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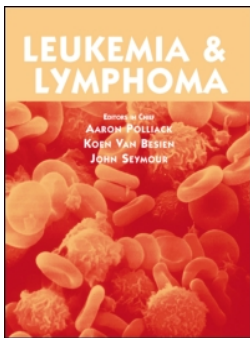
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Efficacy of ibrutinib in a patient with transformed lymphoplasmacytic lymphoma and central nervous system involvement

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Lymphoplasmacytic lymphoma (LPL) is a low-grade B-cell non-Hodgkin lymphoma that typically involves the bone marrow, lymph nodes and spleen and usually has an indolent course. Transformation to a diffuse large B-cell lymphoma (DLBCL) is rare [1], but when it occurs, prognosis is poor [2].

The myeloid differentiation primary response gene 88 (MYD88) p.(L265P) is a somatic mutation that activates the NF κ B pathway and is found in different types of B-cell non-Hodgkin lymphoma. This mutation most frequently occurs in LPL, in which detection of the mutation is of diagnostic as well as therapeutic value [3–5].

Ibrutinib is Bruton's tyrosine kinase (BTK) inhibitor that inactivates the NF κ B pathway [6]. It is registered for the use in mantle cell lymphoma, chronic lymphocytic leukemia and Waldenström macroglobulinemia (LPL with presence of M-protein in the serum). However, there are no data on the use of BTK inhibitor therapy in patients with transformed LPL. Here we present a patient with transformed LPL and loss of MYD88 p.(L265P), showing a significant clinical response to ibrutinib treatment for both systemic as well as central nervous system (CNS) localizations.

A 63 year old female patient presented in 2014 with B-symptoms and pancytopenia due to extensive bone marrow infiltration with LPL (Figure 1). The lymphoma predominantly consisted of small lymphocytes without prominent nucleoli. Occasionally, there was plasmacytic differentiation present. The lymphocytes showed immunohistochemical expression of B-cell markers (e.g. CD20 and CD79A), as well as scattered positivity for plasma cell markers (e.g. CD138). In addition, the plasmacytic B-cells displayed monotopia for kappa.

At that time, there was no extramedullary localization or M-protein in the serum. The patient was treated with

eight cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) chemotherapy and achieved complete remission. Hereupon, she was treated with rituximab maintenance therapy.

In 2015, the patient developed vertigo, ataxia and diplopia and a subsequent MRI demonstrated two brain tumors (Figure 2). CT scan of the neck, chest and abdomen and bone marrow biopsy showed no evidence of systemic lymphoma recurrence. A lumbar puncture was performed and a kappa positive clonal lymphocytic proliferation was detected by flow cytometric immunophenotyping of the cerebrospinal fluid (CSF). The patient was diagnosed with CNS relapse of the LPL. No biopsy of the brain lesions was performed as they were poorly accessible. Treatment with high dose systemic methotrexate (MTX), alternating with rituximab, dexamethason, high dose cytarabine and cisplatin (R-DHAP) and intrathecal MTX was started. After three cycles, stem cell mobilization was planned, but this was unsuccessful despite plerixafor administration. Three additional high dose MTX courses were given. Subsequent CSF samples and MRI demonstrated complete remission.

In April 2016 a new lesion developed in a submandibular lymph node and B-symptoms recurred. A biopsy of the submandibular lymph node was performed, which was consistent with DLBCL (Figure 1), non-germinal center type according to the Hans' immunohistochemical algorithm and without translocation of *BCL-2*, *BCL-6* and *cMYC*. Diagnostic work-up, consisting of a CT scan (Figure 2), bone marrow biopsy and brain MRI demonstrated no other signs of systemic recurrent lymphoma. However, the CSF showed again kappa positive clonal lymphocytes by immunophenotyping, demonstrating CNS relapse.

