

Soluble interleukin-2 receptor level on day 7 as a predictor of graft-versus-host disease after HLA-haploidentical stem cell transplantation using reduced-intensity conditioning

Katsuji Kaida · Kazuhiro Ikegame · Junko Ikemoto · Rie Murata · Reiko Irie · Satoshi Yoshihara · Shinichi Ishii · Masaya Okada · Takayuki Inoue · Hiroya Tamaki · Toshihiro Soma · Yoshihiro Fujimori · Shunro Kai · Hiroyasu Ogawa

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Abstract In the present study, we analyzed the kinetics of serum soluble interleukin-2 receptor (sIL-2R) using data from 77 patients undergoing HLA-haploidentical transplantation using reduced-intensity conditioning (RIC), who were at an advanced stage or at high risk for relapse, to clarify the usefulness of sIL-2R as a biomarker of acute graft-versus-host disease (GVHD). Anti-T-lymphocyte globulin and methylprednisolone were used as GVHD prophylaxis. While the median sIL-2R in 38 patients not developing GVHD was suppressed at levels <740 U/ml, sIL-2R in 25 patients developing severe GVHD peaked on day 11 (1,663 U/ml), and thereafter decreased to <1,000 U/ml after day 30. The occurrence of GVHD was not limited to times of high sIL-2R level, but occurred at any time point on the sIL-2R curve. Most patients developing GVHD, however, experienced a higher sIL-2R level early in their transplant course. The combination of RIC and glucocorticoids sufficiently suppressed sIL-2R levels after HLA-haploidentical transplantation. In a multivariate analysis to identify factors associated with GVHD, day 7 sIL-2R >810 U/ml was the only factor significantly associated with the occurrence of severe GVHD ($p = 0.0101$).

Keywords Allogeneic stem cell transplantation · Graft-versus-host disease · Soluble interleukin-2 receptor · Allergic response · HLA-haploidentical transplantation

Introduction

Bone marrow transplantation (BMT) from siblings genotypically matched for human leukocyte antigen (HLA) improves long-term survival in patients with hematologic malignancies [1]. However, more than 70 % of patients who could benefit from allogeneic BMT do not have a matched sibling donor. On the other hand, there is a >90 % chance of promptly identifying an HLA-haploidentical donor within the family; therefore, the number of patients receiving HLA-haploidentical stem cell transplantation (SCT) is gradually increasing [2–6]. The major drawback of HLA-haploidentical SCT is graft-versus-host disease (GVHD). To overcome GVHD after HLA-haploidentical SCT, several breakthroughs in transplant methodology, including drastic ex vivo T cell purging coupled with the use of megadose of stem cells [2], and in vivo T cell purging through the use of anti-T-lymphocyte globulin (ATG) [4, 5, 7], or the use of cyclophosphamide at post-transplant, have been done [6]. We and others have been studying HLA-haploidentical SCT using in vivo T cell purging method using ATG [4, 5, 7]. In this transplant setting, although the severity of GVHD is within a permissible range, GVHD still continues to be the problem, but an appropriate monitoring method of GVHD has not been established yet.

Basically, GVHD is induced by the immunological response of donor T cells. In general, once activated, T cells express the interleukin-2 receptor (IL-2R), consisting of at least three subunits (α , β and γ_c) on their membrane

Katsuji Kaida and Kazuhiro Ikegame contributed equally.

K. Kaida · K. Ikegame · S. Yoshihara · S. Ishii · M. Okada · T. Inoue · H. Tamaki · T. Soma · H. Ogawa (✉)
Division of Hematology, Department of Internal Medicine,
Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya,
Hyogo 663-8501, Japan
e-mail: ogawah@hyo-med.ac.jp

J. Ikemoto · R. Murata · R. Irie · Y. Fujimori · S. Kai
Department of Transfusion Medicine, Hyogo College of
Medicine, Nishinomiya, Hyogo, Japan

[8, 9]. The soluble form of IL-2R is produced by proteolytic cleavage of IL-2R α , and the release of soluble interleukin-2 receptor (sIL-2R) into the circulation has been found to be proportional to its membrane bound expression [10, 11]. Thus, serum sIL-2R levels reflect the magnitude of the T cell immunological response and are associated with the incidence and severity of GVHD in allogeneic BMT settings. In fact, sIL-2R is reported to be the most reliable biomarker among several useful biomarkers [12].

