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LETTER TO THE EDITOR

WILEY

Prognostic impact of soluble interleukin-2 receptor level profiling in smoldering type adult T-cell leukemia-lymphoma

Adult T-cell leukemia-lymphoma (ATL) is a lymphoid malignancy caused by human T-cell leukemia virus type I.[1] ATL is divided into four clinical subtypes (smoldering, chronic, lymphoma, and acute) according to Shimoyama's classification.[2] Smoldering-type ATL, recognized as indolent ATL, sometimes has been shown to transform to acute-type ATL.[3,4] An international consensus meeting recommended watchful waiting (carefully observed unless transformation occurs) or treatment with interferon-alpha and zidovudine (IFN/AZT) for patients with smoldering-type ATL.[5] Determining the risk factors of transformation is important to help determine therapeutic strategies for smoldering-type ATL.

Because ATL cells release a large amount of soluble interleukin-2 receptor (sIL-2R), the serum level of sIL-2R in ATL patients reflects disease activity[6] and tumor burden better than lactate dehydrogenase (LDH).[7] In the latest retrospective nationwide survey, Katsuya et al found that sIL-2R was a probable independent prognostic factor for indolent ATL.[8] However, even the patients with smoldering-type ATL whose levels of sIL-2R are slightly increased (sIL-2R $\leq$ 1000 U/mL, correspond to a low risk in Katsuya's report[8]) sometimes experience early transformation to acute-type ATL. We hypothesized that sIL-2R level profiling in the early phase of smoldering-type ATL is a prognostic factor and could predict the risk of transformation.

We retrospectively examined 61 patients with primary smoldering-type ATL diagnosed at our institute between 1998 and 2016. The analyzed patients underwent monitoring of sIL-2R levels at least twice within the first 4 months and were observed more than 4 months without systemic therapy from the time of diagnosis. According to the maximum rate of increase in sIL-2R level within the first 4 months in the analyzed patients, the value of the third quartile was 1.42, so we used a value of 1.5 as a cutoff for convenience. Patients with a greater than or equal to 1.5-times increase in sIL-2R level within the first 4 months were categorized into the high-risk group. The remaining patients belonged to the nonhigh-risk group. We further categorized the patients of nonhigh-risk into two groups: One was a low-risk group who maintained the levels of sIL-2R $\leq$ 1000 U/mL during the first 4 months, and the other was an intermediate-risk group. Multivariate

TABLE 1 Baseline patient characteristics of the high-risk and nonhigh-risk groups

Characteristics	High Risk (n = 7)	Nonhigh Risk (n = 24)	*P*
Median age, y (range)	66 (54-87)	73 (53-89)	0.353
Sex			
Female, n (%)	3 (43)	12 (50)	greater than 0.999
Male, n (%)	4 (57)	12 (50)	
ECOG performance status			
Less than 2, n (%)	6 (86)	22 (92)	0.55
Greater than or equal to 2, n (%)	1 (14)	2 (8)	
Skin lesions present			
YES, n (%)	6 (86)	16 (67)	0.639
NO, n (%)	1 (14)	8 (33)	
Serum sIL-2R, median U/mL (range)	2320 (975-4270)	1095 (408-5570)	0.129
WBC count, median × 10^9/L (range)	7.3 (5.3-15.8)	6.8 (3.7-14.2)	0.48
Abnormal lymphocyte count, median × 10^9/L (range)	0.5 (0.1-5.2)	0.4 (0-1.6)	0.017
LDH, median IU/L (range)	276 (94-288)	221 (150-314)	0.747
Serum albumin, median g/dL (range)	4 (3.5-5.1)	4.1 (3.3-4.6)	0.627
BUN, median mg/dL (range)	13 (8-19)	15 (1-46)	0.309
Serum creatinine, median mg/dL (range)	0.6 (0.5-0.8)	0.7 (0.3-3.4)	0.333
Corrected calcium, median mg/dL (range)	9.3 (9-10)	9.3 (8.2-10)	0.536

Abbreviations: ECOG, Eastern Cooperative Oncology Group; sIL-2R, soluble interleukin-2 receptor; WBC, white blood cell; LDH, lactic dehydrogenase; BUN, blood urea nitrogen.

analysis was performed by the landmark method.[9] We set the analyzed point at 120 days (4 months) after the time of diagnosis. In multivariate analysis, a stepwise selection of factors with $P < 0.2$ was performed. All statistical analyses were performed using EZR version 1.34 for Windows (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[10] The present study was approved by the Imamura General Hospital's institutional review board.

