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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 PI3Kdelta 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 clinical-pathological diagnosis of WM,[8] need for treatment according to guidelines,[9] at least one prior line of therapy, platelet count ≥50,000/mm³, neutrophil count ≥1000/mm³, creatinine level ≤2 mg/dl, total bilirubin level ≤1.5 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 eleva-
tion 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 experi-
ced 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 expe-
rienced grade 4 ALT elevation and therapy was discon-
tinued; 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 ide-
lalisib combinations in patients with hematologic malig-
nancies due to an increased mortality rate associated
with CMV reactivation and Pneumocystis jiroveci pneu-
monia. When patients 2 and 5 were receiving active ther-
apy, 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 idela-
lisib 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 discon-
tinuation of therapy in 4%.[5] Similar rates of ALT eleva-
tion were also observed in a phase 1 study.[6] Among the 19 WM
patients with previously reported ide-
lalisib 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 eleva-
tion 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 develop-
ing this complication. Hepatotoxicity associated with ide-
lalisib 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, manage-
ment 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 deci-
sion 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 con-
sidered in the context of clinical trials in which different
dosage regimens could be evaluated.

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