The role of sIL-2R as a GVHD biomarker has been studied mainly in the transplant settings of HLA-matched myeloablative SCT for patients mostly in complete remission (CR) [12–17]. Reduced-intensity conditioning (RIC), which has been used also in HLA-haploidentical transplant settings, may contribute to the reduction of the incidence and severity of GVHD [18–20]. We and others reported that HLA-haploidentical reduced-intensity conditioning stem cell transplantation (RIST) was useful for patients who did not have a suitable HLA-matched donor [5, 7]; however, there are no reports analyzing whether sIL-2R is still a useful biomarker of GVHD in this transplant setting.

Despite the usefulness of sIL-2R as a GVHD biomarker, transplant-related complications, including severe infection, graft rejection, and hepatic veno-occlusive disease, are known to increase sIL-2R levels [13, 15, 21]. Furthermore, leukemia- or lymphoma-associated elevation of serum sIL-2R levels has been reported [22–25]. The coexistence of these conditions could reduce the value of sIL-2R as a biomarker of GVHD.

Therefore, in the present study, after excluding data of patients with conditions that increase sIL-2R levels other than GVHD, we retrospectively studied the usefulness of sIL-2R as a GVHD biomarker using data from 77 patients, with poor prognosis or in an advanced stage of disease, who underwent HLA-haploidentical RIST.

Patients and methods

Patients

To retrospectively evaluate the role of the sIL-2R level as a biomarker of acute GVHD, we analyzed data from patients who underwent HLA-haploidentical RIST at the Hospital of Hyogo College of Medicine between January 2009 and June 2012. All patients had hematologic malignancies and were at an advanced stage or had a poor prognosis at the time of transplantation.

The inclusion criteria were as follows: donor-type engraftment, survival for at least 30 days after transplantation, the absence of hepatic veno-occlusive disease, and severe infections (CRP >10), including sepsis [13, 15, 21]. Furthermore, to avoid the effect of tumor-associated sIL-2R

Table 1 Patients' characteristics

	GVHD Grade 0	Grade I	Grade II–III
Number of patients	38	14	25
Sex			
Male/female	24/14	5/9	10/15
Age (years)			
Median (range)	42.5 (17–63)	46.5 (20–61)	55 (14–65)
Disease			
AML/MDS	17	10	12
ALL	11	0	3
Lymphoma	6	2	6
Others	4	2	4
Disease status			
Good (CR/RA/CP)	2	0	2
Intermediate (PR/RAEB/AP)	4	1	1
Poor	32	13	22
HLA disparity in GVH direction			
2 antigen	18	9	13
3 antigen	20	5	12
Number of times of transplant			
First	17	7	20
Second or later	21	7	5
Conditioning combination chemotherapy			
Busulfan-containing	8	3	9
Melphalan-containing	26	8	15
Others	4	3	1
TBI			
Containing	25	8	15
Non-containing	13	6	10

[22–25], data from patients who showed a tumor-associated increase in sIL-2R >2,000 U/ml before conditioning, which did not decrease to <1,000 U/ml on day 0, were excluded. Consequently, data from 20 % of the total transplant patients were excluded based on the exclusion criteria described above, and we analyzed data from 77 patients who underwent transplantation using a graft from an HLA-haploidentical donor (2–3 antigen-mismatches in GVH direction). The patients' characteristics are shown in Table 1.

Institutional review board approval was obtained for the treatment protocol, and written informed consent was obtained from the patients and their families.

Preparative regimen for transplantation

Sixty-nine patients received a regimen consisting of fludarabine (30 mg/m²/day on days –9 to –4), cytarabine (2 g/m² on days –9 to –6), ATG (thymoglobulin: total

2.5 mg/kg divided on days -3 to -1), and busulfan (4.0 mg/kg/day on days -6 and -5) or melphalan (70 mg/m² on days -3 and -2) with or without TBI 3–4 Gy on day 0. The remaining 8 patients received other agents instead of busulfan or melphalan because of chemoresistance. GVHD prophylaxis consisted of tacrolimus and methylprednisolone (mPSL) 1 mg/kg [5]. All patients except 2 received peripheral blood stem cells. T cell depletion was not performed.

