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SHORT REPORT OPEN ACCESS

SGLT-2 Inhibitors Are Potent to Suppress Aggressive Transformation From Indolent Type of Adult T-Cell Leukemia/Lymphoma: Unique Insight Into Therapeutics for Diabetes-Related Hematological Malignancy

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Abstract

Introduction: We previously reported that sodium-glucose co-transporter 2 (SGLT-2) was ectopically overexpressed in adult T-cell leukemia (ATL) cells notably in aggressive type but in indolent type, and widely-used anti-diabetic SGLT-2 inhibitors (SGLT-2i) considerably attenuated proliferation of leukemic cells.

Methods: We performed retrospective analyses for 10 years to see whether SGLT-2i would prevent aggressive transformation in patients with indolent type ATL accompanied by diabetes. Nucleosome occupancy in the promotor region of the *SGLT-2* gene was also assessed to explore the possible involvement of epigenetic modification in such an ectopic overexpression.

Results: In patients of indolent ATL with diabetes, the cumulative progression rate in the non-SGLT-2i-treated group was 71%, while no patients developed aggressive transformation in the SGLT-2i treated group. ATL cells showed an apparent trend to decrease nucleosome occupancy in the promotor region of the *SGLT-2* gene.

Conclusion: Our data suggest that SGLT-2i is advantageous for preventing aggravative transformation in indolent ATL.

Trial Registration: Authors confirmed that clinical trial registration was not requested for the present study and this manuscript.

1 | Introduction

Adult T-cell leukemia/lymphoma (ATL) is an extremely aggressive and intractable hematological malignancy caused by the infection of human T-cell leukemia virus type I (HTLV-1). Virus transmission commonly occurs through breastfeeding or horizontal transmission, and 3–5% of infected individuals finally develop ATL [1, 2]. Most patients with ATL gradually worsened in a couple of decades from indolent ATL (smoldering type and favorable chronic type) to aggressive ATL (unfavorable chronic, lymphoma, and acute type). Because aggressive ATL often resists intensive chemotherapy, a small fraction of patients can benefit from allogeneic hematopoietic stem cell transplantation. Consequently, the three-year survival rate is barely 30%–40% and there has been no established approach to prevent the aggressive transformation in indolent ATL [3].

We previously reported for the first time that sodium-glucose co-transporter 2 (SGLT-2), which is preferentially and highly expressed in renal proximal tubules to reabsorb exaggerated glucose into circulation, was ectopically and abundantly expressed in ATL cells from patients and immortalized cell lines. Notably, the expression level of SGLT-2 in ATL cells was apparently exaggerated during the course of disease aggravation [4]. We also found that inhibitors against SGLT-2 (SGLT-2i), widely used for patients with diabetes, chronic kidney diseases, and heart failure, considerably suppressed glucose uptake and glycolytic metabolic pathways as well as interfering with the cell cycle, thereby attenuating the proliferation of ATL cells. Notably, such an effect was achieved at standard therapeutic doses commonly used for treating patients with type 2 diabetes (T2D). To date, any mutations in the *SGLT-2* gene (known as *SLC5A2*) have not yet been reported in the whole-genome sequence of ATL cells [5, 6], suggesting possible involvement of epigenetic modification in overexpression of SGLT-2 in ATL. In this context, we performed retrospective analyses to see whether a line of data in vitro would be reproducible in real-world clinics, and also analyzed the nucleosome occupancy in the promoter region of *SLC5A2* of ATL cells.

2 | Methods

2.1 | Patients and Blood Samples

We retrospectively analyzed clinical data from patients diagnosed with T2D combined with ATL between July 2014 and December 2023 across 10 medical institutions in Japan (Okinawa Prefecture). ATL was professionally diagnosed according to previous reports [7]. Patients who had received systemic chemotherapy or radiation therapy prior to the observational period were carefully excluded. We also collected peripheral blood mononuclear cells (PBMCs) from five healthy volunteers, thirteen patients with indolent ATL, and four patients with aggressive ATL for quantitative real-time PCR (qRT-PCR) and nucleosome scanning assay in *SLC5A2* by Ficoll-Paque density gradient centrifugation.

2.2 | qRT-PCR and Nucleosome Scanning Assay in SLC5A2

To evaluate nucleosome occupancy in the promoter region of the *SLC5A2*, we designed thirteen pairs of PCR primers targeting putative nucleosome-binding sites (NS 1-NS 13) to evaluate nucleosome occupancy in the promoter region of the *SLC5A2* as reported [8]. To isolate nucleosomal DNA, extracted DNA samples were treated with DNase to digest unprotected DNA, followed by the treatment of Proteinase K to remove histone proteins by the EpiScope Nucleosome Preparation Kit (Takara Bio, Japan). The extracted nucleosomal DNA was used as a template for PCR, and nucleosome occupancy in the *SLC5A2* promoter region was quantified by comparing the nucleosomal DNA enrichment ratio to LINE-1, which served as a reference gene.

