. A flow cytometry analysis showed 90% B cell in peripheral blood with the following immune phenotype: CD19+, CD5+, CD20 low, CD22+, CD23-, kappa+++. A peripheral blood smear revealed the diagnosis of leukemic MCL. Genetic analysis of peripheral blood showed a TP53 deletion. Thus, this patient had high-risk MCL with MIPI of 8.[3,10]

This patient had received one cycle of bendamustine as monotherapy, which was well tolerated. In the second cycle, rituximab was added to the therapy, which resulted in a severe infusion reaction, along with cytokine release syndrome and tumor lysis, so that the patient did not wish to receive further rituximab treatment. In total, he had received six cycles of bendamustine plus only one dose of rituximab in the second cycle as induction followed by a progressive disease (PD) with continuous increase of leukocyte count (68 000/μL) and continuous decrease of blood platelet count (86 000/μL) only four weeks after the end of therapy. A second-line therapy with ibrutinib was initiated. Unfortunately, no response was observed, and the disease progressed further under the treatment (leukocyte count 225 600/μL). This case represented a primary ibrutinib-resistant MCL.

In June 2018, 11 months after primary diagnosis, the patient presented at our hospital for further treatment. At admission, we assessed PD of his leukemic MCL with a leukocyte count of 259 600/μL of which 86% were lymphocytes. A bone marrow biopsy confirmed the diagnosis of MCL with 50% bone marrow infiltration in the immunohistochemistry, and SOX11 was positive in 20% of the tumor cells (Figure 1A). A CT scan further revealed a splenomegaly with a craniocaudal length of 17 cm, without signs of lymphadenopathy (Figure 1B). No gastrointestinal involvement was shown in the gastroscopy and colposcopy. Due to the massive tumor burden and the previous history of tumor lysis syndrome, we cautiously started obinutuzumab at a dose of 20 mg on day 1, 50 mg on day 2-4, 330 mg on day 5, and 1000 mg on day 6. To prevent tumor lysis, the patient received intravenous fluids, rasburicase, and urinary alkalization. The laboratory analysis showed a rapid decrease of leukocyte counts (Figure S1). The patient developed fever of unknown origin (FUO) and was treated with antibiotics. Four weeks later, we repeated the treatment with obinutuzumab at a dose of 1000 mg q4w. To enhance the treatment efficacy, we started the therapy with venetoclax at a dose of 400 mg qd, which could be increased to 800 mg qd from the third cycle. This combination therapy was well tolerated. We only observed grade 1 leukopenia, neutropenia, anemia, and thrombocytopenia. After three cycles, the bone marrow biopsy showed no infiltration by MCL (Figure 1C), and abdominal ultrasound demonstrated normal spleen size. According to the current response criteria, he had achieved a CR.[11]

After six cycles of obinutuzumab and venetoclax, we continued an obinutuzumab maintenance therapy, applying 1000 mg q4w. At the last follow-up in July 2019, laboratory analysis and CT scan showed no sign of relapse (Figure 1B). To date, the patient has a progression-free survival of more than 17 months under obinutuzumab maintenance.

3 | CONCLUSION

Despite the introduction of ibrutinib, patients with RRMCL have a short median progression-free survival (PFS) of 13.9 months.[4] In patients with ibrutinib-resistant RRMCL, the optimal therapeutic approach remains a matter of debate. Recently, Eyre et al observed an ORR of 53% (18% CR, 35% PR) to venetoclax monotherapy in patients with RRMCL that was pretreated with ibrutinib, and among

