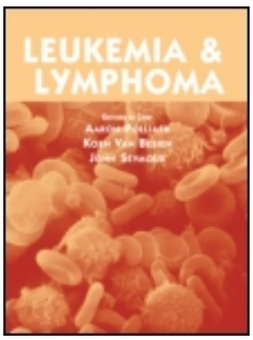

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LETTER TO THE EDITOR

Response to ibrutinib in a patient with IgG lymphoplasmacytic lymphoma carrying the MYD88 L265P gene mutation

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Lymphoplasmacytic lymphoma (LPL) is characterized by involvement of the bone marrow and other sites by a monoclonal population of B-cells, lymphoplasmacytoid and plasma cells. In over 95% of LPL cases, the malignant clone produces an IgM paraprotein consistent with Waldenstrom macroglobulinemia (WM). However, in the remaining LPL cases, the malignant clone can produce IgG or IgA, light chains alone, or be nonsecretory. The identification of the MYD88 L265P gene mutation has been a major advance in the diagnosis of patients with WM.[1] Few cases of nonIgM LPL have been reported demonstrating the presence of MYD88 L265P.[1–3] MYD88 L265P triggers survival signaling through BTK and HCK, and MYD88 L265P expressing cell lines undergo apoptosis in response to ibrutinib, which targets both of these kinases.[4,5] In 2015, the FDA and the EMA approved ibrutinib for the treatment of symptomatic WM based on a clinical trial in previously treated patients. Although treatment for non-IgM LPL usually follows the same guidelines as WM, the use of ibrutinib in non-IgM LPL has not been reported. We present here the first report of a patient with MYD88-mutated IgG LPL who underwent salvage therapy with ibrutinib.

The patient was diagnosed with IgG LPL in August 2000, when experiencing fatigue and night sweats. Her serum IgG level was 5080 mg/dl (normal: 700–1600 mg/dl). Serum protein electrophoresis demonstrated an IgG kappa monoclonal spike. A bone marrow biopsy showed 80% involvement by sheets of small mature lymphocytes with admixed plasma cells. Flow cytometry showed a *kappa*-restricted B-cell population that expressed CD20 and CD38, but not CD5 or CD10. Computed tomography (CT) scans showed no extramedullary disease. Shortly afterwards, the patient developed anemia, progressive fatigue and skin rash consistent with Schnitzler syndrome. She received and was refractory to R-CHOP in late 2000, cladribine in early 2001, and clarithromycin, thalidomide and dexamethasone in mid-2001. Following alemtuzumab, rituximab, and interferon in early 2002, the patient enjoyed a nine-year lapse off therapy with normal serum IgG levels. In November 2011, she presented with anemia and cervical lymphadenopathy. A lymph node biopsy showed LPL without large-cell transformation. The patient then received the mammalian target of rapamycin inhibitor MLN0128 in late 2011. In late 2012, the patient showed disease progression with cervical lymphadenopathy and Bing–Neel syndrome affecting the lumbar spine and received high-dose methotrexate and rituximab followed by bendamustine and rituximab. The patient achieved partial response on the systemic LPL and complete response on the BNS and was placed on maintenance rituximab.

In late 2014, while undergoing maintenance rituximab, the patient presented with worsening right-sided preauricular lymphadenopathy (6.7 cm × 2.7 cm) causing right-sided facial numbness and pain due to trigeminal nerve compression (Figure 1, left panel). Computed tomography (CT) scans showed generalized lymphadenopathy. A cervical lymph node biopsy showed *kappa*-restricted lymphoplasmacytic cells without large-cell transformation. Her serum IgG levels were normal at 697 mg/dl. Serum protein electrophoresis (SPEP) showed an IgG kappa monoclonal spike measured at 0.80 g/dl. A bone marrow biopsy showed that 15% of the intertrabecular space was comprised by LPL. The malignant cells were kappa-restricted and were CD19, CD20, and CD38 positive and negative for CD5, CD10, and CD23. The MYD88 L265P gene mutation was identified using polymerase chain reaction (PCR). Sanger sequencing did not identify CXCR4