2.3 | Statistical Analysis

In retrospective studies, the primary endpoints were death, relapse, and initiation of systemic chemotherapy due to the worsening of the condition. Clinical characteristics were analyzed using the *t*-test or Fisher's exact test, as appropriate. Overall survival and progression-free survival were assessed using the log-rank test, while Gray's test was used to analyze the cumulative incidence of disease progression. For in vitro experiments, data are presented as the mean ± standard error of the mean (SEM) from independent experiments. Statistical significance was determined using one-way analysis of variance (ANOVA), the Welch-Aspin test, or the Kruskal–Wallis test, where applicable.

3 | Results

Data from 127 patients with ATL accompanied by T2D were analyzed including 75 of aggressive ATL (57 of acute type, 17 of lymphoma type, 1 of unfavorable chronic type) and 52 of indolent ATL (20 of favorable chronic type and 32 of smoldering type). Profile of patients stratified by SGLT-2i use in both aggressive and indolent ATL was shown in Tables S1 and S2. Among 68 patients with aggressive ATL who received intensive chemotherapy, SGLT-2i provided no advantage for prognosis (Figure 1a). In contrast, among 52 patients with indolent ATL who were under watchful waiting, no patients developed aggressive transformation in SGLT-2i group ($n = 11$) ($p < 0.01$, Figure 1b). Of note, in the present study, anti-diabetic metformin, which was previously reported to exert anti-proliferative effects on HTLV-1-infected cells [9], did not demonstrate a significantly-beneficial impact in overall survival rate in aggressive ATL between metformin-group ($n = 21$) and non-metformin-group ($n = 47$); $p = 0.35$, as well as in cumulative incidence of disease progression in indolent ATL between metformin-group ($n = 18$) and non-metformin-group ($n = 34$); $p = 0.75$, respectively.

In nucleosome occupancy analyses in the promotor region of *SLC5A2*, cells from aggressive ATL of patients showed an overall trend to decrease the occupancy in the promotor region as compared to healthy PBMCs, raising a possible involvement of epigenetic dysregulation of *SLC5A2* (Figure 2). In cells from indolent ATL, however, the rate was not decreased exclusively in the NS 6 (Figure 2). It has been documented that NS 6 harbors binding sites for GATA3 and ETS1 transcriptional factors, both of which are critical for the progression of ATL [10, 11].

4 | Discussion

Our data demonstrate that SGLT-2i is potent to completely suppress disease progression in indolent ATL in a unique cohort of ATL with diabetes. To date, no definitive treatment has been established for indolent ATL. While watchful waiting is the primary recommended approach, approximately half of the patients eventually progress to aggressive ATL requiring intensive chemotherapy, with a four-year survival rate of less than 60% from initial diagnosis [12]. Once the disease transforms into aggressive ATL, the four-year survival rate drastically declines to approximately 20%, representing a miserable prognosis. In some solid tumors including pancreatic, colorectal, and lung cancer, ectopic overexpression of SGLT-2 has been reported [13]. A retrospective study using a Japanese medical claims database demonstrated that SGLT-2i significantly reduced the incidence of various types of cancer compared to dipeptidyl

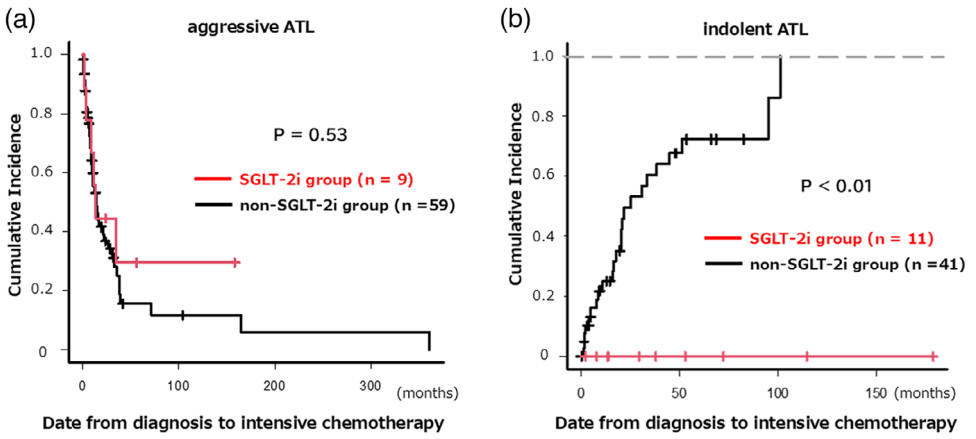

FIGURE 1 | Unexpected impact of SGLT-2 inhibitors (SGLT-2i) on aggressive transformation in diabetic patients with indolent ATL (a) during analyzed period of longer than 10 years for aggressive ATL with type 2 diabetes, there was no beneficial effect for prognosis depend on SGLT-2i. SGLT-2i used in the present study consists of empaglifrozin ($n = 4$), dapagliflozin ($n = 2$), ipraglifrozin ($n = 2$), and canaglifrozin ($n = 1$), respectively. (b) In indolent ATL with type 2 diabetes, all traceable patients in the non-SGLT-2i group transformed into aggressive ATL, and consequently received intensive chemotherapies. On the other hand, no patients in the SGLT-2i group showed such a transformation at all. SGLT-2i used in the present study consists of ipraglifrozin ($n = 4$) and canaglifrozin ($n = 4$), empaglifrozin ($n = 3$), respectively.

