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Clinical Relevance of Elevated Levels of Serum Soluble Interleukin-2 Receptor alpha (sIL-2Rα) in Patients with Non-Hodgkin's Lymphoma

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Levels of soluble interleukin-2 receptor alpha (sIL-2Rα) are known to increase in the sera of patients with certain malignancies, including malignant lymphoma. This study aimed to assess the clinical significance of the sIL-2Rα level in non-Hodgkin's lymphoma (NHL). We used ELISA to measure the sIL-2Rα levels in 48 newly diagnosed and untreated patients with NHL and evaluated the correlation between the sIL-2Rα levels and clinical characteristics and the International Prognostic Index (IPI). We monitored serum sIL-2Rα in 7 patients to compare the changes in their clinical progress with these levels. High levels of serum sIL-2Rα (≥2,000 U/mL) correlated well with parameters defining the high risk group according to the IPI, i.e., high tumor burden at diagnosis (stage III+IV) and lactate dehydrogenase ≥472 U/L. The levels were also associated with B symptoms, bone marrow involvement, and poor response to therapy. The sIL-2Rα level decreased during complete remission and was elevated during disease progression or relapse. A high level of sIL-2Rα was significantly associated with a low survival rate. These results suggest that serum sIL-2Rα might be useful as a biomarker for evaluating the prognosis of patients with NHL at the time of diagnosis and during therapy. A well-controlled, large-scale study is needed to clarify the clinical significance of sIL-2Rα in specific groups of NHL. *(Korean J Lab Med 2010;30:600-5)*

Key Words : *Soluble interleukin-2 receptor (sIL-2R), International Prognostic Index, Non-Hodgkin's lymphoma*

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of neoplasms presenting as an advanced disease with poor outcome [1]. An examination of prognostic factors in NHL is warranted since prediction of prognosis is necessary to select the most appropriate treatment to improve the survival rate [2]. The International Prognostic Index (IPI) is useful as an initial prognostic determinant of NHL [3]. The IPI is based on patient characteristics associated with clinical parameters such as age, performance status, Ann Arbor clinical stage, serum lactate dehydrogenase (LD) level, and the number of extranodal lesions. In recent years, examination of biological prognostic factors has been the focus of research [4, 5]. Soluble interleukin-2 receptor alpha (sIL-2Rα) is the soluble form of the interleukin-2 receptor expressed on activated lymphocytes or in lymphoproliferative disorders, and it plays physiological roles in immunologic reactions [6]. Many immune, neoplastic, and inflammatory disorders are associ-

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ated with increased sIL-2Rα [4, 7]. Some investigators have suggested that the serum sIL-2Rα level may be a prognostic factor for selecting appropriate treatment of NHL and for determining the clinical outcome in aggressive NHL [8-11]. The sIL-2Rα level can be measured rapidly and easily, but it is not widely used by clinicians in Korea to monitor NHL.

