Original Study

Clinical Significance of Serum-Soluble Interleukin-2 Receptor in Patients With Follicular Lymphoma

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Abstract

The role of serum-soluble interleukin-2 receptor (sIL-2R) in follicular lymphoma has not been fully established. We reviewed data on 70 patients with follicular lymphoma and revealed a significant correlation of sIL-2R with clinical stages. We also elucidated that sIL-2R regressed and increased in parallel with tumor regression and relapse. Our data support the usefulness of sIL-2R as a surrogate marker of tumor progression.

Background: Although sIL-2R level has a prognostic value in patients with diffuse large B-cell lymphoma, its clinical role in patients with follicular lymphoma has not been determined. **Patients and Methods:** We reviewed data on 70 patients diagnosed with follicular lymphoma. **Results:** Ann Arbor stage was I, II, III, and IV in 6, 9, 17, and 38 patients, respectively, and grade classification according to the World Health Organization criteria was 1, 2, 3A, 3B, and not available in 28, 15, 11, 4, and 12 patients, respectively. sIL-2R at diagnosis was significantly correlated with Ann Arbor stages ($P < .001$), number of nodal lesions (≥ 5 or not) ($P = .0050$), and Follicular Lymphoma International Prognosis Index risk classification ($P = .0015$). Furthermore, sIL-2R regressed significantly in patients who achieved complete remission, uncertain complete remission, or partial remission ($P < .001$), and increased when regrowth of lymphoma was shown ($P < .001$). Finally, a high level of sIL-2R at diagnosis was correlated with shorter progression-free survival ($P = .018$) and time to next treatment ($P < .001$). **Conclusion:** Serum-soluble interleukin-2 receptor is correlated with tumor burden at diagnosis and during the clinical course of therapies in patients with follicular lymphoma, and our data support its usefulness to function as a surrogate marker of tumor progression.

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Introduction

Interleukin-2 receptor (IL-2R) is expressed on the membrane of activated mononuclear cells, and the soluble form of IL-2R is released from these cells.[1] The level of soluble IL-2R (sIL-2R) reflects inflammation, and is known to be elevated in many conditions such as autoimmune disease, infectious disease, and carcinoma.[2-5] A high elevation of sIL-2R is specifically observed in patients with malignant lymphoma, mostly derived from deregulated expression of IL-2R in lymphoma cells.[6,7] Serum sIL-2R level has a prognostic value in patients with diffuse large B-cell lymphoma[8-11] or entire non-Hodgkin lymphoma.[12,13] However, its prognostic value in patients with follicular lymphoma has been reported in only a few small studies.[14,15]

Follicular lymphoma is the second most common lymphoma in Western countries[16] and Japan.[17] Although follicular lymphoma takes indolent clinical courses, it is difficult to cure and needs frequent monitoring for relapses.[18,19] Therefore, in this retrospective analysis, we evaluated the clinical significance of sIL-2R in follicular lymphoma at the time of diagnosis and during its clinical course.

Patients and Methods

Patients and Study Design

We retrospectively reviewed the medical records of 70 consecutive patients who were diagnosed as having follicular lymphoma at the University of Tokyo Hospital between 1997 and 2009. All

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patients were diagnosed histologically by special pathologists. Patients who had been treated at other hospitals, or whose laboratory data at diagnosis were not available were excluded from this analysis. Therefore, we enrolled only cases who had not been treated before.

We extracted clinical data of the identified cases, including age, serum lactate dehydrogenase (LDH) level (standard value in our facility is 125-237 U/mL), serum sIL-2R level (127-582 U/mL), grade classification according to the World Health Organization (WHO) criteria, Ann Arbor stage, number of nodal lesions, Follicular Lymphoma International Prognosis Index (FLIPI) score at diagnosis, and treatment regimens. sIL-2R and LDH were extracted at several points including at diagnosis, at the start of initial therapies, and at the occurrence of response and relapse/regrowth after therapies. We also collected the data on response to treatments, duration of response for the initial therapies, and timing and regimens of second-line treatments.

We defined the date of response, relapse, or regrowth as the date when diagnostic imaging (computed tomography [CT] or positron-emission tomography [PET]) was performed. We retrospectively categorized response to treatment according to the International Workshop for non-Hodgkin lymphoma.[20] We defined regrowth as enlargement of a lesion or increase of the number of lesions after the response to the previous treatment was acquired.

