Complete response of relapsed adult T-cell lymphoma leukemia to a Bcl-2 inhibitor: a case report

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Abstract: Acute T-cell leukemia lymphoma (ATLL) is a rare type of mature T-cell lymphoma driven by human T-cell leukemia virus type 1 (HTLV-1) that occurs in about 5% of HTLV-1 carriers. Out of the 4 subtypes of ATLL (smoldering, chronic, acute, and lymphomatous), acute and lymphomatous ATLL carry extremely poor prognosis with a median overall survival (OS) of 10 months. Most patients relapse shortly after or during frontline therapy, and there are no effective salvage regimens. We report 2 cases of primary refractory ATLL with complete response to venetoclax, a B-cell lymphoma 2 (Bcl-2) inhibitor. The 2 patients included a 63-year-old African American female and a 40-year-old female from Haiti with confirmed relapsed and refractory ATLL. Next-generation sequencing (NGS) confirmed the presence of anti-apoptotic pathways and mutations of *BCL2* and neurogenic locus notch homolog protein 3 (*NOTCH3*). A decision to start the patients on venetoclax was made, and both patients experienced a significant decline in HTLV-1 viral load leading to complete remission. The 2 cases presented in this case report reveal a significant response to venetoclax in relapsed and refractory ATLL. Targeting Bcl-2 could be a novel treatment in relapsed ATLL, and further investigation of the use of Bcl-2 inhibitors in relapsed ATLL is warranted.

Keywords: Next-generation sequencing (NGS); lymphoma; *BCL2*; human T-cell leukemia virus type 1 (HTLV-1); case report

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Introduction

Human T-cell leukemia virus type 1 (HTLV-1), the first discovered human retroviral pathogen, effects approximately 20 million people worldwide (1,2). It is estimated that about 90% of infected individuals remain asymptomatic carriers during their lives (1). HTLV-1 is endemic in Japan, Africa, the Caribbean islands, and Central and South America (1). An oncoprotein known as transactivator x (Tax), encoded from the HTLV-1 genome, activates the viral and cellular gene expression involved in T-lymphocyte proliferation and modulates this expression through the cAMP response element-binding protein/activating transcription factor (CREB/ATF), serum response factor (SRF), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathways, promoting tumorigenesis (3).

About 5% of HTLV-1 carriers develop acute T-cell leukemia lymphoma (ATLL) (1). ATLL occurs in patients aged 20 to 80 years, with an average age of 58 years, and has a preference for males, with a male to female ratio of 1.5 to 1 (4,5). Survival ranges from 8 years for the chronic and smoldering subtypes to less than a year for the acute and lymphomatous subtypes (6). Treatment of the acute and lymphomatous subtypes includes multiagent regimens, antiviral therapies, and allogeneic hematopoietic stem cell transplantation for highly selected patients (7). Mogamulizumab, an anti-C-C chemokine receptor type 4 (CCR4) antibody, was approved in Japan for relapsed

ATLL based on a phase II study (8). We present the following article in accordance with the CARE reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-21-23/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. A copy of the written consent is available for review by the editorial office of this journal.

The first patient was a 63-year-old African American female with a past medical history of type 2 diabetes mellitus who presented to the emergency room (ER) with progressive onset of nausea and dizziness beginning 2 weeks prior. She originally presented at an outdoor hospital and was found to be hypercalcemic on laboratory studies. She subsequently had a computed tomography (CT) scan of her chest, abdomen, and pelvis, which revealed extensive lymphadenopathy above and below the diaphragm, raising suspicion for ATLL. The patient was transferred to our hospital for further examination. She had previously worked as a paralegal and had a family history of unspecified cancer through her father. She denied drug use or smoking history but had a history of occasional alcohol use. On physical examination, the patient was afebrile, with a respiratory rate (RR) of 16 breaths/min, a heart rate (HR) of 95 bpm, a peripheral oxygen saturation (SpO_2) of 95%, and a blood pressure (BP) of 117/60 mmHg. She was found to be lethargic but alert and oriented to person, place, and time. The remainder of the physical examination was normal.