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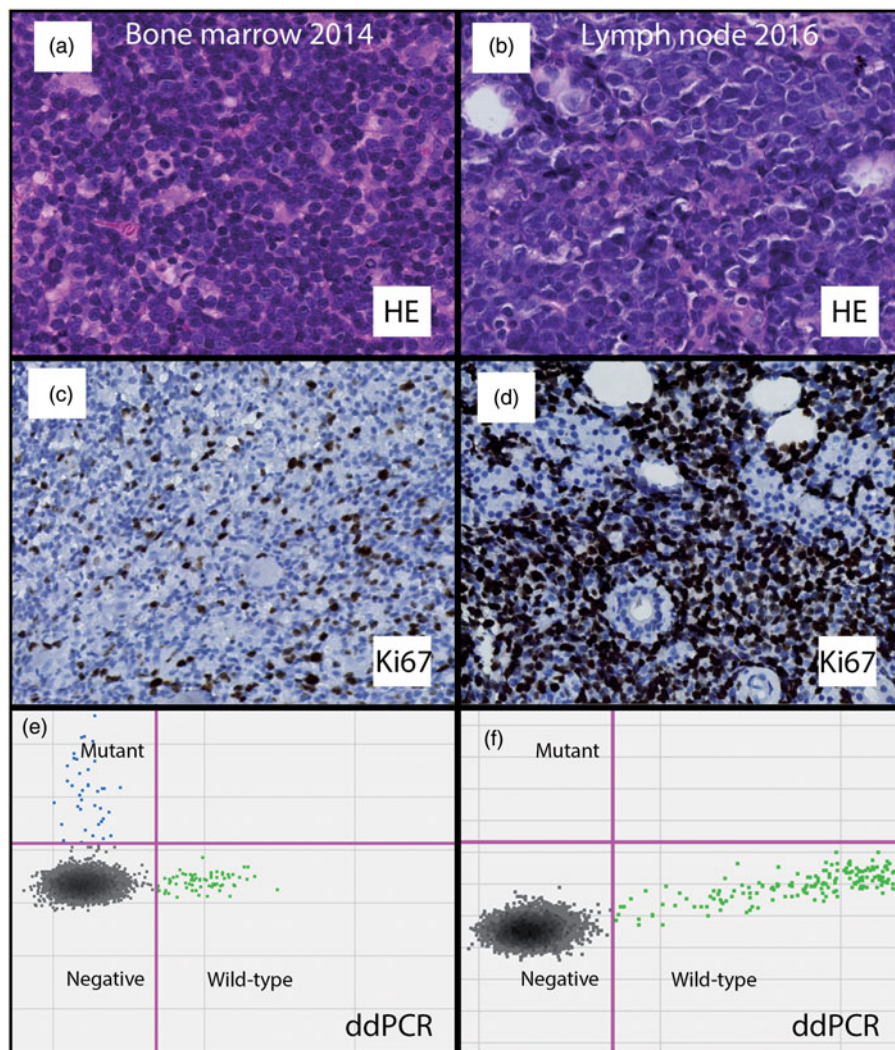


Figure 1. Loss of MYD88 p.(L265P) during transformation of LPL (2014) to DLBCL (2016). Morphology (HE) of bone marrow (a) and lymph node biopsy (b) showing small lymphocytes without prominent nucleoli and blastoid lymphocytes with prominent nucleoli respectively. Ki67 staining of bone marrow (c) and lymph node biopsy (d) showing low and high proliferation index respectively. ddPCR for MYD88 p.(L265P) mutation of bone marrow (e) and lymph node biopsy (f) showing presence and absence of MYD88 p.(L265P) respectively. Upper left quadrant (blue): mutant positive droplets. Lower right quadrant (green): wild-type positive droplets. Lower left quadrant (grey): negative droplets, depicting droplets without measurable PCR product. Abbreviations: DLBCL: diffuse large B-cell lymphoma; ddPCR: droplet digital polymerase chain reaction; HE: hematoxylin & eosin staining; LPL: lymphoplasmacytic lymphoma.

The patient was diagnosed with transformed LPL and concurrent localization in the CSF. In addition, clonality analysis was performed according to the Identiclone assay (Invivoscribe) [7], showed that the B-cell clone detected in the lymph node, the diagnostic bone marrow aspirate (2014) and the first CSF sample (2015) were identical. Remarkably, MYD88 p.(L265P) was detected by droplet digital PCR (ddPCR) in the bone marrow biopsy (2014; mutation frequency 23.3% with an assay sensitivity of 2.1%) and CSF sample (2015; mutation frequency 42.0% with an assay sensitivity of 3.9%), but not in the lymph node biopsy (2016; assay sensitivity 1.2%) (Figure 1).

As the patient was considered to be refractory to chemotherapy, treatment with a daily dose of 420 mg ibrutinib was started. Levels of ibrutinib were measured

in the blood and CSF, using liquid chromatography-tandem mass spectrometry [8]. Serum ibrutinib levels, 16 hours after administration, were 20.1 ± 0.9 ng/mL and were also positive in the CSF (<5 (0.43 ± 0.24) ng/mL; approximately 2% of the serum level), which is in accordance with previous publications [9].

Within two days after start of ibrutinib therapy an extremely fast response occurred, with complete clinical resolution of the enlarged submandibular lymph node, which was confirmed by CT scan after 16 weeks of therapy. In addition, B-symptoms disappeared as well, although some CNS related symptoms persisted. CSF examination was repeated after three months of therapy which demonstrated a persistence of clonal B lymphocytes, albeit with a decline in number. Also, clonality

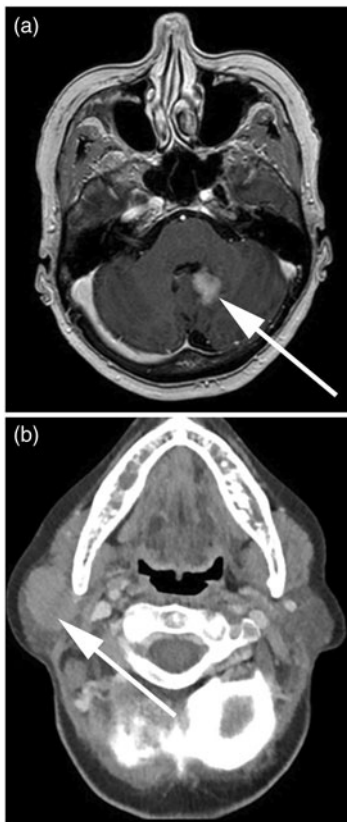


Figure 2. Radiological images of brain tumor (2015) and submandibular lymph node lesion (2016). (a) Brain tumor, located at the right frontal lobe, detected by T1 weighted MRI. (b) Submandibular lymph node lesion (left), detected by CT-scan.

