CASE REPORT

B-cell lymphoma 2 inhibitor venetoclax treatment of a patient with cutaneous T-cell lymphoma

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INTRODUCTION

There remains a need for effective, durable therapies for cutaneous T-cell lymphoma (CTCL), a skin-homing T-cell non-Hodgkin lymphoma (NHL) that in advanced stages may involve the blood and lymph nodes. Overall response rates for approved CTCL agents range from ~30% to 50%, with available oral agents limited to bexarotene (a third-generation retinoid) and vorinostat (a histone deacetylase inhibitor). The US Food and Drug Administration recently approved the oral agent venetoclax, a selective inhibitor of B-cell lymphoma 2 (BCL-2), for chronic lymphocytic leukemia, small lymphocytic lymphoma, and acute myeloid lymphoma. In several leukemia and NHL cell lines, BCL-2 expression correlates with venetoclax sensitivity. We also recently reported that patient-derived CTCL cells exhibited variable sensitivity to venetoclax, with a portion showing picomolar-range 50% inhibitory concentrations, and that venetoclax sensitivity was correlated with baseline BCL-2 expression. Herein, we present a CTCL patient with skin and blood involvement treated with daily venetoclax.

CASE REPORT

A 75-year-old man developed scaly, erythematous patches symmetrically distributed on his trunk and extremities over approximately 15% of his body surface area. Histologic examination of multiple skin biopsies was consistent with mycosis fungoides CTCL. Polymerase chain reaction analysis performed on blood samples was positive for T-cell receptor (TCR) clonality. Flow cytometry of peripheral blood revealed an abnormal TCR Vβ13.1+ population comprising 70.95% of his TCRβ repertoire and an absolute count of >1000 phenotypically abnormal (CD4+CD26–CD7–) cells, consistent with ISCL stage IVA mycosis fungoides CTCL with B2 blood involvement. Over a 5-year period, he was treated with narrow band-ultraviolet B up to 3 times a week, with limited response. Extracorporeal photochemotherapy was initiated twice monthly, along with 150 mg of oral bexarotene daily, which was increased to 375 mg daily over 2 years. Subsequently, 1 million IU of subcutaneous interferon-α2b administered 3 times per week was added to the treatment regimen, but blood and skin involvement progressed over the following year.

A full body skin examination revealed widespread scaly, erythematous patches involving his torso and extremities (Fig 1, A). No palpable cervical, axillary, or inguinal lymph nodes were found on examination. Several other treatment options were discussed with the patient, including intravenously

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administered romidepsin and mogamulizumab, but the patient expressed preference for an oral agent. Under an investigator-initiated, single-arm, open-label pilot study (NCT04171791), the patient received venetoclax monotherapy daily according to a 28-week study protocol, consisting of a 5-week ramp-up dosing schedule: 20, 50, 100, 200, and the 400-mg maximum dosage at weeks 1, 2, 3, 4, and 5, respectively. The patient received insurance coverage to continue venetoclax beyond the 28-week study protocol, and remains on 400 mg daily venetoclax at this time. At the most recent 39-week follow-up, blood involvement measured by multicolor flow cytometric quantification found that the level of abnormal CD4⁺CD26⁻CD7⁻ lymphocytes decreased from 2356 to 287 cells/μL and the CD4⁺CD8 ratio improved from 16.6 to 7.1. Consistent with this, there were also decreases in CD4⁺CD7⁻ (from 1797 to 411 cells/μL) and CD4⁺CD26⁻ (from 1829 to 463 cells/μL) lymphocyte counts (Fig 2).

The patient tolerated venetoclax treatment, with no evidence of bone marrow suppression, tumor lysis syndrome (TLS), or clinical sequelae of TLS, including renal insufficiency, cardiac arrhythmia, and seizures. The patient reported feeling well, with some persistent patches noted on his chest and extremities (Fig 1, B). The overall modified severe weighted assessment tool² skin score improved from 23, 18, 19, 6, to 5 at weeks 0, 14, 21, 28, and 39, respectively.

Before venetoclax initiation and again at the 28-week treatment time point, the patient’s malignant T cells were isolated from peripheral mononuclear blood cells using magnetic bead negative selection, and in vitro dose-response viability assays were performed by adenosine triphosphate quantification (Fig 3). The 50% inhibitory concentration values of 0.01653 μM pretrial and 0.02391 μM at week 28 indicated persistently high venetoclax sensitivity without evidence of development of drug resistance.
DISCUSSION

The most serious reported side effects of venetoclax therapy include neutropenia and TLS (eg, acute renal failure, cardiac arrhythmia, seizures, and sudden death) as a consequence of rapid and high levels of induction of tumor cell apoptosis. Complete blood counts, blood chemistries, liver function tests, kidney function tests, and urinalyses were performed throughout the treatment, including following the first dose and following each dose increase. The patient exhibited no evidence of bone marrow suppression, renal insufficiency, or hepatic toxicity during treatment. At the 13-week follow-up, serum uric acid was elevated at 8.4 mg/dL, but it resolved to normal levels following initiation of 300 mg allopurinol daily.

As detailed, the patient showed substantial but not complete responses in skin and blood involvement. Although positron emission tomography/computed tomography revealed slightly to moderately elevated metabolic activity in the axillary, hilar, and inguinal lymph nodes, these improved relative to pretreatment values, with standardized uptake values of fludeoxyglucose that ranged up to 3.1 pretreatment noted as non-fludeoxyglucose-avid post-treatment with venetoclax. The largest noted lymph node pretreatment was a right inguinal lymph node measuring 1.4 cm in the short axis, and this remained
stable. No lymph node biopsies to histologically evaluate involvement or response were performed prior to or after treatment.

A conservative maximal dose of 400 mg was selected for our patient for safety considerations. At 400 mg, the mean (SD) venetoclax steady state (Cmax) was 2.42 ± 1.27 μM. Within a safety expansion cohort in a phase I study for other types of NHL, patients received target doses of venetoclax of up to 1200 mg daily. No TLS was observed in these patients. After 6 months of daily treatment with venetoclax monotherapy following the 5-week ramp-up dosing schedule, our in vitro viability assays indicated no significant change in drug sensitivity, consistent with the absence of development of resistance to venetoclax (Fig 3). Responders to venetoclax monotherapy for chronic lymphocytic leukemia had progression-free survival of approximately 70% at 12 to 15 months. Evidence of clinical efficacy in our patient, supported by our previously reported in vitro viability assays and CTCL patient malignant cell BCL-2 expression profiles, suggests venetoclax as a potential oral therapy for CTCL that warrants further investigation of clinical safety, dosing, and efficacy.

Conflicts of interest
None disclosed.

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