Diagnosis of graft-versus-host disease and supportive care

Acute GVHD was graded according to standard criteria [26]. GVHD was treated as previously described [5]. Each patient was isolated in a laminar air-flow room or protective environment room, and standard decontamination procedures were followed. Oral antibiotics (ciprofloxacin, vancomycin, itraconazole or voriconazole) were administered to sterilize the bowel. Patients who were negative for cytomegalovirus (CMV) IgG received blood products from CMV-seronegative donors. Intravenous immunoglobulin was administered at a minimum dose of 100 mg/kg every 2 weeks until day 100. Cotrimoxazole was given for at least 1 year for prophylaxis of *Pneumocystis carinii* infections. Acyclovir was administered at a dose of 1,000 mg/day for 5 weeks after transplantation to prevent herpes simplex virus or varicella-zoster virus infection, and then the agent was continued for at least 2 years at a dose of 200 mg/day. Ganciclovir 7.5 mg/kg divided into 3 doses per day was administered from day -10 to day -3 as prophylaxis for CMV infection.

Measurement of serum sIL-2R

The serum sIL-2R level was monitored from the start of conditioning three times a week until hospital discharge. The serum sIL-2R concentration was evaluated using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) with two murine anti-human sIL-2R antibodies (CELLFREE Human sIL-2R ELISA Kit; Thermo Fisher Scientific Inc., Rockford, IL, USA). The normal sIL-2R level is <534 U/ml.

Statistics

The background levels of serum sIL-2R were decided using data from 38 patients who did not develop GVHD. The difference in sIL-2R levels on day 7 between patients who developed grade 0–I and grade II–III GVHD was analyzed using the Mann–Whitney *U* test. In addition, we determined the appropriate cutoff value of the sIL-2R level on day 7 to discriminate patients with and without severe

GVHD through receiver operating characteristic (ROC) analysis, in which sensitivity and specificity were calculated as a function of the cutoff value, (1-specificity) was plotted against the sensitivity, and the area under the ROC curve (AUC) was calculated. Cumulative incidence of GVHD for patients with sIL-2R on day 7 of >810 or <810 U/ml was estimated using the Kaplan–Meier method, treating death and relapse as competing risks. Gray's test was used for comparison of cumulative incidence in the 2 groups. To identify factors associated with GVHD, using variables including the donor source, age, disease status before transplantation, sex, number of times of transplantation, HLA disparity in GVH direction, disease, and day 7 sIL-2R level, univariate and multivariate analyses were performed using the Cox proportional hazards model. Results were considered significant when $p \leq 0.05$. Statistical analyses were performed with EZR [27, 28].

Results

Background level of sIL-2R based on the data from patients who did not develop GVHD

Serum sIL-2R levels were monitored 3 times a week to analyze the relationship between sIL-2R levels and the development of GVHD in detail. We first identified the serum background level of sIL-2R based on data from 38 patients who did not develop acute GVHD. As shown in Fig. 1, sIL-2R was slightly high, but mostly <1,200 U/ml during 2 weeks after transplantation, and thereafter slightly decreased to <1,000 U/ml. The median value of sIL-2R

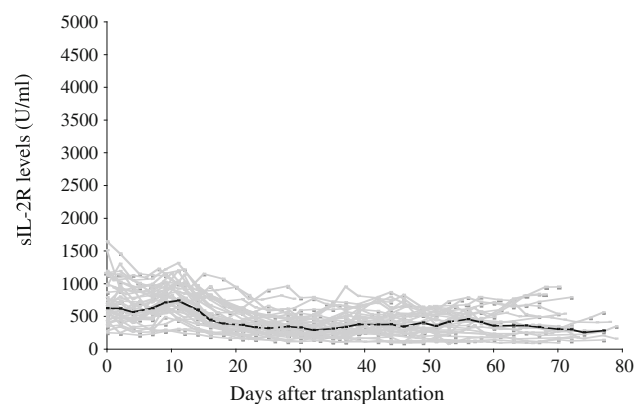


Fig. 1 The kinetics of sIL-2R in patients not developing acute GVHD. To identify the background levels of sIL-2R, changes of serum sIL-2R of 38 patients who did not develop GVHD were plotted. The normal sIL-2R level is <534 U/ml. sIL-2R was slightly high, but mostly <1,200 U/ml during 2 weeks after transplantation, and thereafter slightly decreased to <1,000 U/ml. The **bold line** shows a median sIL-2R level

was slightly increased after transplantation, peaked on day 11 (the peak level was 740 U/ml), and thereafter decreased to levels as low as between 290 and 450 U/ml.