analysis on this CSF sample detected the same clone as before. Interestingly, no MYD88 p.(L265P) was detected in this CSF sample by ddPCR (assay sensitivity 1.5%), which is concordant with loss of this mutation in the DLBCL of the submandibular lymph node biopsy (2016).

The patient remained in stable clinical remission for five months. She then presented with an epileptic seizure due to a new brain lesion. The patient received whole brain radiotherapy but with minimal clinical effect. She died one month later after a total period of six months of ibrutinib treatment.

To our knowledge, this is the first report of a patient with transformed LPL, who has shown a remarkably fast and prolonged response to ibrutinib monotherapy, 420 mg once daily. The patient retained a clinical remission for five months after start of treatment, although she eventually died as a result of progressive CNS lymphoma. Even though the presence of ibrutinib was demonstrated in the CSF, measured levels (<5 ng/mL) were probably too low for proper clearance of all pathological B-cells.

Although the same B-cell clone was detected in the bone marrow aspirate (2014), CSF samples (2015 and 2016) and lymph node biopsy (2016), MYD88 p.(L265P) was present in the bone marrow aspirate (2014) and first CSF sample (2015), but could not be detected in the lymph node biopsy (2016) and last CSF sample (2016).

Loss of MYD88 p.(L265P) might be explained by clonal selection as a result of BTK inhibitor therapy, leading to expansion of a MYD88 p.(L265P) negative subclone. However, loss of MYD88 p.(L265P) already occurred before start of ibrutinib treatment. Furthermore, as MYD88 p.(L265P) regards a driver mutation [10,11], it seems unlikely that loss of this mutation would occur as a result of clonal evolution. Despite the loss of the MYD88 p.(L265P), our patient still responded to BTK inhibitor therapy. It could be hypothesized that an alternative BTK-activating mechanism was involved, such as CD79B mutation, which results in chronic active B-cell receptor signaling [12,13]. Interestingly, CD79B mutation has been reported in 75% of transformed LPL patients [14]. On the other hand, response to ibrutinib treatment has also been described in DLBCLs ABC-type, classified according to gene expression profiling, without MYD88 mutations or other targets of ibrutinib, such as CD79B [13]. This indicates that an activating mutation is not a prerequisite for effective BTK inhibitor treatment. Unfortunately, there was not enough material left for further genetic analysis.

In conclusion, the described case shows clinically relevant activity of ibrutinib in transformed LPL, despite loss of MYD88 p.(L265P) during transformation. This underlines the need to further investigate mechanisms for loss of MYD88 p.(L265P) during LPL transformation, as well as the need to further investigate the use of BTK inhibitor therapy in transformed LPL.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at <https://doi.org/10.1080/10428194.2017.1369074>.

References

- [1] Castillo JJ, Gustine J, Meid K, et al. Histological transformation to diffuse large B-cell lymphoma in patients with Waldenström macroglobulinemia. *Am J Hematol.* 2016;91:1032–1035.
- [2] Castillo JJ, Olszewski AJ, Kanan S, et al. Survival outcomes of secondary cancers in patients with Waldenström macroglobulinemia: an analysis of the SEER database. *Am J Hematol.* 2015;90:696–701.
- [3] Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med.* 2012;367:826–833.
- [4] Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature.* 2011;470:115–119.
- [5] Gachard N, Parrens M, Soubeyran I, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenström macroglobulinemia/lymphoplasmacytic lymphomas. *Leukemia.* 2013;27:183–189.
- [6] Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol.* 2013;31:88–94.
- [7] van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia.* 2003;17:2257–2317.

- [8] Rood JJ, van Hoppe S, Schinkel AH, et al. Liquid chromatography-tandem mass spectrometric assay for the simultaneous determination of the irreversible BTK inhibitor ibrutinib and its dihydrodiol-metabolite in plasma and its application in mouse pharmacokinetic studies. *J Pharm Biomed Anal.* 2016;118:123–131.
- [9] 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.
- [10] Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell.* 2013;152:714–726.
- [11] Rossi D, Ciardullo C, Spina V, et al. Molecular bases of chronic lymphocytic leukemia in light of new treatments. *Immunology Letters.* 2013;155:51–55.
- [12] Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell.* 2017;31:833–843.
- [13] Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med.* 2015;21:922–926.
- [14] Alonso S, Jimenez C, Alcoceba M, et al. Whole-exome sequencing of Waldenstrom macroglobulinemia transformation into aggressive lymphoma. *Blood.* 2016;128:4101.