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High Level of Serum Soluble Interleukin-2 Receptor at Transplantation Predicts Poor Outcome of Allogeneic Stem Cell Transplantation for Adult T-cell Leukemia.

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Running title: SIL-2R at Allo-SCT for ATL

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Abstract

Prognosis for adult T-cell leukemia/lymphoma (ATL) is very poor, and only allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered to be a curative treatment for ATL. In this study, we retrospectively analyzed data for patients who had received allo-SCT for ATL in Hokkaido, the northernmost island of Japan, to determine prognostic factors. Fifty-six patients with a median age of 57 years received allo-SCT. Twenty-eight (50.0%) of the patients had acute type and 22 (46.4%) had lymphoma type. Twenty-three (41.1%) of the patients received allo-SCT in complete remission (CR), while the others were in non-CR. Seventeen (30.4%) of the patients received myeloablative conditioning, while the others received reduced-intensity conditioning. With a median follow-up period of 48 months (range, 17-134 months), 1-year overall survival (OS) and 5-year OS rates were 55.4% and 46.1%, respectively. The survival curve reached a plateau at 22 months after SCT. Male sex, high level of serum soluble interleukin-2 receptor (sIL-2R) at SCT and non-CR at SCT were determined to be significant risk factors for OS. High level of sIL-2R at SCT was a risk factor for poor OS in patients with non-CR at SCT by univariate analysis (P=0.02), and it remained significant after adjustment by sex [hazard ratio: 2.73 (95% confidence interval: 1.07-7.90)]. High level of sIL-2R at SCT was also determined to be a risk factor for disease progression (P=0.02). This region-wide study showed encouraging results for survival after allo-SCT for ATL and demonstrated for the first time that a high level of sIL-2R at SCT predicts worse SCT outcome.

Key words: adult T-cell leukemia; allogeneic stem cell transplantation; region-wide study; soluble interleukin-2 receptor; prognostic factor

Introduction

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell lymphoma caused by human T-cell lymphotropic virus type 1 (HTLV-1), and the prognosis of aggressive subtypes (acute type and lymphoma type) of ATL is very poor [1]. Although only allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered to be a curative treatment for aggressive subtypes of ATL [2], less than 40% of patients who have received allo-SCT could be cured [3,4,5]. We previously reported excellent outcomes for ATL patients who received allo-SCT from two institutions in Hokkaido the northernmost island of Japan [6], and overall survival (OS) rate in that study was 73.3 % at 3 years after allo-SCT. We therefore conducted a region-wide retrospective study in this area to determine prognostic factors for patients with ATL who received allo-SCT.

Patients and methods

Collection of data

Clinical data for 56 patients who received allo-SCT for ATL between January 2000 and March 2012 were collected from all SCT centers in Hokkaido, Japan, and the patients included all of the patients with ATL who received allo-SCT in this area. This study was conducted with the approval of the institutional review board of Hokkaido University Hospital. Conditioning regimens and other procedures of SCT were performed according to the decision of the clinicians at each center.

Definitions

Shimoyama's classification was used for the definition of ATL subtypes [7]. Neutrophil engraftment and platelet engraftment were defined as the first of 3 days with absolute neutrophil count $>0.5\times10^9$/L and the first of 7 days with an untransfused platelet count $>50\times10^9$/L, respectively. The Hematopoietic Cell Transplant Co-morbidity Index was scored by the criteria previously described [8]. Acute graft-versus-host disease (AGVHD) and chronic GVHD (CGVHD) were graded by standard criteria [9,10]. Transplant-related mortality (TRM) was defined as any death other than death from ATL. OS was calculated from the day of SCT until death or last follow-up. Progression of ATL was defined as relapse after remission, development of new lesions, or increase in measurable disease or in the number of circulating leukemic cells by 25% or more. [11]. Progression-free survival (PFS) was defined as survival without progression of ATL.