To identify the reliability of sIL-2R monitoring as a correlation factor, 30 patients with smoldering-type ATL were excluded, and 31 patients were analyzed. Reasons for exclusion were following: 20 patients underwent sIL-2R profiling only once within the first 4 months after diagnosis, 6 experienced transformation to acute-type ATL with 4 months after primary diagnosis, 3 received chemotherapy within the first 4 months, and 1 followed up less than 4 months after diagnosis. There were 7 patients in the high-risk group and 24 patients in the nonhigh-risk group (14 intermediate risk and 10 low risk). The patient characteristics of both the high-risk and nonhigh-risk groups at diagnosis are summarized in Table 1. Only the abnormal lymphocyte count was significantly greater in the high-risk group than in the nonhigh-risk group ($P = 0.017$); all other characteristics were similar between the two groups. The 5-year OS rate of the high-risk group was significantly inferior to that of the nonhigh-risk group (0% vs 74.8%, Figure 1A, $P = 0.006$). Eleven (36%) of 31 analyzed patients had experienced transformation. Six patients (86%) in the high-risk group experienced transformation within 12 months after diagnosis (Figure 1B). Only 1 (4%) patient in the nonhigh-risk group experienced transformation within 12 months after diagnosis (Figure 1D). Four patients (57%) in the high-risk and 6 patients (43%) in the intermediate-risk groups died. Of the 10 patients who died, 4 died of ATL and 6 died of other reasons (1 carcinoma of the hard palate, 1 renal pelvis-ureteral cancer, 1 fulminant hepatitis, 1 interstitial pneumonia, 1 alveolar bleeding, and 1 traffic accident). All patients in the low-risk group were alive without transformation at the end of the study (Figure 1C and 1D, $P = 0.021$). In univariate analysis, the rate of sIL-2R increase and the level of LDH were significantly poor prognostic factors. In multivariate analysis, after stepwise selection of four