Laboratory studies at presentation were significant for an elevated white blood cell count (WBC) of 105,500/mcL, a hemoglobin level of 14.5 g/dL, a platelet count of 212,000/mcL, a lactate dehydrogenase (LDH) level of 1,890 IU/L, and a calcium level of 8.0 mg/dL. A magnetic resonance imaging (MRI) scan of the brain showed mild leptomeningeal enhancement. Flow cytometric analysis from a peripheral blood sample showed an abnormal T-cell population which was >75% positive for CD3, CD4, CD5, and CD25; positive for T-cell receptor (TCR) alpha/beta and CD52; and negative for CD7, CD2, CD8, and CD30. Flow cytometric analysis from the cerebrospinal fluid (CSF) revealed a subpopulation of T cells showing an abnormal immunophenotypic profile positive for CD3, CD4, CD2 (dim), CD5, and CD25 and negative for CD8, CD7, and CD56. The diagnosis of ATLL was confirmed. Next-generation sequencing (NGS) from a peripheral blood sample revealed the following mutations: *NOTCH1* biallelic mutation beta-actin-Rac family small GTPase 2 (*ACTB-RAC2*) (7:22) fusion; hook microtubule tethering protein 3-tetraspanin-14 (*HOOK-3-TSPAN14t*) (8:10) fusion; forkhead box protein O1-zinc finger MYM-type containing 2 (*FOXO1-ZMYM2t*) (13:13) fusion; and a high expression of *BCL11b*, *2a*, *2l1*, *3*, and *6*. Serology for HTLV-1/2 revealed anti-HTLV-1 immunoglobulin G (IgG). Qualitative polymerase chain reaction (PCR) returned positive for HTLV-1 and negative for HTLV-2.

The patient began treatment with cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, and high-dose cytarabine. She experienced immediate improvements in her neurological status with recovery to her baseline and normalized WBC. After 3 cycles of chemotherapy, a positron emission tomography (PET) scan revealed complete remission, and an MRI scan showed resolution of lymphadenopathy and leptomeningeal findings. A donor search was initiated. However, the patient's WBC started to increase with reversal of normal differential. After 4 cycles, she experienced disease progression, and quantitative PCR returned positive for HTLV-1 with a viral load of 1,200,000 copies per mL (cpm). The patient was started on mogamulizumab.

After 3 cycles of mogamulizumab, there was no improvement in the patient's WBC. She was started on venetoclax 100 mg daily, which was increased to 400 mg over a period of 3 days after NGS revealed expression of B-cell lymphoma 2 (Bcl-2). After 1 month of venetoclax administration, she achieved complete response with resolution of lymphadenopathy on PET/CT. Quantitative PCR for HTLV-1 detected a viral load of 700 cpm. Bone marrow biopsy and peripheral blood showed no evidence of ATLL, and NGS of peripheral blood showed no evidence of mutations. Tolerability was assessed with monthly visits at the lymphoma clinic. The patient experienced no adverse events from venetoclax. She underwent allogeneic stem cell transplant from an unrelated donor and continues to be in remission 12 months later. The latest PCR did not detect HTLV-1. She has no transplant-related morbidity.

The second patient was a 40-year-old female from Haiti with a past medical history of hypertension who presented with pruritis and multiple small papular cutaneous lesions for 1 year, suspected to be from new onset cutaneous lupus. She underwent a course of prednisone with no

improvement. The patient immigrated from Haiti in 2005 and had no family history of malignancies, including lymphoma. She had no history of alcohol use, smoking, or drug use. She previously worked as a house cleaner. She presented to our institution with pruritus, cutaneous lesions, and worsening dyspnea. On physical examination, she was afebrile with an RR of 16 breaths/min, an HR of 95 bpm, an SpO_2 of 96%, and a BP of 129/75 mmHg. The patient appeared in no acute distress. Her skin examination revealed a diffuse nodular rash. The remainder of the physical examination was normal.