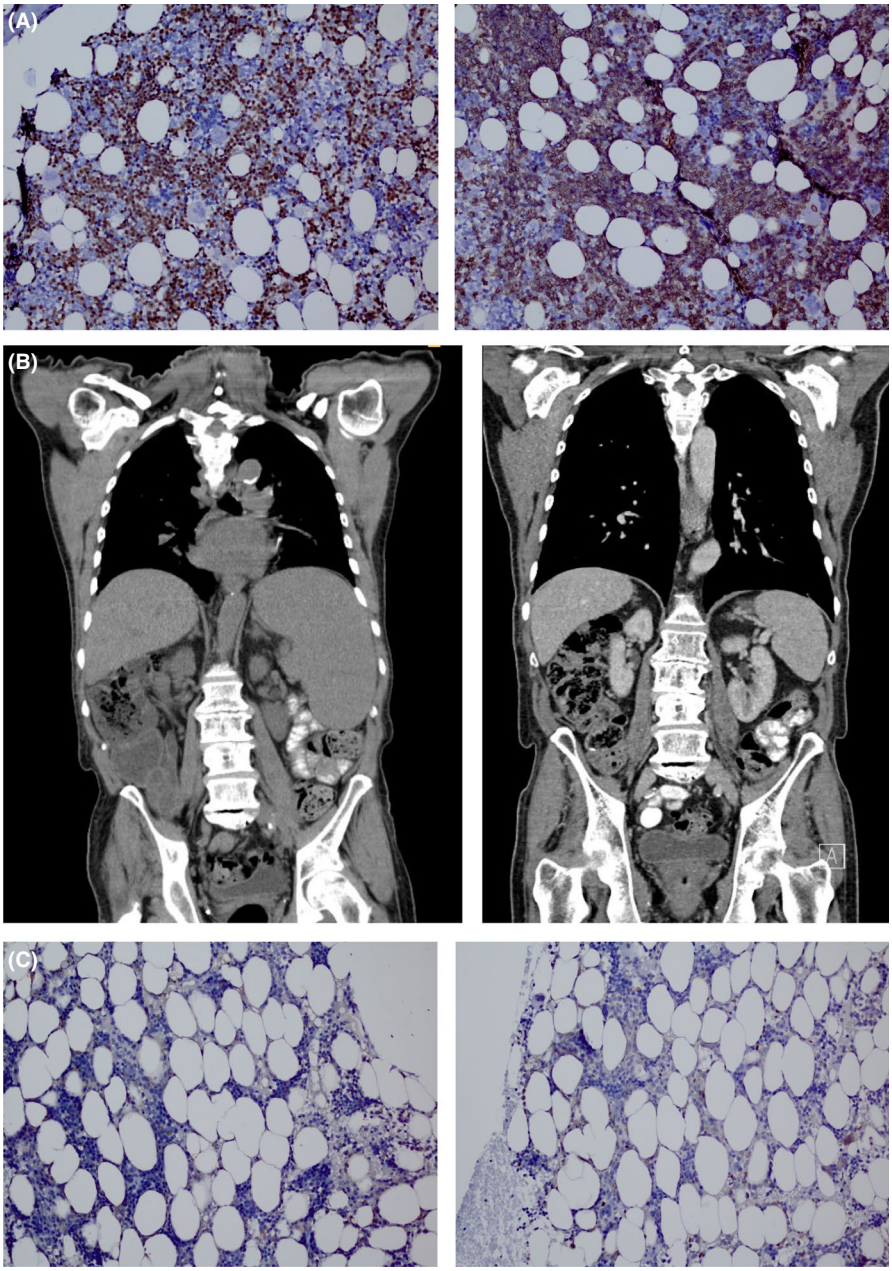

FIGURE 1 A, Bone marrow biopsy at start of obinutuzumab/venetoclax with immune coloring for CD20 (left) and cyclin D1 (right) revealed a bone marrow infiltration of 50%. B, Computer tomography on 4 June 2018 (left) with splenomegaly and 8 July 2019 (right) with normal-sized spleen. C, Bone marrow biopsy after three cycles of obinutuzumab/venetoclax with immune coloring for PAX5 (left) and cyclin D1 (right) showed no infiltration

the patients who were primarily resistant to ibrutinib, the ORR to venetoclax was 38%.[12]

Primary resistance to ibrutinib might be caused by diverse pathogenic mechanisms such as PIK3-AKT pathway activation and activation of the NFkB pathways.[13] Moreover, increased expression of cyclin D1 (CCND1) gene due to mutations or forced expression of the wild-type gene could lead to increased resistance of MCL cell.[14] In our patient, the immunohistochemistry showed that the expression of CCND1 was strongly positive at the start of the treatment with obinutuzumab and venetoclax. Of note, Li et al reported that BCL-2 expression positively correlated with BTK expression, and therefore, targeting BCL-2 with venetoclax could be a new strategy to overcome ibrutinib resistance in MCL.[15] Furthermore, in vitro data showed that additional treatment with venetoclax significantly enhanced the effect of obinutuzumab.[16] Therefore, the combination of venetoclax and obinutuzumab could be a promising treatment strategy for ibrutinib-resistant MCL. The sustained response to the combination therapy obinutuzumab and venetoclax of our patient was consistent with these findings.

To the best of our knowledge, this is the first report about obinutuzumab and venetoclax induced CR in rituximab-intolerant patient with an ibrutinib-resistant leukemic MCL. The combination of obinutuzumab and venetoclax might be effective for patients with and ibrutinib-resistant RRMCL.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest relevant to the submitted manuscript.

ORCID

Xiang Zhou https://orcid.org/0000-0003-3885-0919

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Zhou X, Steinhardt MJ, Düll J, et al. Obinutuzumab and venetoclax induced complete remission in a patient with ibrutinib-resistant non-nodal leukemic mantle cell lymphoma. *Eur J Haematol*. 2020;104:352–355. https://doi.org/10.1111/ejh.13382