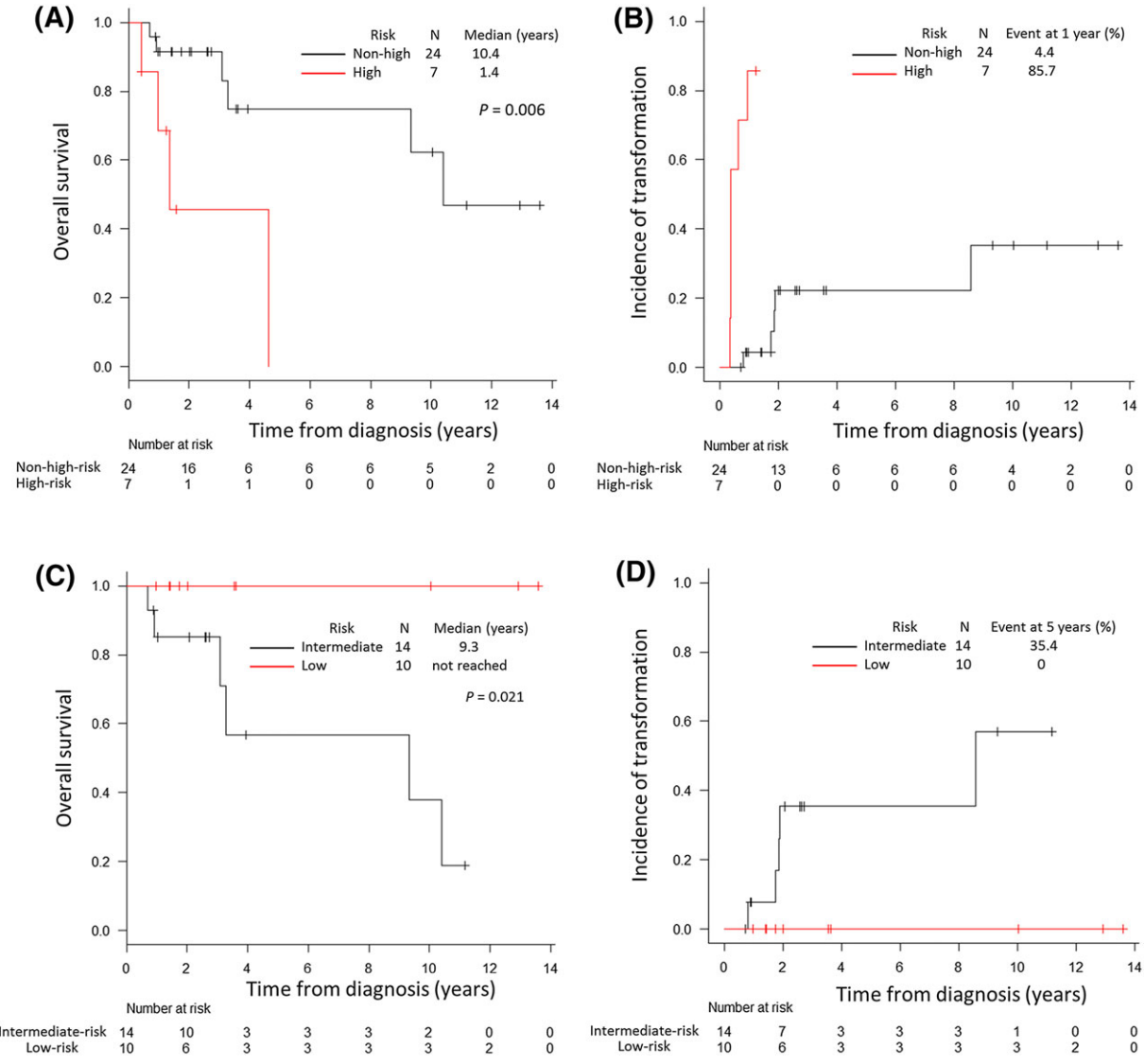

FIGURE 1 OS and incidence of transformation to acute-type ATL. A, Overall survival (OS) of the high-risk and nonhigh-risk groups; B, incidence of transformation to acute-type adult T-cell leukemia-lymphoma (ATL) for the high-risk and nonhigh-risk groups; C, OS of the low-risk and intermediate-risk; D, incidence of transformation for the low-risk and intermediate-risk groups

variables (skin lesions, rate of sIL-2R increase, and abnormal lymphocyte and LDH levels), only the rate of sIL-2R increase remained a significant prognostic factor (hazard ratio 5.8; 95% confidence interval, 1.4-23.7; $P = 0.015$).

sIL-2R level profiling during the early phase of smoldering-type ATL was useful for sorting and forecasting both long-term survival without transformation and high risk of transformation. In the present study, the result that all patients in the low-risk group were alive without transformation supports the therapeutic policy of "watchful waiting" especially for patients in the low-risk group. Transformation often occurred in 11 (36%) of 31 analyzed patients, which is similar to the result of previous report (60%).[4] In the high-risk group, except for 1 patient with a temporary increase in sIL-2R due to the onset of pulmonary nocardiosis, all of the patients experienced transformation within 12 months after diagnosis. Combination of IFN/AZT, which is not covered by health insurance in Japan, is regarded as the standard treatment for smoldering-type ATL in other countries.[5] Patients with a high risk of transformation need to consider early treatment with IFN/AZT or chemotherapy. The different frequencies of sIL-2R level measurement caused us to exclude many patients from the analysis. It is difficult to secure a sufficient number of patients in one institute for a prospective study because smoldering-type ATL is rare, accounting for only 5% to 10%[2,3] of all ATL cases. A prospective multicenter study is required to verify the use of sIL-2R levels as a prognostic marker in the future.

In conclusion, the sIL-2R level profiling during the early phase of smoldering-type ATL is useful for predicting the prognosis, including the risk of transformation to acute-type ATL.

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CONFLICT OF INTEREST

A.U. received honoraria from Kyowa Hakko Kirin and Celgene. The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTION

A.K. and A.U. were involved in the conception and design of the study; N.N., T Miyazono, T.I., Mayumi T, T Makino, Masahito T, S.T., K.Y., and Y.T. followed up patients and were responsible for the data; A.K., N.N., Masahito T, and A.U. analyzed and interpreted the data; A.K., N.N., and A.U. wrote the manuscript; and all authors reviewed and approved the final version of the manuscript.

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