The patient's CT scans revealed multiple pulmonary nodular and ground-glass opacities and scattered lymphadenopathy in the axilla and inguinal regions. Complete blood count (CBC) tests showed mild anemia and normal WBC with normal differential. Her chemistry was unremarkable, except for elevated uric acid and LDH 10 times the normal upper limit. Flow cytometry of peripheral blood revealed $CD45^+$, $CD3^+$, $CD2^+$, $CD5^+$, $CD4^+$, $CD25^+$, $CD52^+$, $CD7^-$, $CD8^-$, and $CD30^-$ T-cell clones consistent with adult T-cell leukemia. Biopsy of the right inguinal lymph node revealed diffuse effacement with sheets of large and atypical lymphocytes with the following phenotype: $CD3^+$, $CD7^-$, $CD25^+$, $CD4^+$, $CD8^-$, and $CD30^+$ (subset). Skin biopsy revealed an atypical dermal and periadnexal infiltration of large, atypical lymphocytes similar to those identified in the right groin lymph node. HTLV-1 serology at diagnosis was positive. NGS from a bone marrow biopsy revealed no detected genomic alterations; however, during disease progression, a notch homolog protein 3 (*NOTCH3*) mutation was detected in the peripheral blood. Diagnosis of the lymphomatous subtype of ATLL was established, and a donor search was initiated.

The patient was treated with 3 cycles of hyper-CVAD alternating with ifosfamide, high-dose methotrexate, and etoposide with complete remission. During the 2 months of the last cycle, she experienced disease progression and was enrolled in a clinical trial of a dual spleen-associated tyrosine kinase/Janus kinase (SYK/JAK) inhibitor with a brief partial response. She received an interleukin-2-inducible T-cell kinase (ITK) inhibitor as part of trial with no response, followed by brentuximab vedotin (a CD30-directed antibody drug) and bendamustine for 3 cycles. The patient experienced a brief response to these drugs; however, her disease progressed with new bulky tumoral cutaneous lesions and extensive lymphadenopathy. She was started on venetoclax 400 mg daily after *NOTCH3* was detected in the peripheral blood by NGS. The patient's HTLV-1 viral load prior to the initiation of venetoclax was 702,000 cpm, which declined to less than <1,000 after 30 days of therapy. Tolerability was assessed with monthly visits at the lymphoma clinic. The patient experienced no adverse or unanticipated events from venetoclax. She exhibited complete response on PET scan with resolution of bulky cutaneous lesions. The patient received a haploidentical allogeneic stem cell transplant from her son. She continues to be in remission 12 months after the transplant. The patient's PCR-detected HTLV-1 viral load increased to 17,000 cpm, but she continues to be in clinical remission.

Discussion

ATLL is biologically different in Asian and non-Asian populations. According to the median survival time, non-Asian patients with ATLL experience a worse prognosis than do Japanese patients (9). One possible explanation for this is that the more aggressive forms of ATLL, including the acute and lymphomatous subtypes, are more common in non-Asian populations than in the Japanese population (10).

A previous retrospective analysis of North American patients with non-Asian ATLL attempted to identify the genetic mutations in this population. Targeted sequencing of 30 North American ATLL patients revealed a similar frequency of tumor protein P53 (*TP53*) when compared with that of Japanese patients; however, the North American patients had a higher frequency of epigenetic mutations, most commonly effecting the E1A binding protein P300 (*EP300*) gene, which ultimately leads to compromised function of TP53 (9).

TP53 and Tax oncoprotein play a key role in non-Asian ATLL. The function of p53 is dependent on the Tax 1 oncoprotein, an activator of NF-kB. Chronic activation of Nf-kB plays a crucial role in tumorigenesis. This Tax protein inhibits p53 by constitutive phosphorylation, leading to inactivation of p53 and affecting the CREB-associated pathway, thus causing compromised function in the regulation of the cell cycle and apoptosis (10). In addition, Tax causes uncontrolled replication in infected T cells and destabilizes the genome by interfering with telomerase and topoisomerase I and by inhibiting DNA repair. This prevents cell cycle arrest and apoptosis caused by unrepaired DNA damage, thus enabling an accumulation of mutations (3).