The kinetics of sIL-2R in patients who developed severe GVHD

Next, we analyzed the kinetics of sIL-2R in 25 patients who developed severe (grade II–III) GVHD. Four patients developed skin-only GVHD, 16 gut-only GVHD, and 5 skin/gut GVHD. Those patients developed grade II–III GVHD at a median 28 days (range 3–67 days). The sIL-2R curves were found to vary patient-to-patient in the peak level or in the timing of the peak. The median sIL-2R levels increased after transplantation, reach on day 11 (the peak value of 1,663 U/ml), and thereafter decreased to low levels of <1,000 U/ml after day 30 (Fig. 2).

Regarding the relationship between the kinetics of sIL-2R and the onset of GVHD, 4 patterns were observed. Eight (32 %) patients, in whom sIL-2R increased rapidly after transplantation, developed GVHD at an increasing phase or at the peak level of sIL-2R curve by day 30 (Fig. 3a). These patients developed GVHD at a median of 9 days (range 5–26 days), with the median value of sIL-2R of 1,795 U/ml (range 1,134–4,341 U/ml) at the onset of GVHD. Four (16 %) patients developed GVHD at a decreasing phase of sIL-2R over the peak of sIL-2R (Fig. 3b). These patients developed GVHD at a median of 18.5 days (range 14–21 days), with the median value of sIL-2R of 1,465.5 U/ml (range 618–2,004 U/ml) at the onset of GVHD. Ten (40 %) patients, in whom sIL-2R increased to a high level after transplantation, with the median peak level of 1,711 U/ml (range 1,200–2,977 U/ml) at a median 5.5 days (range 0–16 days), developed

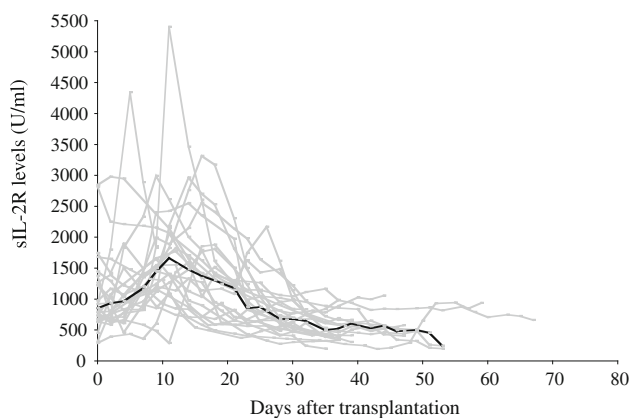


Fig. 2 The kinetics of sIL-2R in 25 patients who developed acute GVHD (grade II–III). Changes of serum sIL-2R in 25 patients who developed severe GVHD were plotted. The sIL-2R curves were found to vary patient-to-patient in the peak level or in the timing of the peak. The **bold line** shows a median sIL-2R level

GVHD after sIL-2R levels decreased to almost the normal range of sIL-2R (Fig. 3c). These patients developed GVHD at a median of 38 days (range 28–67 days), with the median value of sIL-2R of 642.5 U/ml (range 336–950 U/ml) at the onset of GVHD. Three (12 %) patients, in whom sIL-2R did not increase over the background levels of sIL-2R after transplantation, developed GVHD after day 30, when sIL-2R was slightly increasing over the background level of sIL-2R (Fig. 3d). GVHD in this group of patients occurred latest at a median of 44 days (range 37–59 days), with the median value of sIL-2R of 984 U/ml (range 935–1,054 U/ml) at the onset of GVHD. These results show that GVHD can occur on any point of the sIL-2R curve of patients with GVHD.

