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Spotting the elusive Siberian tiger: Complete response to ibrutinib in a patient with Waldenström macroglobulinemia

To the Editor:

Ibrutinib is approved in the United States and Europe for the treatment of symptomatic Waldenstrom macroglobulinemia (WM). The approval was based on results of a phase II study in which 63 patients with previously treated WM received ibrutinib at 420 mg PO once daily until progression or unacceptable toxicity.[1] The overall response rate (ORR; at least 25% decrease in IgM level) was 91% with a major response rate (at least 50% decrease in IgM level) of 73%, based on the 6th International Workshop for WM. However, the rate of very good partial response (VGPR; ≥90% decrease or normalization of IgM, but with detectable IgM monoclonal spike in serum protein electrophoresis [SPEP]) was 16%, and no complete response (CR; normalization of IgM, absence of monoclonal spike and normal bone marrow) was seen. In 2 additional prospective studies, one in patients with WM who were refractory to rituximab and one in previously untreated WM patients, no CR to ibrutinib therapy was attained.[2,3] We would like to report a WM patient who achieved a CR on ibrutinib monotherapy.

The patient is a 62-year-old woman diagnosed with WM in January 2004. At the time, bone marrow biopsy revealed 70% involvement by lymphoplasmacytic lymphoma (LPL). Serum IgM level was 2210 mg/dL, and blood counts were normal. As she was asymptomatic, she was followed expectantly until December 2008, when she developed anemia (hemoglobin <10 g/dL). Bone marrow biopsy showed 95% involvement by LPL. Serum IgM level was 2470 mg/dL. The patient received 8 cycles of rituximab, cyclophosphamide, and prednisone. Her IgM level dropped to 183 mg/dL but with persistent IgM monoclonal spike in SPEP, consistent with VGPR. She received maintenance rituximab for 2 years, until June 2011. She remained in VGPR and was followed expectantly. She met criteria for disease progression by November 2014, and in March 2015, she presented with increased shortness of breath and decreased breath sounds on the left lung. CT scans revealed generalized lymphadenopathy and left pleural effusion. Flow cytometry analysis of the pleural fluid showed monoclonal B-cells. Bone marrow biopsy showed 60% involvement by LPL. PCR for MYD88 L265P was positive in pleural fluid and bone marrow. No CXCR4 mutations were identified by Sanger sequencing. Serum IgM level was 1955 mg/dL. The patient was started on ibrutinib at 420 mg PO once daily. By June 2015, the patient had achieved a VGPR. In October 2015, the patient's IgM monoclonal spike was no longer detectable. In July 2016, a bone marrow biopsy showed no evidence of disease, consistent with CR. The MYD88 L265P mutation was detected by PCR, however. CT scans showed resolution of lymphadenopathy and trace pleural effusion. In June 2017, bone marrow biopsy showed no evidence of disease, and the MYD88 L265P gene mutation was no longer detected by PCR. The patient continues on ibrutinib. The toxicity has been mild with grade 1 bilateral lower extremity edema and cough, which resolved within first 3 months of therapy. There have been no bleeding or arrhythmias.

In addition to standard testing, quantitative PCR for MYD88 L265P was performed in CD19-selected tumor samples from March 2015, July 2016, and June 2017. A standard curve for MYD88 L265P was generated using serial dilutions of 50%, 10%, 2%, 0.4%, and 0.08% using mutant and wild-type DNA. Tumor samples of the 3 timepoints were run on the same plate as the standard curve to determine MYD88 L265P mutation status over time. Levels of mutant MYD88 L265P in each time point was calculated based on the standard curve. Following this methodology, the percentage of MYD88 L265P cells in samples were 8%, 6%, and 0.99%, respectively. This suggests that the absence of MYD88 L265P reported by standard PCR in June 2017 might have been false negative.

Mounting data suggest that genomic profile can impact responses to ibrutinib in WM. WM patients with only MYD88 L265P have deeper and more durable responses than patients with MYD88 L265P and CXCR4 mutations.[1,3] However, CR in WM patients receiving ibrutinib monotherapy has not been previously reported. CR is an otherwise rarely attained response in WM. In a recent report, we evaluated 182 patients who received primary therapy with rituximab-containing regimens.[4] The CR rate was approximately 10%.