Endpoint and statistical analysis

The primary endpoint of this study was OS rate of the patients. Descriptive statistical analysis was performed using the chi-square test or Fisher's exact test as appropriate for categorical variables and using the 2-sided Wilcoxon rank sum test for continuous variables. The probabilities of OS and PFS were estimated using the Kaplan-Meier method. Disease progression rates and TRM rates were estimated using cumulative incidence analysis and considered as competing risks, and Gray's test was used for group comparison of cumulative incidence. The effects of various patient and disease categorical variables on survival probabilities were examined using the log-rank test, and the following variables were included in subgroup analyses: age of the patients, sex of the patients, levels of sIL-2R at diagnosis and SCT, disease status at SCT, disease subtypes, months from diagnosis to SCT, levels of LDH at diagnosis and at SCT, donor, stem cell source, intensity of the conditioning regimen, GVHD prophylaxis and chronic GVHD. All *P*-values were two-sided and a *P*-value of 0.05 was used as the cutoff for statistical significance. Multivariate analysis for OS was performed using the Cox proportional-hazards regression model.

Results

Patients and Transplantation Characteristics

Patients and SCT characteristics are summarized in Table 1. The median age of the patients was 57 years, and the half of the patients were male. Twenty-eight (50.0%) of the patients had acute type and 22 (46.4%) of the patients had lymphoma type. HTLV-1 serostatus of donors were available in 47 patients, and only 2 (4.3%) of the donors were positive for HTLV-1. After induction chemotherapies that were mainly CHOP or VCAP-AMP-VECP regimens [12], twenty-three (41.1%) of the patients received allo-SCT in complete remission (CR) and 33 (58.9%) of the patients received allo-SCT in non-CR. Nineteen patients had high level of sIL-2R at SCT. Among the patients with high level of sIL-2R at SCT, only one patient was in CR at SCT and the other 18 patients were not in CR at SCT. There was a correlation between disease status at SCT and sIL-2R at SCT [median, 824 U/ml (range, 351-2530) in CR patients versus a median of 2325 U/ml (range, 435-37384 U/ml) in non-CR patients, *P*=0.02]. Seventeen (30.4%) of the patients received myeloablative conditioning, which consisted of high-dose cyclophosphamide and total body irradiation (TBI) with or without VP-16, and 39 (69.6%) of the patients received reduced-intensity conditioning

(RIC), which consisted of fludarabine with either busulfan or melphalan ±□low-dose TBI of 2-4 Gray.

Transplantation Outcomes

Engraftment and GVHD

Except for three patients who died before engraftment, 53 (94.6%) of the patients achieved neutrophil engraftment at a median day of 16 (range, 9-31 days). Platelet engraftment could be assessed in 52 patients, and 40 (76.9%) of the patients achieved platelet engraftment at a median day of 27 (range, 14-415 days). All patients who achieved neutrophil engraftment were assessed for AGVHD. Overall AGVHD, grade II-IV AGVHD, and grade III-IV AGVHD occurred in 40 (75.5%), 31 (58.5%), and 8 (15.1%) of the evaluable patients, respectively. The median onset day of AGVHD was 29 (range, 8-101 days). CGVHD was assessed in 43 patients who survived beyond day 100 after SCT. CGVHD occurred in 24 (55.8%) of the evaluable patients at a median onset day of 168 (range, 69-495 days), and extensive CGVHD occurred in 16 patients (37.2%).

Disease progression and TRM

Cumulative incidences of disease progression and TRM are shown in Figure 1. Fourteen (25.0%) of the patients showed disease progression at a median day of 74 after SCT (range, 12-273 days). Twelve patients with disease progression after SCT died of ATL. One of the other two patients with disease progression died of a transplant-related complication in remission and the other is alive in remission. The median day from disease progression to death was 92 (range, 32-399 days). Eighteen (32.1%) of the patients died of TRM at a median day of 148 (range, 12-2143 days). The causes of TRM included infection (n=6), AGVHD (n=4), veno-occulusive disease (n=2), CGVHD (n=2), thrombotic microangiopathy (n=1), cerebral infarction (n=1), chronic renal failure (n=1) and suicide (n=1). Univariate analysis showed that high level of serum soluble interleukin-2 receptor (sIL-2R) at SCT (>=2,000 U/ml) was significantly associated with disease progression (*P*=0.02), whereas male sex tended to be its risk (*P*=0.06). Non-CR at SCT was marginally significant for TRM (*P*=0.07).

