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LETTER TO THE EDITOR

Idelalisib in Waldenström macroglobulinemia: high incidence of hepatotoxicity

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Waldenström macroglobulinemia (WM) is a rare B-cell lymphoma characterized by the accumulation of IgM-secreting lymphoplasmacytic cells.[1] Despite therapeutic advances, WM remains incurable, and novel treatment options are needed. Over 90% of patients with WM carry the MYD88 L265P gene mutation, which promotes the survival of WM cells through activation of the Bruton tyrosine kinase (BTK) pathway.[2] In a phase II study evaluating the BTK inhibitor ibrutinib in 63 patients with relapsed and/or refractory disease, an overall response rate (ORR) of 90% with acceptable toxicity was observed.[3] These results prompted the approval of ibrutinib by the United States Food and Drug Administration for use in patients with symptomatic WM.

MYD88 L265P also promotes activation of the phosphatidylinositol-3-kinase (PI3K) pathway and exposure to the PI3K-delta inhibitor idelalisib induced robust killing in MYD88-mutated WM cells.[4] In a prior phase 2 study, 80% ORR was reported in 10 patients with WM, refractory to anti-CD20 and alkylating agents, treated with idelalisib 150 mg twice daily.[5] In addition, a phase 1 study including nine relapsed/refractory WM patients treated with idelalisib reported 56% ORR.[6] Given these results, we initiated a prospective investigator-initiated phase 2 study to evaluate the safety and efficacy of idelalisib in patients with relapsed and/or refractory symptomatic WM (ClinicalTrials.gov identifier NCT02439138).

The study was activated on 10 September 2015. All patients provided written informed consent after approval of the study by the Institutional Review Board at the Dana-Farber Cancer Institute. Gilead Sciences provided research funding and study drug. The primary objective was to determine response rates to idelalisib as defined by the 6th International Workshop in WM.[7] Serum IgM level, complete blood count, blood chemistries, liver function tests, bone marrow biopsy, and computed tomography (CT) scans were obtained at the

beginning of the study. Eligibility criteria included a clinicopathological diagnosis of WM,[8] need for treatment according to guidelines,[9] at least one prior line of therapy, platelet count $\geq 50,000/\text{mm}^3$, neutrophil count $\geq 1000/\text{mm}^3$, creatinine level $\leq 2\text{ mg/dl}$, total bilirubin level $\leq 1.5\text{ mg/dl}$, aspartate and alanine aminotransferase levels ≤ 2.5 times the upper limit of normal, ECOG performance status of 2 or lower, and no active HIV, hepatitis B or C infection. The treatment regimen consisted of idelalisib at 150 mg PO twice daily until disease progression or unacceptable toxicity. An allele-specific PCR assay was used to detect the MYD88 L265P mutation. CXCR4 mutational status was determined by Sanger sequencing. A one-stage design was used with alpha level at 0.05 and beta level at 0.20. This assumed a null ORR of 40% and a successful ORR of 70%. Our accrual goal was 30 patients.

Five patients were enrolled in the study and received therapy. The median age at study entry was 66 years (range 57–80 years). Two patients met criteria for treatment due to anemia, one due to constitutional symptoms, one due to hyperviscosity, and one for evidence of renal involvement by lymphoplasmacytic lymphoma. The median number of prior therapies was 4 (range 3–9). All the patients were previously exposed to rituximab and bortezomib, four to alkylating agents, two to nucleoside analogs, and one to ibrutinib. The median bone marrow involvement was 40% (range 20–80%), the median IgM level was 4512 mg/dl (range 3970–6190 mg/dl), and the median hemoglobin level was 11 g/dl (range 7.7–12.4 g/dl). According to the International Prognostic Scoring System for WM, three patients were intermediate, one was low and one was high risk. The MYD88 L265P gene mutation was identified in all patients and CXCR4 mutations in two.

Four patients were evaluable for response and exhibited stable disease on idelalisib. Patient 1 had previously progressed on ibrutinib therapy, and was not evaluable

for response since he died of progressive disease three weeks after initiation of idelalisib. Patient 2 experienced grade 4 ALT elevation at day 32 of therapy. Idelalisib was held for 19 days until ALT elevation was grade 1. The patient then received idelalisib 100 mg PO twice daily and developed grade 3 ALT elevation 28 days later. Idelalisib was reinitiated six days later, when ALT elevation was grade 1, at 150 mg PO once daily. Idelalisib was continued until day 84 when patient decided to stop therapy; ALT elevation was grade 1. Patient 3 experienced grade 3 ALT elevation at day 29. Idelalisib was held for 10 days then restarted at 150 mg PO twice daily. Within three days of idelalisib reinitiation, the patient experienced grade 4 ALT elevation and therapy was discontinued; 11 days later ALT elevation was at grade 1. Patient 4 experienced grade 3 ALT elevation at day 29. The patient then decided to stop idelalisib. It took 22 days for ALT to decrease to grade 1. Patient 5 did not experience ALT elevation at day 28. Bilirubin levels were normal during idelalisib therapy in all patients. On 11 March 2016, Gilead Sciences stopped six prospective studies with idelalisib combinations in patients with hematologic malignancies due to an increased mortality rate associated with CMV reactivation and *Pneumocystis jiroveci* pneumonia. When patients 2 and 5 were receiving active therapy, both patients decided to stop idelalisib. All surviving patients were tested for CMV viral load without evidence of active infection. The study was permanently closed on 23 March 2016.

Herein, we present our experience on the use of idelalisib in previously treated patients with WM. Our study was not successful; however, it provides an opportunity to advance the therapeutic field by avoiding exposure to an agent with high toxicity rates. In a previous study, ALT elevation of any grade was seen in 47% of patients, of which 13% were grade 3 or higher, and prompted the discontinuation of therapy in 4%.^[5] Similar rates of ALT elevation were also observed in a phase 1 study.^[6] Among the 19 WM patients with previously reported idelalisib exposure, six (32%) experienced grade 3 or higher ALT elevation, prompting treatment discontinuation in one patient (5%). In our study, grade 3 or higher ALT elevation was observed in three out of four (75%) evaluable patients within a median 29 days of idelalisib exposure. Despite our limited experience, we report higher rates of ALT elevation in patients with WM than previously reported. A recent study evaluated 24 patients with chronic lymphocytic leukemia who received idelalisib as frontline treatment.^[10] In this study, approximately 80% and 50% of patients exposed to idelalisib experienced grade 1 or higher and grade 3 or higher transaminitis, respectively. With a median time to transaminitis of 28 days, younger patients were at a higher risk of developing this complication. Hepatotoxicity associated with idelalisib appears immune-mediated as liver biopsy in some of these cases showed a lymphocytic infiltrate with high serum levels of CCL3 and CCL4. In contrast with the study

mentioned above, our patients were heavily pretreated with a median age of 66 years. Nevertheless, management of patients treated with idelalisib who experience transaminitis may include drug interruptions and/or dose reductions, and ultimately permanent discontinuation, if warranted.^[11]

Although we were not mandated to stop our study, we felt accrual would be affected. It was our final decision to close the study to further accrual. It is possible, however, that a subset of patients with WM could benefit from idelalisib therapy as patient 5 did not experience ALT elevation and had a 16% reduction on IgM levels by day 28 of therapy, when idelalisib was stopped. Further development of idelalisib in WM would have to be considered in the context of clinical trials in which different dosage regimens could be evaluated.

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