In current response criteria, however, there is not a category of "molecular" CR, which could be defined by CR in addition to lack of detection of MYD88 L265P using a high-sensitivity PCR method. Our report is a double-edged sword. On one hand, it suggests that CR in WM patients is possible with ibrutinib. On the other hand, it also suggests that a "molecular" CR is even more difficult to demonstrate in WM patients, when using CD19-sorted samples or PCR testing with higher sensitivity cutoffs.

The present case provides additional insights on the clinical heterogeneity of the responses to ibrutinib in WM patients, and poses additional questions that could have management impact in the near future. It is important to note that this is the only known patient who achieved CR on ibrutinib monotherapy. It is likely that there are others. The depth of response could have prognostic implications with regards to progression-free survival (PFS). We showed that response duration associated with depth of response to chemoimmunotherapy.[5] It is unclear, however, whether depth of response correlates with response duration on ibrutinib. In a recent update from the pivotal phase II study on ibrutinib in previously treated WM patients, patients without CXCR4 mutations had a longer median PFS than patients with CXCR4 mutations, whose responses to ibrutinib tend to be slower and more superficial.[6] We also believe this case can promote the design and execution of clinical trials using ibrutinib

combinations with other agents looking for deep response as primary outcome. The results of the INNOVATE study, which randomized WM patients to ibrutinib and rituximab versus rituximab alone, are eagerly awaited (NCT02165397). Given the relatively benign toxicity profile of ibrutinib, combinations with monoclonal antibodies, proteasome inhibitors, alkylators, and other agents are likely to be well tolerated have greater efficacy at inducing deep responses in WM patients.

DISCLOSURE OF INTERESTS

JJC has received honoraria and/or research funds from Abbvie, BeiGene, Gilead, Janssen, Millennium, and Pharmacyclics. SPT has received honoraria and/or research funds from Pharmacyclics. All other authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

JJC, TD and SPT took care of the patient and gathered the data. AK, MD, NT, LX, and ZRH performed the MYD88 L265P mutational testing. JJC drafted the manuscript. All authors read and approved the manuscript.

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Genetic biomarkers of sensitivity and resistance to venetoclax monotherapy in patients with relapsed acute myeloid leukemia

To the Editor:

Acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by chromosomal aberrations and somatic mutations that identify biologically distinct subsets and guide risk stratification for therapy.[1] Treatment-associated changes in clonal architecture are common in AML, with emergence or clearance of specific sub-clones driving sensitivity and resistance to therapy. Therefore, the molecular characterization of emerging clones may facilitate the selection of optimal targeted therapies and rational combinations.

Venetoclax, a selective BCL-2 inhibitor, induced a complete response or complete response with incomplete blood recovery (CR/CRi) in 6/32 (19%) patients with AML who either had relapsed/refractory disease or were medically unfit for intensive chemotherapy.[2] In this report, we present a comparison of genetic biomarkers observed in pre- and post-treatment specimens from 29 of the 32 patients enrolled on this phase II study. Measurable reduction in bone marrow (BM) blast counts was observed in 15/29 (52%) of the patients, including CR/CRi in 6, a ≥50% reduction in BM blasts in 5, and a more modest blast reduction of <50% in 4 (Supporting Information Figure 1). The remaining patients (14/29, 48%) had no blast reduction.

We investigated the presence of somatic mutations commonly associated with AML in baseline and end-of-treatment samples. DNA isolated from blood and bone marrow specimens was analyzed by next-generation sequencing using the TruSight Myeloid panel (Illumina), the FoundationOne Heme panel (Foundation Medicine), or whole exome sequencing (MD Anderson Cancer Center, Khalifa Institute). Comparison of mutations at baseline and end of treatment is shown in Figure 1A.

At baseline, 10/29 (34%) patients had mutations in isocitrate dehydrogenase 1/2 (*IDH1/2*) genes. Of these, 7 (70%) had a reduction in BM blasts, including 3 CR/CRi. At baseline, 11/29 (38%) patients had spliceosome mutations in *SRSF2* or *ZRSR2*. Ten (88%) of these patients had a decrease in BM blasts, including 3 CR/CRi. Seven patients had both *IDH1/2* and spliceosome mutations with BM blast reductions observed in 6 (86%). In total, 11/14 (79%) patients with