Prediction of severe acute GVHD by serum sIL-2R levels on day 7

The relationship between sIL-2R change and the onset of GVHD (Fig. 3a–d) shows that the occurrence of GVHD is not limited at the time of high level of sIL-2R or at an increasing phase of sIL-2R; however, the majority of patients who developed severe GVHD showed a high level of sIL-2R early in their transplant course. Therefore, we considered that sIL-2R in the early phase of transplantation may be associated with the development of severe GVHD.

We compared sIL-2R levels on day 7 in patients who developed grade II–III GVHD or grade 0–I GVHD. Consequently, patients with grade II–III GVHD showed significantly higher sIL-2R on day 7 than those with grade 0–I GVHD ($p < 0.0001$). To determine the appropriate cutoff value of sIL-2R on day 7 to discriminate patients with and without severe GVHD, ROC analysis (Fig. 4a) was performed, and the optimal grade II–III GVHD cutoff point was found to be 810 U/ml. The area under the ROC curve (AUC) was 0.790 (CI 0.675–0.904). The relationship between the incidence of severe GVHD and day 7 sIL-2R levels was analyzed using competing risk analysis, treating death and relapse as competing risks. As shown in Fig. 4b, the cumulative incidence of severe GVHD was 43.2 % (CI 28.2–57.3 %) and 6.5 % (CI 1.1–18.9 %) for patients with day 7 sIL-2R >810 U/ml and those with day 7 sIL-2R <810 U/ml, respectively. Patients with day 7 sIL-2R >810 U/ml had a significantly higher risk of GVHD than those with day 7 sIL-2R <810 U/ml ($p = 0.00076$, log-rank test).

Next, using variables including the donor source (off-spring vs others), HLA disparity (2 antigen vs 3 antigen) in the GVH direction, older age (>47 years), disease status before transplantation (CR vs non-CR), sex, number of times of transplantation, disease (ALL vs others), and day 7 sIL-2R, factors that were significantly associated with the development of severe GVHD were analyzed using the

