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Received: April 5, 2023.
Accepted: September 25, 2023.


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Tucidinostat restores CCR4 expression in adult T-cell leukemia/lymphoma

Takahito Kawata¹², Takuya Shimizu², Takero Shindo²*, Kensuke Fujiwara¹, Suguru Morimoto¹, and Mitsumasa Watanabe¹

¹Department of Hematology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan; ²Department of Hematology/Oncology, Kyoto University Graduate School of Medicine, Japan

Running title: Restored CCR4 in tucidinostat-treated ATL

*Correspondence to: Takero Shindo, M.D., Ph.D.
Department of Hematology/Oncology, Kyoto University Graduate School of Medicine
54 Kawahara-cho, Shogo-in, Sakyō-ku, Kyoto, 606-8507 Japan
Phone: +81-75-751-4964, Fax: +81-75-751-4963
E-mail: takeros@kuhp.kyoto-u.ac.jp

Authors’ contribution: T.K. managed the patient, acquired samples, and wrote the manuscript. K.F., S.M. managed the patient. T. Shimizu performed the analysis and wrote the manuscript. T. Shindo designed the research, conceived the concept, and wrote the manuscript. M.W. managed the patient and supervised the analysis.

Acknowledgements: None

Trial registration: Not applicable

Data sharing statement: Data are available and please contact the corresponding author.

Disclosure: The authors have no conflicts of interest.
Adult T-cell leukemia/lymphoma (ATLL) is a hematological malignancy that develops from human T-lymphotropic virus type 1 (HTLV-1)-infected T cells (1). ATLL quickly acquires therapy-resistance to cytotoxic chemotherapeutic agents, and its prognosis is still dismal (2). Whereas allogeneic hematopoietic stem cell transplantation may lead to long-term remission, its indication is limited due to high non-relapse mortality and higher age of the patients (3). 90% of ATLL cells express a chemokine receptor 4 (CCR4) (4), and mogamulizumab, the monoclonal antibody targeting CCR4, effectively depletes ATLL cells through antibody-dependent cellular cytotoxicity (5). Next-generation sequencing of HTLV-1-infected cells recently revealed genomic instability of ATLL (6), which made its epigenetics a therapeutic target. The histone deacetylase (HDAC) inhibitor tucidinostat (7) and the Enhancer of Zeste Homolog 2 (EZH2) inhibitor valemetostat (8) have been approved for clinical use against relapsed or refractory ATLL. However, as our experience of their use is still limited, their modes of function and interaction still need careful investigation. A concern has been raised that HDAC inhibitors might interfere the effects of mogamulizumab, because vorinostat down-regulated CCR4 expression in ATLL and peripheral T-cell lymphoma through inhibition of the HDAC2 pathway (9). However, it is unclear whether these results can be obtained with other HDAC inhibitors and are reproducible in the patients. At this point, we experienced an ATLL case in which CCR4 expression was conversely restored during treatment by tucidinostat.

A man in his 70s was admitted due to general malaise and body weight loss. Peripheral blood count revealed elevated white blood cells (9,200 /µL), 72% of which were abnormal lymphocytes with characteristic nucleus morphology and a phenotype of CD3dimCD4+CD25+CADM1+(cell adhesion molecule 1+)CD7CCR4+. Computed tomography scan revealed systemic lymphadenopathy and hepatosplenomegaly, and blood test showed elevated soluble IL-2 receptor of 69,727 U/mL, hypercalcemia of 11.5 mg/dL and renal dysfunction. Southern blot analysis of peripheral blood showed monoclonal integration of HTLV-1 provirus, which made the diagnosis of acute type ATLL.
Six courses of modified lymphoma study group-15 (LSG-15) chemotherapy (VCAP-AMP-VECP) with mogamulizumab achieved complete remission, and abnormal lymphocytes in peripheral blood disappeared. However, skin tumors grew at the back of the left knee joint shortly after the treatment. It was pathologically diagnosed involvement of ATLL, and local irradiation was initially performed. Irradiation was successful, but skin eruption and tumors appeared on the bilateral hips and left ankle one after another. Since local therapy could not control tumor progression, resumption of systemic chemotherapy was considered. As his ATLL cells were negative for CD30, brentuximab vedotin, an anti-CD30 antibody–drug conjugate, was not indicated. Therefore, tucidinostat was given at 40 mg/day twice a week. All the lymph nodes stopped growing and some of them once shrank. The maximum treatment response was partial remission, but the lymph nodes showed regrowth three months later. Then he was treated with other salvage chemotherapy with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC), followed by mogamulizumab.