We examined the effect of sIL-2R and LDH on clinical parameters at diagnosis, overall survival (OS), progression-free survival (PFS), and time to next treatment (TTNT). OS was calculated from the time of disease diagnosis to that of death from any cause. PFS was calculated from the time of the first treatment to that of disease progression or death, whichever came first. TTNT was defined as the time from the initial treatment to that of the next treatment. Patients were categorized by these parameters measured at diagnosis for OS analysis and at the first treatment for PFS and TTNT. Therefore, in the analyses of PFS and TTNT, we excluded the cases who received no treatment during the observation period and the cases whose value of sIL-2R at the first treatment was not available. This study was approved by the Ethical Committee of the Tokyo University Hospital and adhered to the Declaration of Helsinki. Informed consent was obtained from all patients.

Methods for Measuring Biochemical Data

The concentration of sIL-2R was measured using a chemiluminescent enzyme immunoassay (IMMULITE 2000 IL-2R, Siemens Healthcare Diagnostic Co) according to the instruction manual. The baseline value described in the manual, which was set from data of healthy control subjects, was adopted. The concentration of LDH and C-reactive protein (CRP) were measured using an enzyme kinetics assay (Quick Auto Neo LD, Shino-Test Co) and an antigen-antibody reaction assay (CRP-LATEX X2 SEIKEN Assay kit, Denka Seiken Co), respectively.

Statistical Analysis

Data were analyzed using the statistical software R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria). Differences between groups in sIL-2R and LDH were examined using the Kruskal-Wallis test. PFS, OS, and TTNT were estimated using Kaplan-Meier methods and compared using the log-rank test. A P-value $< .05$ was assumed significant.

Results

Patient Data

Seventy patients were studied (35 male, 35 female). Their clinical features are summarized in Table 1. Grade classification according to the WHO criteria was 1, 2, 3A, 3B, and no data in 28, 15, 11, 4, and 12 patients, respectively; Ann Arbor stage was I, II, III, and IV in 6, 9, 17, and 38 patients, respectively; and FLIPI risk classification at diagnosis was low, intermediate, and high in 25, and 20 patients, respectively. The median value of sIL-2R and LDH at diagnosis were 1208 U/mL (range, 195-12,520 U/mL) and 203.5 U/mL (range, 107-475 U/mL). Values of 50 and 16 patients were above the upper normal limit for sIL-2R and LDH, respectively.

Correlation with Clinical Parameters at Diagnosis

First, we examined the relation of sIL-2R or LDH with various parameters at diagnosis (Figure 1).

Soluble IL-2R at diagnosis was significantly correlated with Ann Arbor stages ($P < .001$; Figure 1A) and number of nodal lesions (≥ 5 or not) ($P = .0050$; Figure 1C), and LDH had no association with these factors ($P = .62$ for stages; Figure 1B) and $P = .53$ for nodal lesion numbers (Figure 1D). sIL-2R and LDH were correlated with FLIPI risk classification ($P = .0045$ and $P = .0036$, respectively; Figure 1E and F). sIL-2R was not significantly correlated with the other factors that comprise FLIPI such as anemia (< 12 g/dL or not; $P = .12$), age (> 60 years old or not; $P = .58$), and LDH (above the facility standard value or not; $P = .81$). sIL-2R and LDH were not significantly correlated with advanced histological grades ($P = .14$ and $P = .74$, respectively). Because sIL-2R also reflects inflammation from any cause, we also conducted an analysis excluding patients with elevated CRP (> 0.3 mg/dL) (15 patients). In this CRP-negative group, sIL-2R retained correlation with clinical stages ($P = .0012$) and number of nodal lesions ($P = .0038$). The subsequent analyses were conducted with CRP-positive cases included.

Clinical Effect on Treatment Efficacy and Relapses

Patients received a wide variety of treatments as the initial therapies. One was not treated, 1 was treated with operative resection, 6 with focal radiation, 6 with rituximab alone, 7 with chemotherapy not combined with rituximab, 49 with chemotherapy containing rituximab. Among the 69 patients who received treatment, 37 patients achieved complete remission (CR), 6 uncertain CR (CRu), 20 partial remission (PR), and 6 were considered as having stable disease. No patients had progressive disease (PD).

Next, we assessed the relation of the value of sIL-2R after treatments and at relapses. If a patient underwent treatments or relapses several times, each treatment or relapse was counted as a distinct episode. In total, 103 episodes of treatment (of 61 patients who were enrolled; treatments were counted once in 34 patients, in 19 patients twice, in 3 patients 3 times, in 3 patients 4 times, and in 2 patients 5 times) and 61 episodes of relapse (in a total of 39 patients; relapse was counted in 26 patients once, 7 patients twice, 4 patients 3 times, 1 patient 4 times, 1 patient 5 times) were subjected to this analysis (Figure 2). sIL-2R regressed significantly in patients who achieved CR, CRu, or PR after therapy (the median before treatment was 1074 U/mL, after treatment was 419 U/mL;

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