This study aimed to assess the clinical significance of sIL-2Rα levels in 48 patients with previously untreated and histologically diagnosed NHL between June 2006 and August 2008 at Pusan National University Hospital. Twenty-four healthy controls were also included. There were 36 cases of B-cell type lymphoma, including 27 of diffuse large B-cell lymphoma, 4 of follicular lymphoma, 2 of marginal zone B-cell lymphoma, and 3 of B-cell malignant lymphoma. There were 12 cases of T-cell type lymphoma, including 3 of extranodal NK/T-cell lymphoma, 2 of peripheral T-cell lymphoma, 3 of angioimmunoblastic T-cell lymphoma, 2 of anaplastic large cell lymphoma, 1 of $CD4^+CD56^+$ hematodermic neoplasm, and 1 of T-cell malignant lymphoma. Serum sIL-2Rα levels were measured in serial samples from 7 patients to evaluate their therapeutic response. The mean period of observation was 20 months, ranging from 2 to 30 months. All of the patients had undergone staging investigations, including physical examination, blood analysis, bone marrow (BM) examination, computed tomography, and positron emission tomography. Clinical and laboratory data, such as age, gender, serum LD level, Ann Arbor stage, IPI, number and sites of extranodal lesions, BM involvement, B symptoms, performance status, date of diagnosis, type of treatment, radiological response to therapy, and date of remission, relapse, or death, were also collected. The patients were categorized into either a low-risk or a high-risk group for each of the following characteristics: age <60 vs. ≥60 yr, Ann Arbor stages I+II vs. III+IV, LD levels <472 vs. ≥472 U/L, presence of extranodal lesions, B symptoms, BM involvement, and response to treatment. The serum sIL-2Rα level was determined twice consecutively by using the Human IL-2R alpha ELISA kit (R&D Systems, Minneapolis, MN, USA). We obtained a standard linear curve by plotting the mean absorbance for each standard on the y-axis against the concentration on the x-axis. The data was linearized by plotting the sIL-2Rα concentrations versus the optical density of the samples ($y=0.920\times-2.548$, $R^2=0.983$). The measurement range was from 0 to 16,500 U/mL, and the detection limit was 10 U/mL. The serum sIL-2Rα level was considered either high or low by comparing it with the median measurement level of 2,000 U/mL, as reported elsewhere [8, 11]. The differences between groups in terms of median values were tested using the nonparametric Mann-Whitney *U*-test. The overall survival was calculated from the date of diagnosis until death from any cause. The survival curve was estimated using the Kaplan-Meier method, and survival difference was determined using the log-rank test. Cox's proportional-hazards regression analysis was applied to estimate the independency of prognostic parameters. We subjected the pretreatment characteristics to univariate analysis. Next, we performed a multivariate analysis to define the prognostic impact of selected parameters that were found to be significant in the univariate analysis including the sIL-2Rα level. We set the level of statistical significance at $P<0.05$. Data were analyzed using SPSS software version 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

The median serum sIL-2Rα level in patients with NHL (2,338 U/mL; range, 283-15,032) was significantly higher than that in healthy controls (573 U/mL; range, 291-1,010) (Mann-Whitney *U*-test, $P<0.001$). Statistical correlation was found between high levels of serum sIL-2Rα and the high-risk group in the following clinical parameters: Ann Arbor stage III+IV, LD≥472 U/L, B symptoms, BM involvement, poor response to chemotherapy (Mann-Whitney *U*-test, $P<0.05$) (Table 1), and IPI risk (Kruskall-Wallis test, $P<0.05$) (Fig. 1). We observed 7 patients who underwent serial monitoring of sIL-2Rα and evaluated their radiographic clinical response. Among them, 3 patients who achieved clinical remission after chemotherapy showed a marked reduction in the sIL-2Rα level to the median level of healthy controls (Fig. 2). However, 3 patients who did not achieve remission because of recurrence or progressive disease showed sustained high levels of sIL-2Rα of above 2,000 U/mL (Fig. 3). There was one exceptional case

Table 1. Serum sIL-2Rα levels according to the characteristics of NHL patients

Clinical factors	N of cases	sIL-2Rα (U/mL)		*P* value*
		Median	Range	
Gender				
Male	29	1,940	283-15,033	NS
Female	19	2,433	495-11,334	
Age				
<60	30	1,611	283-13,367	NS
≥60	18	3,840	594-15,033	
Stage				
I+II	25	1,197	283-11,849	0.001
III+IV	23	4,559	546-16,033	
LD (U/L)				
<472	19	1,197	476-8,369	0.004
≥472	29	3,826	283-15,033	
Extranodal involvement				
Absent	15	1,394	283-15,033	NS
Present	32	2,358	476-13,367	
B symptom				
Absent	26	1,646	283-8,369	0.001
Present	17	4,099	546-15,033	
Bone marrow involvement				
Absent	34	1,735	283-11,849	0.004
Present	14	5,833	569-15,033	
Treatment response (CR)				
Yes	21	688	283-4,812	0.001
No	25	4,386	739-15,033	

*P values were obtained by non-parametric Mann-Whitney *U*-test, $P<0.05$.

