1126 Significance of sIL-2R and LD in predicting time to first treatment in Japanese CLL patients with early asymptomatic disease.

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Purpose

A prospective nationwide registry study (CLLRSG-01) was conducted to determine the clinical status of chronic lymphocytic leukemia (CLL) and related diseases, which are rare in Japan. Our previous reports in the iwCLL held in 2015, 2017, 2019, and 2021 have provided insights into the characteristics and prognosis of CLL in the Japanese population.

As part of this research, we evaluated the effectiveness of the international prognostic score for predicting the time to first treatment (TTFT) in CLL patients with early, asymptomatic disease, known as the "International Prognostic Score for Early-stage CLL (IPS-E)" (Condoluci A, et al. Blood. 2020; 135: 1859).

Additionally, we evaluated other factors that could serve as prognostic indicators in this population.

Methods

The study included 58 patients with Binet stage A CLL from the CLLRSG-01 trial, who were divided into three IPS-E risk groups (Fig.1). The IPS-E model was used to calculate the risk scores by assigning points based on the absolute lymphocyte count (ALC) >15×10^9/L, unmutated immunoglobulin heavy-chain variable-region (*IGHV*) gene, and the presence of palpable lymph nodes. Patients were categorized as low-risk (score 0), intermediate-risk (score 1), or high-risk (score 2-3).

Kaplan–Meier survival curves were used to estimate the TTFT, defined as the time from enrollment to the initiation of CLL treatment due to progression to symptomatic disease as per the iwCLL guidelines. The log-rank test was used to assess differences in the TTFT among the risk groups.

Furthermore, univariate and multivariate Cox regression analyses were performed to identify independent correlations of outcome variables, including lactate dehydrogenase (LD) and the soluble interleukin 2 receptor (sIL-2R).

Results

(1) The patients had a median age of 65 years (range: 34-84 years), and 34 of the 58 patients were males (59%). After a median follow-up of 59.5 months (range, 0 -107 months), 22 patients (38%) underwent treatment.

Based on the IPS-E, 25 patients were classified as low-risk, 25 as intermediate-risk, and 8 as high-risk (Fig.1). The scoring system revealed that the 5-year cumulative risk of treatment initiation was 19% for low-risk patients, 42% for intermediate-risk patients, and 75% for high-risk patients. However, no significant differences were observed between the intermediate and high-risk groups (P=0.097) (Fig.1).

(2) Univariate analyses were performed; however, the ALC was not a significant factor associated with TTFT (Table 1).

Multivariate analyses were performed using 17 baseline factors, and three covariates were independently correlated with TTFT: unmutated *IGHV* gene, LD (>upper limit of normal range), and sIL-2R (>1,000 U/mL) (Table 1).

(3) Patients with sIL-2R<1,000 U/mL (median not reached) exhibited significantly longer TTFT compared to those with sIL-2R ≥1,000 U/mL (median 40 months, P<0.001) (Fig. 2). Similarly, CLL patients with LD within the normal range (median not reached) experienced significantly longer TTFT compared to those with LD above the upper limit of the normal range (median 12 months, P<0.001) (Fig. 3).

(4) We constructed a new scoring system that assigns points based on unmutated *IGHV* gene, elevated sIL-2R >1000, and LD> upper limit of the normal range. Patients were classified as low risk (score 0), intermediate risk (score 1), or high risk (score 2-3) (Fig.4).

Based on this system, 31 patients were classified as low-risk, 17 as intermediate-risk, and 10 as high-risk. These groups showed significant differences in terms of TTFT (Fig.4).

Table 1 Cox regression analysis of TTFT

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
sIL-2R>1,000	4.24 (1.79-10.02)	0.001	3.28 (1.32-8.15)	0.010
palpable LN	3.49 (1.45-8.40)	0.005		
unmutated *IGHV*	3.62 (1.46-8.92)	0.006	4.71 (1.77-12.58)	0.002
Ly>15,000	1.49 (0.65-3.46)	0.349		
Age>65	0.69 (0.29-1.64)	0.399		
Male	0.97 (0.42-2.28)	0.946		
PS>0	0.05 (0.00-1269.91)	0.556		
LDH>ULN	5.36 (1.88-15.29)	0.002	4.86 (1.54-15.29)	0.009
CD38(+)	4.20 (1.68-10.51)	0.002		
ZAP70(+)	2.92 (1.11-7.67)	0.030		
MYD88 mutation	1.36 (0.18-10.11)	0.766		
β2MG>3.5	1.24 (0.28-5.36)	0.773		
del(17p)	3.03 (0.70-13.07)	0.137		
del(11q)	5.47 (1.24-24.17)	0.025		
del(11q)/del(17p)	4.31 (1.43-13.00)	0.009		
del(13q)	0.53 (0.23-1.25)	0.532		
+12	3.19 (1.01-10.12)	0.049		