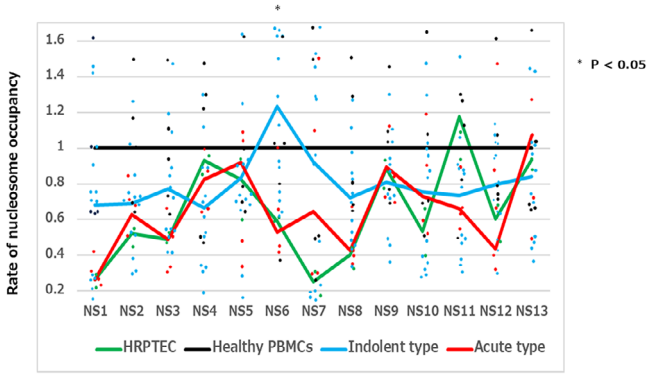

FIGURE 2 | Nucleosome occupancy of the promotor region in SGLT-2 gene (SLC5A2) in ATL cells, Enriched nucleosomal DNA was assessed by quantitative PCR with overlapping 13 primer pairs in the promotor region of SLC5A2. Relative nucleosome occupancy in each sample was determined after the correction of level without the micrococcal nuclease treatment, and was demonstrated by connecting lines of midpoints in each amplicon. The dots represent results for each specimen (green: human renal proximal tubular epithelial cells (HRPTEC), black: healthy PBMCs, blue: PBMCs from patients with indolent ATL, red: PBMCs from patients with aggressive ATL, respectively). *: The rate of NS 6 in aggressive type was markedly decreased as compared to that in indolent type ($p < 0.05$).

peptidase-4 inhibitors [14]. Furthermore, it has been shown that administration of SGLT-2i in xenograft models may inhibit tumor growth, at least partly, by disturbing immune evasion [13]. A previous case report in a patient with recurrent hepatocellular carcinoma (HCC) demonstrated that administration of SGLT-2i provoked spontaneous regression of HCC with a marked decrease in serum levels of vascular endothelial growth factor (VEGF) [15]. Because the serum level of VEGF is known to correlate with disease progression in ATL, it is tempting to speculate that modulation of cytokine production by SGLT-2i would be related to such an unexpected therapeutic impact as observed in the present study [16]. In this context, further studies are warranted to clarify underlying precise mechanisms whereby SGLT-2i may impact each type of malignancy.

In the present study, we demonstrated a malignancy-dependent reduction in nucleosome occupancy at the *SLC5A2* promoter in an aggressive type of ATL cells comparable to those of normal renal proximal tubular epithelial cells. Regarding the molecular basis for kidney-preferred augmented expression of SGLT-2, a previous report showed that an apparently decreased level of nucleosome occupancy at the *SLC5A2* promoter region was attributable to exaggerated expression of SGLT-2 by modulating the binding of key transcription factors such as hepatocyte nuclear factor (HNF) -1 alpha [17]. In line with this notion, mechanisms, whereby SGLT-2 overexpresses ectopically in ATL, are possibly related to epigenetic dysregulation similar to that in normal kidneys. Indeed, a variety of epigenetic dysregulation plays a critical role in the molecular pathophysiology of ATL [18]. In cells of indolent ATL, the nucleosome occupancy at NS 6 was substantially elevated compared to that in aggressive ATL. NS 6 harbors binding sites for *GATA3* and *ETS1* [10, 11], both of which are transcriptional regulators that may play a pivotal role in the progression of ATL, thereby promoting malignant cell proliferation [10, 11]. Hence, a lower degree of nucleosome occupancy exclusively in NS 6 in indolent ATL would serve as an early prediction sign of aggressive transformation.

Although the numbers studied are considerably limited, the present study is the first to demonstrate that SGLT-2i is advantageous to suppress aggressive transformation in diabetic patients with ATL characterized by a unique fashion of multi-stage carcinogenesis, thereby providing novel insight into pathophysiology and therapeutics for diabetes-associated malignancy. Given that SGLT-2i has long been widely used for the treatment of diabetes, SGLT-2i may offer a safe and effective opportunity for preventing aggravation in some forms of intractable hematological malignancies.

Author Contributions

KM and HM contributed to the research design. KM collected clinical data and analyzed in vitro data. KM drafted the manuscript, and KT, TF, and HM revised it and approved the final version.

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Ethics Statement

The present study was conducted with the approval of the Ethics Review Committee of the University of the Ryukyus, OKINAWA, Japan (Approval No. 2046).

Consent

All patients provided informed consent for sample collection and research. Materials are original and not reproduced from other sources.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data shown in the present study are available on request from the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supplemental Table 1. Clinical data at diagnosis with aggressive ATL