Abbreviations: sIL-2Rα, soluble interleukin-2 receptor alpha; NHL, non-Hodgkin's lymphoma; NS, not specific; LD, serum lactate dehydrogenase level; CR, complete remission.

that showed radiographic remission along with an elevated sIL-2Rα level of 6,508 U/mL, but the pretreatment level in this case was 569 U/mL. Soon after, brain involvement of lymphoma was found. Univariate analysis showed that the overall survival rate was significantly lower in patients with B symptoms and high sIL-2Rα levels (log-rank test, $P<0.05$) (Table 2, Fig. 4). Multivariate analysis showed that B symptoms were an independent prognostic factor for overall survival ($P<0.05$).

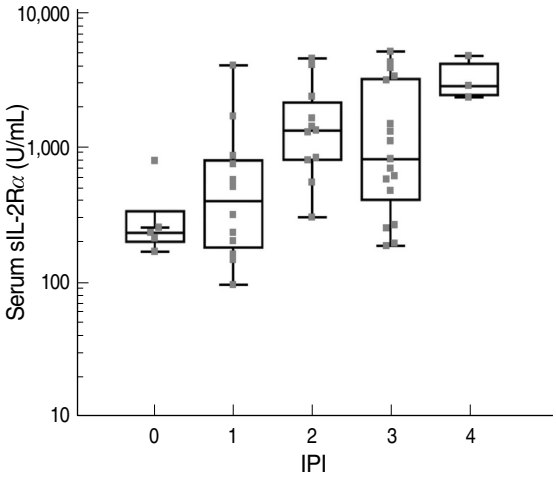

Fig. 1. Serum soluble interleukin-2 receptor alpha (sIL-2Rα) levels according to the International Prognostic Index (IPI) risk group (Kruskall-Wallis test, $P=0.005$).

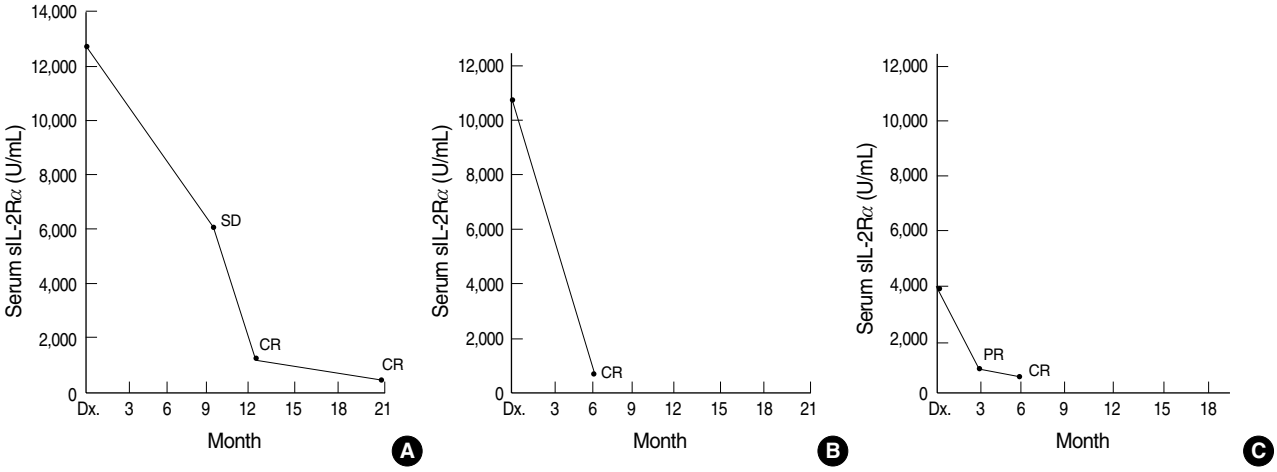

Fig. 2. Serial analysis of serum soluble interleukin-2 receptor alpha (sIL-2Rα) levels in non-Hodgkin's lymphoma patients showing complete remission (CR), through stable disease (SD) or partial remission (PR); sIL-2Rα levels in relation to the timing of chemotherapy, and with respect to radiographic evaluations. (A) A 36-yr-old man with anaplastic large cell lymphoma in the inguinal lymph nodes treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). (B) A 40-yr-old man with diffuse large B cell lymphoma in the small bowel lymph nodes treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). (C) A 60-yr-old man with B cell malignant lymphoma in the oral cavity treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP).