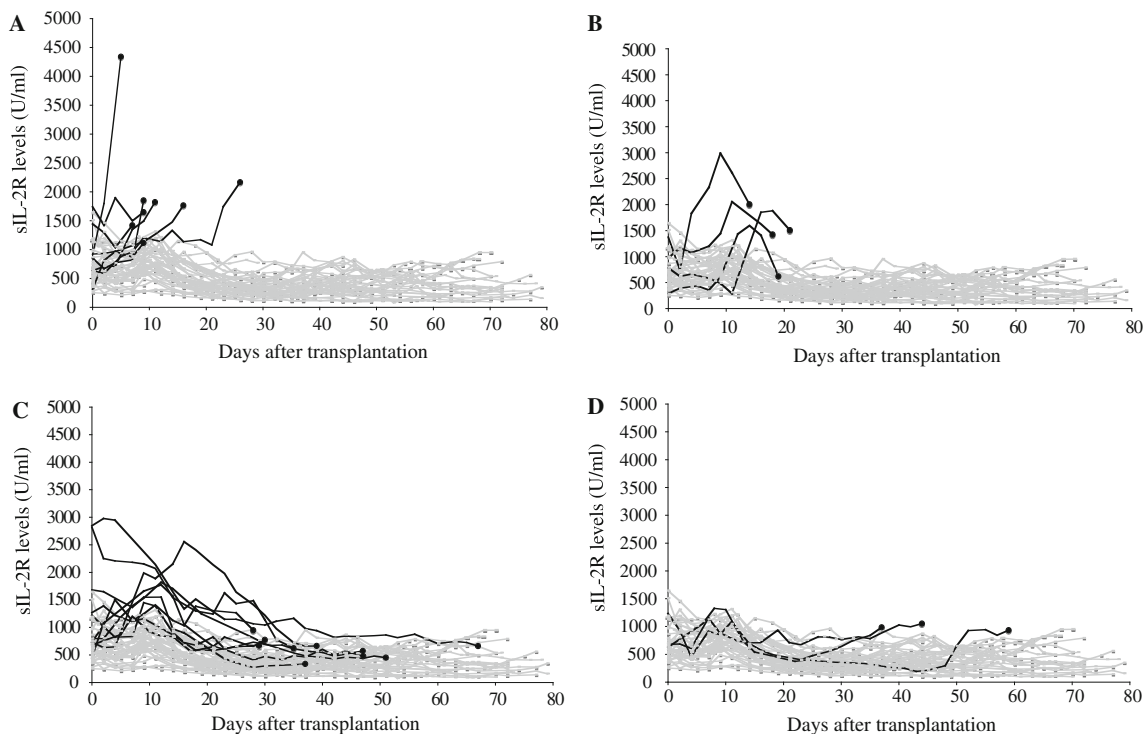


Fig. 3 The relationship between the kinetics of sIL-2R and onset of GVHD in patients who developed severe acute GVHD. *Bold lines* show changes of sIL-2R in patients who developed severe GVHD. *Closed circles*, which are at the end of the *bold lines*, show the onset of GVHD. *Gray lines* show changes of sIL-2R in patients not developing GVHD. **a** GVHD occurred at an increasing phase of sIL-

2R or at the peak level by day 30. **b** GVHD occurred at a decreasing phase of sIL-2R (still at a high level) over the peak of sIL-2R. **c** GVHD occurred after returning to the background level of sIL-2R, which passed through the high levels after transplantation. **d** GVHD occurred at a time point slightly increased from the background level of sIL-2R after day 30

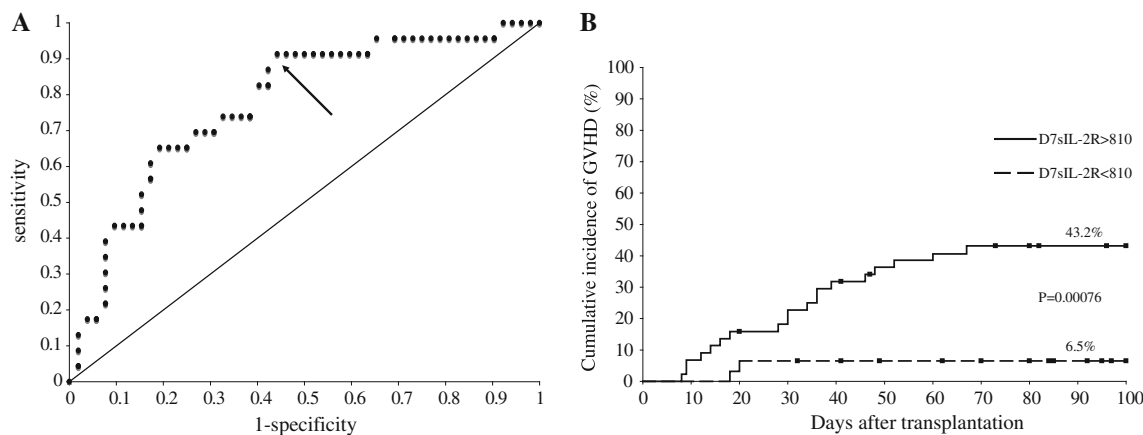


Fig. 4 a ROC curve of sIL-2R level on day 7 for the prediction of severe GVHD. To determine the appropriate cutoff value of sIL-2R levels on day 7 to discriminate patients with and without severe GVHD, ROC analysis was performed, and the optimal grade II–III GVHD cutoff point was found to be 810 U/ml, shown by the *arrowhead*. The area under the ROC curve (AUC) was 0.790. **b** Cumulative incidence of severe GVHD for patients with sIL-2R on day 7 of >810 and <810 U/ml. Cumulative incidence of acute GVHD

for patients with sIL-2R on day 7 of >810 U/ml and <810 U/ml was estimated using the Kaplan–Meier method, treating death and relapse as competing risks. Gray’s test was used for comparison of cumulative incidence in the 2 groups. Patients with sIL-2R on day 7 of >810 U/ml had a significantly higher risk of severe acute GVHD than those with day 7 sIL-2R of <810 U/ml ($p = 0.00076$, log-rank test)