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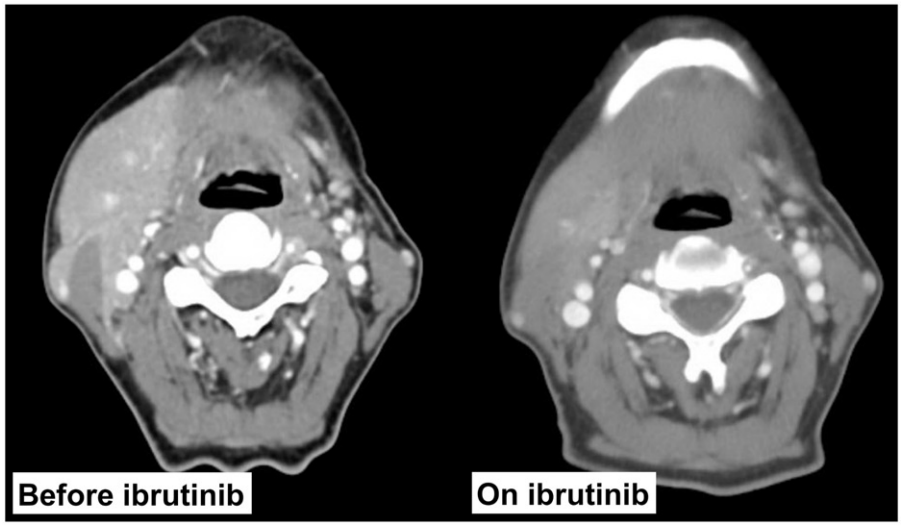

Figure 1. Computed tomography scans showing a partial radiological response to ibrutinib therapy in a patient with MYD88-mutated IgG lymphoplasmacytic lymphoma.

mutations. The patient was then initiated on ibrutinib 420 mg PO once daily. Within four weeks, the patient experienced clinical decrease in her lymphadenopathy, and symptoms related to facial nerve compression improved. Serum IgM level was 473 mg/dl, and SPEP showed an IgG kappa monoclonal spike measured at 0.40 g/dl consistent with a partial response. During her most recent visit in late 2015, the patient underwent CT scans. Her preauricular lymphadenopathy measured 4.5 cm × 1.5 cm (Figure 1; right panel), serum IgG level further decreased to 213 mg/dl, and SPEP showed an IgG kappa monoclonal spike measuring 0.25 g/dl. The patient continues on active ibrutinib therapy.

Non-IgM LPL is rare and comprises less than 5% of the cases with LPL. Recently, a case series on 17 patients with non-IgM LPL has been published.[6] In that series, nine (60%) of the 15 cases tested carried the MYD88 L265P gene mutation and six were wild type. In a Spanish study, the MYD88 L265P gene mutation was not identified in nine patients with non-IgM LPL,[7] suggesting a higher degree of heterogeneity in non-IgM LPL than in WM with relation to MYD88 L265P mutational status. Whole-genome sequencing studies identified the presence of the MYD88 L265P gene mutation in over 90% of patients with WM.[1] In a phase-II study, ibrutinib induced an overall response rate of 91% with a major response rate of 73%.[8] The MYD88 mutational status had a major impact on the response to ibrutinib. Wild-type MYD88 patients experienced overall and major response rate of 72% and 29%, respectively. More recently, using gene sequencing, two of the seven patients who were wild-type MYD88 were found to have non-L265P MYD88 mutations, decreasing the rate of overall and major response to ibrutinib in true wild-type MYD88 patients to 43% and 0%, respectively.[9]

The MYD88 L265P gene mutation has also been identified in up to 30% of cases with activated B-cell (ABC) diffuse large B-cell lymphoma.[10] Interestingly, ibrutinib therapy induces preferential responses in patients with ABC DLBCL when compared with germinal center-type DLBCL, with overall response rates of 37% and 5%, respectively.[11] In that study, ABC DLBCL patients with concurrent MYD88 L265P gene mutation experienced the highest rate of response at 80%.

Our patient had previously been exposed to alkylators, nucleoside analogs, immunomodulators, as well as anti-CD52 and anti-CD20 monoclonal antibodies for relapsed IgG LPL. Her therapeutic options at the time of her most recent relapse were limited, and given the identification of the MYD88 L265P gene mutation in the bone marrow, ibrutinib appeared as a reasonable option. In the phase II study of ibrutinib in relapsed and/or refractory WM, approximately, 70% of the patients, who had lymphadenopathy, experienced improvement, further supporting the use of ibrutinib in this patient. The patient tolerated treatment well with grade 1 bruising, arthralgias, and diarrhea, which improved and resolved with continued treatment. The partial response has been sustained for approximately one year at the time of this report.

In conclusion, we present the case of a heavily pretreated patient with MYD88-mutant IgG LPL, who has obtained a partial response to ibrutinib that is ongoing following a year of therapy. Additional research is

needed to better understand the pathophysiology of non-IGM LPL. As in WM patients, ibrutinib appears to be a potentially effective agent in treated patients with MYD88 mutated non-IgM LPL.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.3109/10428194.2016.1157875.

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