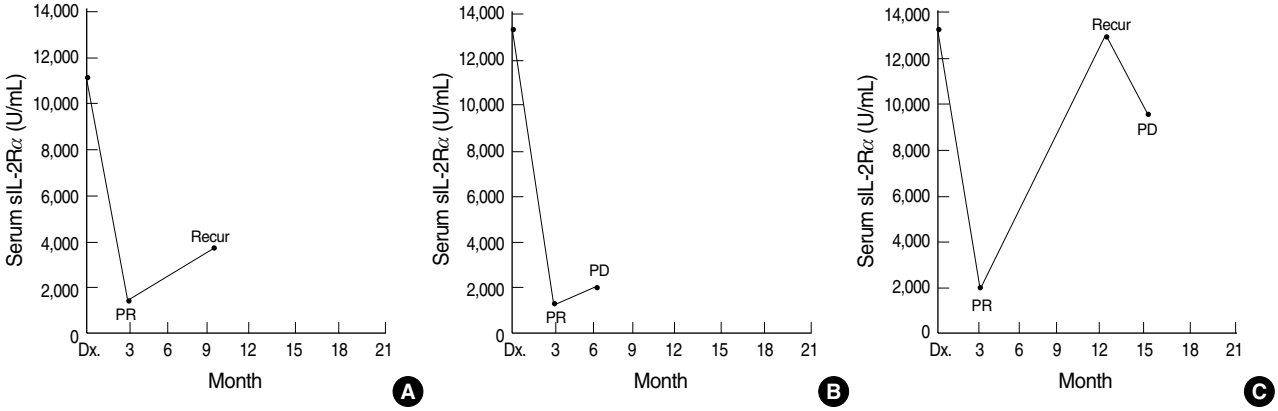

Fig. 3. Serial analysis of serum soluble interleukin-2 receptor alpha (sIL-2Rα) levels in non-Hodgkin's lymphoma patients showing recurrence or progressive disease (PD) after partial remission (PR); sIL-2Rα levels in relation to the timing of chemotherapy, and with respect to radiographic evaluations. (A) A 48-yr-old woman with follicular lymphoma in the axillary lymph nodes treated with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). (B) A 64-yr-old man with angioimmunoblastic T cell lymphoma in the neck treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). (C) A 53-year-old man with angioimmunoblastic lymphoma in the cervical lymph nodes treated with CHOP.

Table 2. Univariate analysis on overall survival in NHL patients

Clinical factors	N of cases	Overall survival, months (rate, %)	*P* value*
Gender			
Male	29	24.1 (72)	NS
Female	19	28.7 (89)	
Age			
<60	30	24.0 (73)	NS
≥60	18	27.4 (88)	
Stage			
I+II	25	27.5 (88)	NS
III+IV	23	23.7 (69)	
LD (U/L)			
<472	19	28.2 (89)	NS
≥472	29	24.3 (72)	
Extranodal involvement			
Absent	15	29.0 (93)	NS
Present	32	24.0 (71)	
B symptom			
Absent	26	28.7 (92)	0.01
Present	17	21.8 (58)	
Bone marrow involvement			
Absent	34	21.8 (85)	NS
Present	14	21.0 (64)	
sIL-2Rα (U/mL)			
<2,000	22	27.9 (90)	0.041
≥2,000	26	23.0 (69)	

*P values were obtained by log-rank test.
Abbreviations: NHL, non-Hodgkin's lymphoma; NS, not specific; LD, serum lactate dehydrogenase level; sIL-2Rα, soluble interleukin-2 receptor alpha.