Fig. 2 TTFT of patients with CLL based on serum sIL-2R levels

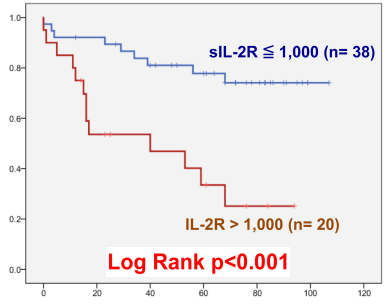


Fig. 3 TTFT of patients with CLL based on serum sIL-2R levels

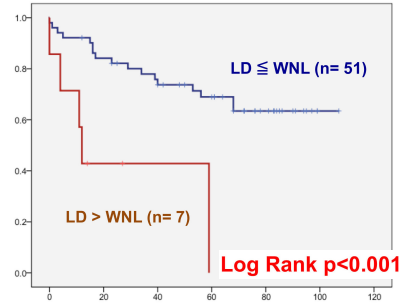


Fig. 1 TTFT by IPS-E

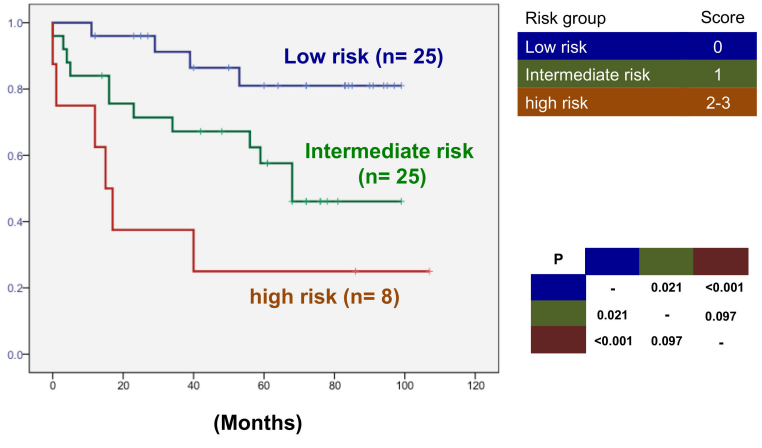
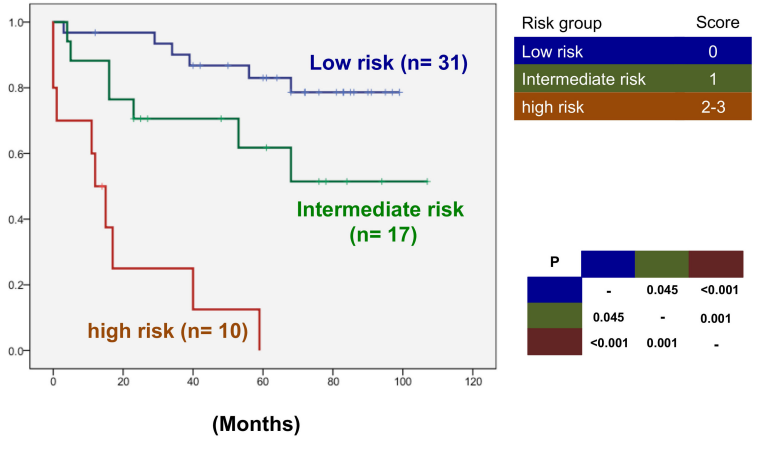


Fig. 4 TTFT by New scoring system



Conclusions

Our results suggest that sIL-2R and LD may serve as robust novel biomarkers for predicting the likelihood of treatment necessity among patients with early-stage CLL. However, further validation using a larger dataset is necessary to substantiate these findings.