In the meantime, CCR4 expression on ATLL cells in peripheral blood was sequentially analyzed by flow cytometry HAS-flow method focusing on ATLL cells (10) (Figure). Notably, whereas CADM1+ cells were negative for CCR4 at the start of tucidinostat, their CCR4 expression showed clonal restitution for three months after starting tucidinostat. However, its expression was again down-regulated simultaneously with resistance to tucidinostat. As CCR4 expression was partially seen on CADM1+ cells on day 90, mogamulizumab was given again in combination with DeVIC, which resulted in partial remission. Once the treatment seemed to be successful, the disease kept recurring, and each time, local irradiation, and other drugs such as lenalidomide were tried to control the disease, but the tumor eventually led to his death.

CCR4 expression on T cells is modulated through inflammatory signaling (11) or gene mutation, which might be associated with the response to mogamulizumab. Whereas vorinostat might down-regulate CCR4 expression (9), our case showed restored CCR4 expression during the treatment of tucidinostat, which may potentiate the effects of second mogamulizumab treatment.
Vorinostat and tucidinostat have slightly different points of action on HDACs. That is, vorinostat acts on HDAC1/2/3/6, whereas tucidinostat acts on HDAC1/2/3/10 (12). HDAC6 and 10 are included in the same class 2b, but naturally their intracellular functions are different. Differences in selectivity by HDAC inhibitor may be also important factor in their effects on CCR4 expression in tumor cells. Given that HTLV-1 carriers contain several different clones with HTLV-1 in developing ATLL (13), epigenetics and CCR4 expression may be different among these clones. Therefore, their behaviors would be different for each clone in response to HDAC inhibitors. CCR4 expression might be modulated even in a single case, which should be considered at treating ATLL. Whereas CCR4 expression on tumor cells may not be associated with the response to mogamulizumab (14), it is still important given that the indication of mogamulizumab is limited to CCR4⁺ ATLL (5). Treatment strategies for maintaining CCR4 expression on ATLL cells may be beneficial, provided there are no underlying genomic mutations that render the expression ineffective.

Previous literature highlights that HDAC inhibitors may have a minimal impact on the responses of mogamulizumab in cutaneous T-cell lymphoma (15), suggesting that HDAC inhibition might not interfere mogamulizumab’s in vivo activity. While the connection between CCR4 expression on tumor cells and the effects of mogamulizumab might not be linear, it is crucial to consider this relationship because mogamulizumab was firstly approved for CCR4-positive ATL in Japan (5). Hence, strategies that maintain CCR4 expression in ATLL cells are preferred. Kitadate et al. suggested that HDAC inhibitors might decrease CCR4 expression in ATLL cells (9), but our case raises the need for further studies, particularly focusing on the effects of inhibiting HDAC 6 and 10. By understanding these specific effects on CCR4 expression, clinicians can personalize their approach and select the most appropriate HDAC inhibitors to enhance or maintain CCR4 expression in ATLL cells.
References


Chemokine receptor 4 (CCR4) expression on adult T-cell leukemia/lymphoma (ATLL) cells was sequentially analyzed by flow cytometry, and schema of treatment courses and clinical responses with soluble IL-2 receptor (sIL-2r) is shown (A). (B) Freshly isolated peripheral blood mononuclear cells from the patient were stained for CD3, CD4, CD7, cell adhesion molecule 1 (CADM1), and CCR4. Scattergrams of CADM1/CD7 gating CD3⁺CD4⁺ T cells are shown upper, and histograms of CCR4 gating on CADM1⁺CD7⁺ (P fraction) and CADM1+ cells are shown below (B). Mean fluorescence intensity (MFI) of CCR4 was compared between P fraction (CADM1⁺CD7⁺, dashed rectangle) and CADM1⁺ fraction (solid rectangle) within CD3⁺CD4⁺ lymphocytes.

Specimen collection and use were conducted in accordance with Kyoto University's comprehensive consent form (G0697), which was ethically reviewed and approved by Kyoto University Hospital and Hyogo Prefectural Amagasaki General Medical Center (AGMC). Peripheral blood was collected at AGMC with the patient’s consent. Utilized anti-CCR4 antibody derived from a clone #205410 (R&D systems).