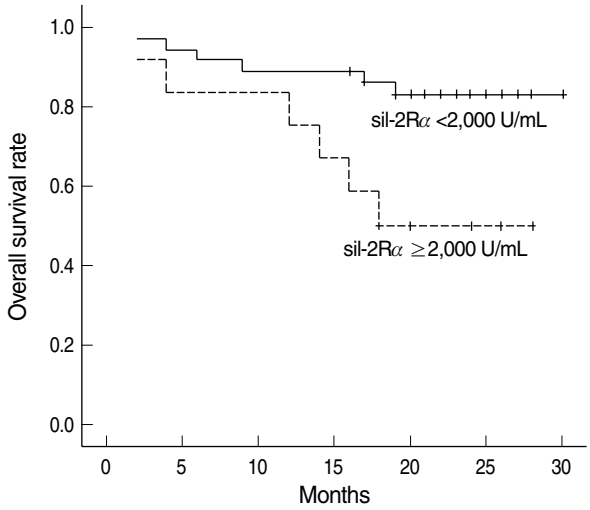

Fig. 4. Overall survival curves for non-Hodgkin's lymphoma patients in relation to soluble interleukin-2 receptor alpha (sIL-2Rα) level; overall survival curves according to low (<2,000 U/mL) versus high (≥2,000 U/mL) level of sIL-2Rα (Log-rank test, *P*=0.041).

In the present study, it was found that the sIL-2Rα level may be prognostically useful for NHL patients at the time of diagnosis and for monitoring disease progress continuously. As shown in Fig. 1, the sIL-2Rα level is closely correlated with IPI risk at the time of diagnosis. We found a significant correlation between sIL-2Rα and disease course and response to treatment. Survival analysis showed that a high serum level of sIL-2Rα is a predictor of poor prognosis.

Some reports have indicated that sIL-2Rα levels are increased in aggressive NHL, peripheral T-cell lymphoma

or diffuse large B-cell lymphoma at the time of diagnosis, and a high level of this cytokine receptor could be a prognostic factor, which could aid in predicting the outcome of these diseases in patients [8, 9, 11]. Others have suggested using serum sIL-2Rα levels to monitor the therapeutic response in anaplastic large cell lymphoma or malignant lymphoma [2, 10, 12]. Our data showed that the sIL-2Rα level provides valuable information for better management of patients with NHL and can be used as a biomarker to predict prognosis and to monitor disease activity. In the one case with radiologic remission, the sIL-2Rα levels were elevated and brain involvement of lymphoma was observed. This finding was similar to that of Yoshida and Morii who observed increased levels of sIL-2Rα in malignant brain tumors [13], which could be caused by pathological changes occurring before radiological changes.

This study had several limitations. First, we targeted various histological types of NHL to evaluate the significance of sIL-2Rα as a comprehensive prognostic marker, similar to IPI. Second, in multivariate analysis, a high level of sIL-2Rα was not an independent prognostic factor. Therefore, a longer period of observation and patients with lymphoma of a specific histological type should be studied in order to clearly understand the prognostic impact of sIL-2Rα. Further, the sIL-2Rα level might be a non-specific biomarker that is increased in immunologic or tumorigenic disease conditions such as rheumatoid arthritis or non-small cell lung cancers [14, 15]. However, Sakata et al. [16] reported that the serum sIL-2Rα level is increased more in invasive cancers than in activated immune states. Huang et al. [17] also reported that in malignant tumors, sIL-2Rα is produced through a pathway other than the one through which it is produced in conditions involving T-cell upregulation.

The serum sIL-2Rα level could be a noninvasive, rapid, and convenient biomarker of NHL. It has better objective validity than IPI at the time of diagnosis. Furthermore, there was good correlation between the sIL-2Rα level and radiologic findings during follow up. However, the clinical significance of the sIL-2Rα level remains underestimated as compared to that of the IPI. This is probably because sIL-2Rα has been evaluated in small populations with unified pathologic features of NHL. More large-scale studies in diverse clinical settings are required to clarify the significance of sIL-2Rα as a biomarker in NHL.

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