Additional mutations in the North American population include mutations in the notch receptor family (NOTCH

1-4) (11). The different notch receptors play a distinct role in T-cell differentiation. NOTCH3 plays a crucial role in thymocyte development, and the activation of mutations in this pathway can eventually lead to the overdevelopment of T-cell lymphoblastic lymphomas. NOTCH3-induced activation of Nf-kB has been found to promote T-cell lymphoma survival. A previous study investigating this activating mutation found that in Notch3 intracellular domain driven by lack of Lck promoter (*NOTCH3-IC*)-generated mice, induced inactivating mutations at the kB site of Nf-kB led to a hyperplastic thymus and massive infiltration by monotonous lymphoblastic cell populations in the spleen, lymph nodes, liver, lungs, bone marrow, and peripheral blood, indicating that a leukemic phase of neoplastic disease was present. Notch3 mutations were ultimately shown to lead to the activation of the antiapoptotic mechanism (Bcl-2). Investigators from a previous study reported overexpression of *BCL2* in T cells of transgenic-positive mice with splenic lymphoma (12). This study is relevant to our second patient, as this patient had a *NOTCH3* mutation detected through NGS. Benetoclax was started as an indirect method of targeting Bcl-2.

In contrast, Japanese patients have been found to have increased occurrence of JAK/signal transducer and activator of transcription (STAT) signaling pathway mutations. A previous study investigated the role of the HTLV-1 and JAK/STAT pathways. The authors found that in 8 of 12 patients with ATLL, the leukemic cells displayed constitutive DNA-binding activity of the STAT proteins and that constitutive activation of the JAK/STAT pathway persisted over time in 2 patients. These results imply that constitutive activation of the JAK/STAT pathway is associated with uncontrolled replication of leukemic cells (13).

ATLL is known to have a high degree of resistance to chemotherapy, with a median survival time for acute and lymphomatous ATLL reported to be about 1 year (6). The first nonchemotherapeutic agent, mogamulizumab (a fucosylated anti-CCR4 antibody), was approved in Japan for relapsed ATLL. Mutations in CCR4 are frequently present in ATLL (8). Interestingly, in one study (14), 2 patients of Caribbean descent with an activating mutation in CCR4 Y331I achieved long-lasting complete remission after treatment with mogamulizumab. However, a North American trial did not confirm significant activity of mogamulizumab in patients of predominantly Caribbean and African descent.

In the most recent literature, several case reports have described patients with ATLL who were treated with venetoclax. However, these cases involved a treatment of combined venetoclax and chemotherapy (15,16). Here, we report 2 cases of complete response to venetoclax, a Bcl-2 inhibitor, which allowed successful bridging to an allogenic stem cell transplant. The patients continue to be in remission 12 months after the allogenic stem cell transplant.

Both patients displayed mutations affecting the antiapoptotic pathways, which became unique targets for venetoclax. In the first case, NGS identified multiple mutations in the *BCL2* genes: a Notch1 biallelic mutation; *ACTB-RAC2* (7:22) fusion; *HOOK-3-TSPAN14t* (8:10) fusion; *FOXO1-2MY2t* (13:13) fusion; and a high expression of *BCL11b*, *2a*, *2l1*, *3*, and *6*. In the second case, a Notch3 mutation was identified. Limitations in this case report include a lack of comparison or control group and the inability to establish a cause—effect relationship. A larger research trial would provide necessary statistical evidence relating to the efficacy of venetoclax for relapsed and refractory ATLL.

Rapidly accumulating knowledge about the molecular mechanisms of ATLL development and resistance will hopefully lead to the identification of novel therapies to control this typically fatal disease. Clinical trials with a molecular-based approach are sorely needed to identify potential therapies. Targeting *BCL2* could be one of these strategies. Further investigation of the use of Bcl-2 inhibitors in relapsed and refractory ATLL is warranted.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://aol.amegroups.com/article/view/10.21037/aol-21-23/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aol.amegroups.com/article/view/10.21037/aol-21-23/coif). TF reports payment/honoraria received from AbbVie, BMS, Celgene, Janssen, Pharmacyclics, SeattleGenetics, Takeda, ADC Therapeutics, Astrazeneca, Daiichi Sakyo, Karyopharm, MorphoSys, KITE, and reports serving advisory role for AbbVie, ADC Therapeutics, Astrazeneca, Daiichi Sakyo, Karyopharm, KITE, MorphoSys. MA reports that work and

own stocks in Genomic Testing Cooperative (Irvine, CA, USA). The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the word in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient. A copy of the written consent is available for review by the editorial office of this journal.

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