Cox proportional hazards model (Table 2). In a univariate analysis, day 7 sIL-2R >810 U/ml, offspring, age >47 years, and first transplantation were significantly

associated with the occurrence of severe GVHD. In a multivariate analysis, day 7 sIL-2R >810 U/ml was only a factor significantly associated with the occurrence of

Table 2 Analysis of factors related to the development of severe GVHD

	Univariate analysis		Multivariate analysis	
	<i>p</i>	CI	<i>p</i>	CI
sIL-2R on day 7 (>802 vs <802)	0.0024	2.214–40.431	0.0101	1.597–31.999
Donor source (offspring vs others)	0.0125	1.287–8.102	0.6601	0.238–9.617
Age (>47 vs <47 years)	0.0089	1.389–9.905	0.8337	0.144–11.068
Disease status before transplantation (CR vs non-CR)	0.7203	0.307–5.527	0.1965	0.576–14.591
Sex (female vs male)	0.1877	0.769–3.820	0.526	0.525–3.523
Number of times of transplant (retransplantation vs first transplantation)	0.0155	0.112–0.795	0.2003	0.100–1.621
HLA disparity in GVH direction (2 antigen vs 3 antigen)	0.8831	0.430–2.067	0.5993	0.322–1.922
Disease (ALL vs others)	0.2713	0.152–1.698	0.490	0.181–2.265

CI confidence interval, CR complete remission, non-CR non-complete remission

severe GVHD ($p = 0.0101$, CI 1.597–31.999). Offspring, age >47 years, and first transplantation had no significant impact on the occurrence of severe GVHD.

Discussion

In the present study, using data from 77 patients who underwent HLA-haploidentical RIST, we investigated the thorough kinetics of serum sIL-2R after transplantation to elucidate the usefulness of sIL-2R as a GVHD biomarker, and found that sIL-2R on day 7 was useful as a predictor of severe GVHD.

In the present study, data from other pathological situations that increase serum sIL-2R were excluded from the analysis. Serum sIL-2R levels reflect the magnitude of the activation and proliferation of T cells, but are not specific to the GVH reaction. This is an inevitable drawback in the diagnosis of GVHD using sIL-2R, as a non-specific T cell reaction of donor or recipient origin produces sIL-2R in some particular transplant complications, such as infection. To avoid the effect of these complications on sIL-2R analysis, other researchers also excluded data from patients with these complications, who represent 15 % of allogeneic recipients [12]. In the present study, a tumor-associated increase in sIL-2R was observed in a slightly high incidence because the majority of patients treated in our institute were in non-CR at the time of transplantation; therefore, data from a slightly higher proportion (20 %) of patients were excluded.

In the absence of GVHD, the median serum sIL-2R was slightly increased after transplantation, peaked on day 11 (the peak level was 740 U/ml), and thereafter decreased to as low as between 290 and 450 U/ml (Fig. 1). On the other hand, in the presence of GVHD, the median serum sIL-2R increased after transplantation, peaked in a median of 11 days (the peak level was 1,663 U/ml), and thereafter decreased to low levels of <600 U/ml (Fig. 2). Compared

with the previous studies [14, 16], in which sIL-2R levels peaked 2–3 weeks after transplantation with the peak level of 3,000–5,000 U/ml, sIL-2R in the present study reached the peak level slightly earlier, but the peak levels were lower. The use of ATG-containing RIC regimen and the incorporation of glucocorticoids into the GVHD prophylaxis are considered to contribute to the decrease in the peak level of sIL-2R, which is probably the main reason for a low incidence of severe GVHD observed in our regimen for HLA-haploidentical RIST [5]. Miyamoto et al. [14], in the study of allogeneic SCT using myeloablative conditioning, reported that sIL-2R in patients with GVHD started to increase on day 3, and that the elevation of sIL-2R on day 3 predicted the occurrence of acute GVHD. In the present study, sIL-2R in patients with GVHD started to increase on day 7, as shown in Fig. 2. This discrepancy may be explained by the use of RIC in this study, which induces mixed chimerism status between donor and recipient in the early transplant period, retarding the start of GVH reaction.

