沖縄県におけるhuman T-cell leukemia virus type I (HTLV-1)のtax genotype解析

（様式第３－２号）

Abstract

Title

Human T-cell leukemia virus type I *Tax* genotype analysis in Okinawa, the southernmost and remotest islands of Japan: Different distributions compared with mainland Japan and the potential value for the prognosis of aggressive adult T-cell leukemia/lymphoma

Name

Shugo Sakihama

Abstract

Background

Human T-cell leukemia virus type I (HTLV-1) is the causative retrovirus of adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy (HAM). The southwest part of Japan, particularly Kyushu region and Okinawa prefecture, is the most endemic area for HTLV-1 in the world. Central Africa, Caribbean coast, South America and Melanesia are also known as highly endemic areas. HTLV-1 is transmitted by contact between HTLV-1-infected cells and uninfected cells via breastfeeding and sexual intercourse. HTLV-1 exists in a provirus form, consisting of a 5′LTR, *gag*, *pro*, *pol*, *env*, *pX*, and a 3′LTR region, within a host genome. HTLV-1 is classified into three major phylogenetic subtypes—Melanesian, Central African, and Cosmopolitan—based on the 5′LTR sequence. The cosmopolitan subtype, which is widely disseminated worldwide, is further divided into four subgroups: transcontinental, Japanese, West African and North African. Among them, the Japanese and the Transcontinental subgroups have been isolated in Japan, and the former is the dominant subgroup in mainland Japan. HTLV-1 was also classified into two genotypes by *tax* gene sequence, namely *tax*A and *tax*B. It was demonstrated that the *tax*A and *tax*B genotypes correspond to the Transcontinental subgroup and the Japanese subgroup, respectively. The *tax*A and *tax*B genotypes were 11% and 89%, respectively, in Kagoshima prefecture, Kyushu.

Recently, we conducted a large-scale retrospective study of 659 patients with aggressive ATL (acute, lymphoma, and unfavorable chronic types) in Okinawa prefecture and demonstrated worse prognosis compared with previous results obtained for patients in mainland Japan. Based on these observations, we hypothesized that the genetic background differs between ATL patients in Okinawa and mainland Japan. Hence, in this

study, we examined the HTLV-1 *tax* genotype in Okinawa Prefecture to clarify the distribution of *tax* genotypes. In addition, we explored the association between the *tax* genotype and the prognosis of patients with aggressive ATL.

Patients, materials and Methods

We collected specimens from 29 HTLV-1 carriers, 74 ATL patients (acute, n = 45; lymphoma, n = 12; chronic, n = 7; smoldering, n = 10) in Okinawa from January 2013 to October 2015. The *tax* genotype was determined by nested PCR-restriction fragment length polymorphism method using genomic DNA from peripheral blood mononuclear cells (PBMCs) or lymph nodes, skin legions. Collection of PBMCs and subsequent analyses of 33 patients with HAM in Okinawa Prefecture were conducted by multiple collaborating laboratories at the Department of Microbiology, Kawasaki Medical School, Okayama Prefecture. We also collected clinical data at the time of diagnosis from 45 patients with aggressive ATL (acute, n = 35; lymphoma, n = 10), and followed their clinical courses. Fisher's exact test was used to compare the distributions of *tax* genotypes for clinical status of patients and clinical data, sensitivity to chemotherapy in aggressive ATL patients. The Kaplan–Meier method was applied to calculate the overall survival (OS) of patients with aggressive ATL and the log-rank test was used to assess the discrepancy between *tax* genotypes. The Cox proportional hazard model was used to estimate the effect of *tax* genotype on OS with additional four variables; age, performance status (PS), corrected calcium, and soluble interleukin-2 receptor (sIL-2R), that were previously identified as prognostic factors for aggressive ATL.

Results

Of all 136 cases, 60 (44%) had *tax*A and 76 (56%) had *tax*B. We observed 13 (45%) and 16 (55%) patients with the *tax*A and *tax*B genotypes among 29 HTLV-1 carriers, 26 (35%) and 48 (65%) among 74 patients with ATL, and 21 (64%) and 12 (36%) among 33 patients with HAM ($P = 0.022$). We compared the clinical characteristics and outcome of 45 patients (*tax*A, 14; *tax*B, 31) with adequate follow-up data (among 57 patients with aggressive ATL) with respect to the *tax* genotype. In total, 79% (11/14) of patients in the *tax*A group and 74% (23/31) in the *tax*B group received adequate intensity chemotherapy with VCAP-AMP-VECP, CHOP, and THP-COP. We found that fewer patients achieved a complete or partial response in the *tax*A group compared with the *tax*B group [50% (7/14) and 71% (22/31), respectively; $P = 0.296$]. The 1-year OS rates were 35% in patients with

*tax*A and 49% in those with *tax*B (P= 0.35). We further conducted a multivariate analysis to adjust for confounding factors. We selected four variables (age, PS, corrected calcium, and sIL-2R) that were previously identified as prognostic factors for aggressive ATL, in addition to the *tax* genotype. We detected significant hazard ratios (HR) for the old age (≥70 years), high PS (2–4), and high sIL-2R (≥20000 U/mL) groups compared with each control group, but not for corrected calcium. The estimated HR of the *tax*A group compared with the *tax*B group was 2.68 (95% confidence interval, 0.87–8.25; P= 0.086).

Conclusion

We revealed that the *tax* genotype distribution in Okinawa prefecture—60 (44%) *tax*A cases and 76 (56%) *tax*B cases—was different from that of a previous report in Kagoshima prefecture, mainland Japan (*tax*A, 11%; *tax*B, 89%). Our results also suggest the potential value of the *tax* genotype as a prognostic factor for aggressive ATL, despite the small number of patients, heterogeneous treatments, and short follow-up periods. To detect the genes associated with molecular pathology and sensitivity to chemotherapy of aggressive ATL, we are performing a comparative analysis of the gene profiles of patients with ATL between the *tax*A and *tax*B genotypes. The different distribution pattern of the *tax* genotype suggests that the propagation pathway of HTLV-1 into Japan might differ between *tax* genotypes. We are currently conducting genotypic studies of HTLV-1 carrier cohorts of each remote island in Okinawa and other parts of Southeast Asia to elucidate the transmission route of HTLV-1 in Japan.