The previous studies of sIL-2R only showed that sIL-2R peaked on weeks 2 and 3, or that the peak level of sIL-2R was associated with the severity of GVHD [14, 16]. From the analysis of the onset of GVHD, GVHD was found to occur in 4 different phases of sIL-2R curve: GVHD occurred (1) at an increasing phase or at the peak level of sIL-2R after transplantation (Fig. 3a), (2) at a decreasing phase of sIL-2R (still at a high level) over the peak of sIL-2R (Fig. 3b), (3) after returning to the background level of sIL-2R, which passed through the high levels after transplantation (Fig. 3c), and (4) at a time point slightly increased from the background level of sIL-2R after day 30 (Fig. 3d). Although the prophylactic use of glucocorticoids is considered to contribute to the reduction in sIL-2R levels, as described above, there was no difference among 4 patterns of patients with GVHD in the administration schedule of steroids until the onset of GVHD. The occurrence of GVHD in 4 different phases of sIL-2R curve of

GVHD is not limited to HLA-haploidentical RIST, but observed also in other types of allogeneic SCT, including related HLA- matched, unrelated bone marrow, and umbilical cord blood SCT (data not shown). These results show that GVHD occurs at any time point on the sIL-2R curve, indicating that sIL-2R is not a suitable marker for real-time monitoring of the development of GVHD. Host organ-associated factors [29–31], other than donor T cell activation, must be also associated with the ultimate development of GVHD.

In fact, while sIL-2R peaked at a median of 11 days in patients developing GVHD, GVHD occurred at a median of 28 days. This time lag between the peak level of sIL-2R and the onset of GVHD may be explained as follows. According to the pathophysiology of GVHD that Ferrara et al. [32] proposed, donor T cell activation precedes a series of the subsequent various immunological reactions leading to the development of GVHD. In addition, GVHD may become clinically evident as the dose of immunosuppressive agents is tapered.

On the other hand, the fact that the majority of patients developing GVHD showed a high level of sIL-2R early in their transplant course indicates that sIL-2R levels in the early transplant phase could be a predictor of severe GVHD. In a univariate analysis, day 7 sIL-2R >810 U/ml, offspring, age >47 years, and first transplantation were significantly associated with the occurrence of severe GVHD; however, in a multivariate analysis, day 7 sIL-2R >810 U/ml was only a factor significantly associated with the occurrence of severe GVHD (Table 2). Thus, for the first time, we showed that sIL-2R in the early transplant phase was useful as a GVHD predictor.

The occurrence of events, such as VOD or sepsis, until day 7 may result in non-specific increase in sIL-2R on day 7, which make it unable to predict GVHD using day 7 sIL-2R; however, the predictability of GVHD by sIL-2R on day 7 is not basically affected by such pathological events that occur after day 7. Regarding non-specific increase in sIL-2R on day 7, whether we can detect or diagnose such events (inducing increase in sIL-2R) on day 7 is practically important because the GVHD predictor should not be applied if a given patient has such events and shows sIL-2R >810 U/ml. The diagnosis of VOD or severe infections is relatively easy, whereas accurate quantification of residual tumor burden that may lead to tumor-associated increase in sIL-2R may be sometimes difficult. In general, in case of tumor-associated increase, sIL-2R levels are usually high since before transplantation or during conditioning, and tend to gradually or rapidly decrease after transplantation in this early transplant period, whereas, in GVHD-associated increase, sIL-2R levels are increasing at day 7 in most cases, as shown in Fig. 2. Therefore, when applied to patients undergoing allogeneic SCT in CR status, sIL-2R

will be more useful as a GVHD predictor. In addition, even if such a non-specific increase blunts the usefulness of sIL-2R as GVHD predictor, when sIL-2R levels are <810 U/ml on day 7, the incidence of GVHD is only 6.5 %, as shown in Fig. 4b, indicating that patients with such low sIL-2R levels have an extremely low risk of developing severe GVHD even in HLA-haploidentical SCT.

In conclusion, in this HLA-haploidentical SCT using the combination of ATG-containing RIC regimen and the incorporation of glucocorticoid into GVHD prophylaxis, sIL-2R levels were mostly suppressed after transplantation compared with other studies on sIL-2R, which possibly lead to a low incidence of severe GVHD. sIL-2R on day 7 was useful as a predictor of GVHD in this transplant setting.

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Conflict of interest The authors declare no conflict of interest.

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