Survival

The median follow-up period for survivors was 48 months (range, 17-134 months). One-year OS and 5-year OS rates were 55.4% and 46.1%, respectively. One-year

PFS and 5-year PFS were 51.1% and 45.6%, respectively. The survival curve reached a plateau at 22 months after SCT (Figure 2). Male sex (P=0.002), high level of sIL-2R both at diagnosis (>= 10,000 U/ml, P=0.02) and at SCT (>= 2,000 U/ml, P<0.001, Figure 3) and non-CR at SCT (P<0.001) were identified as significant risk factors for OS by univariate analyses. Disease subtypes and other factors were not risk factors for OS. We tested several cutoff points of sIL-2R for determining the most significant cutoff points for survival and found that the cutoff levels of 10,000 at diagnosis and 2,000 at SCT were most significantly associated with survival. Worse survival for male patients and patients in non-CR at SCT were confirmed by using multivariate analysis [hazard ratio of 3.40 (95% confidence interval: 1.44-8.02) for male patients and hazard ratio of 4.45 (95% confidence interval: 1.82-10.87) for non-CR patients]. The levels of sIL-2R at SCT were not included in multivariate analysis which included disease status, because the levels of sIL-2R at SCT were correlated with the disease status at SCT. In the patients in non-CR at SCT, the level of sIL-2R was significantly associated with OS (P=0.02, Figure 3B) regardless of disease subtype (P=0.02 for acute type and P=0.01 for lymphoma type, Figure 3C and 3D), and a high level of sIL-2R at SCT was determined to be a prognostic factor when it was used as an alternative variable to disease status at SCT in multivariate analysis [hazard ratio: 5.95 (95% confidence interval: 2.14-17.9)]. We performed multivariate analysis for non-CR patients using level of sIL-2R at SCT and sex of the patients as variables, and a high level of sIL-2R at SCT remained significant even after adjustment by sex of the patients [(hazard ratio: 2.73 (95% confidence interval: 1.07-7.90)]. The other variables were not confirmed to be significant by multivariate analysis.

Discussion

A previous retrospective study on allo-SCT for ATL in Japan [4] demonstrated 3-year OS of 36.0%, and a prospective study on allo-SCT using an RIC regimen showed 5-year OS of 34.0% [5]. The 5-year OS rate in the present study was 46.1% and the survival curve reached a plateau at 22 months after SCT. Although the results of the present study are worse than the results we previously reported [6], the difference in results is probably due to the selection bias of the patients or might simply reflect a multi-institutional study versus a selected institutional study.

In previous nationwide studies on ATL in Japan, advanced age, male sex, non-CR at SCT, poor performance status, SCT from unrelated donors or SCT using cord blood

were associated with poor survival after allo-SCT [3,4]. Multivariate analysis in this study confirmed that male patients and patients in non-CR at SCT were at risk for poor OS. There was no difference in characteristics of the patients and SCT between male and female patients (data not shown), and incidence of disease progression after allo-SCT was increased in male patients with marginal significance (P=0.06). There has been no report showing worse survival in male patients after chemotherapy for ATL. It is thus tempting to speculate that this difference is due to the difference in allogeneic immune responses between male and female recipients after allo-SCT.

Although a high level of sIL-2R has been reported to reflect disease progression of ATL [13,14], the clinical significance of sIL-2R for patients who received allo-SCT remains to be determined. In this study, a high level of sIL-2R at SCT was identified as a significant risk factor for OS by univariate analysis. We did not include sIL-2R at SCT in multivariate analysis because the level of sIL-2R at SCT was stringently correlated with disease status at SCT. However, high level of sIL-2R at SCT was determined to be a prognostic factor when it was used as an alternative variable to disease status at SCT in multivariate analysis, and high level of sIL-2R at SCT was a risk factor for OS in patients with non-CR at SCT regardless of the sex of the patient. Only sIL-2R at SCT was identified as a risk factor for disease progression. Thus, sIL-2R at SCT could be a useful surrogate marker for disease status. Although transplant outcomes in non-CR patients were inferior to those in CR patients as has been previously reported [3,4], the level of sIL-2R at SCT was significantly associated with OS in non-CR patients, indicating that sIL-2R level at SCT could be used as a decision-making parameter for selection of allo-SCT for patients in non-CR. Additional chemotherapies or a novel anti-CCR4 antibody therapy [15] prior to SCT for patients who have high level of sIL-2R may improve the outcome of allo-SCT, although this hypothesis needs to be tested in a prospective study.

In conclusion, although the current study has several limitations that should be considered when reviewing the findings, including the use of a retrospective design and a small number of patients, it showed encouraging results of allo-SCT for ATL in both CR and non-CR with low level of sIL-2R at SCT.

Financial disclosure: The authors have declared no conflicts of interests.

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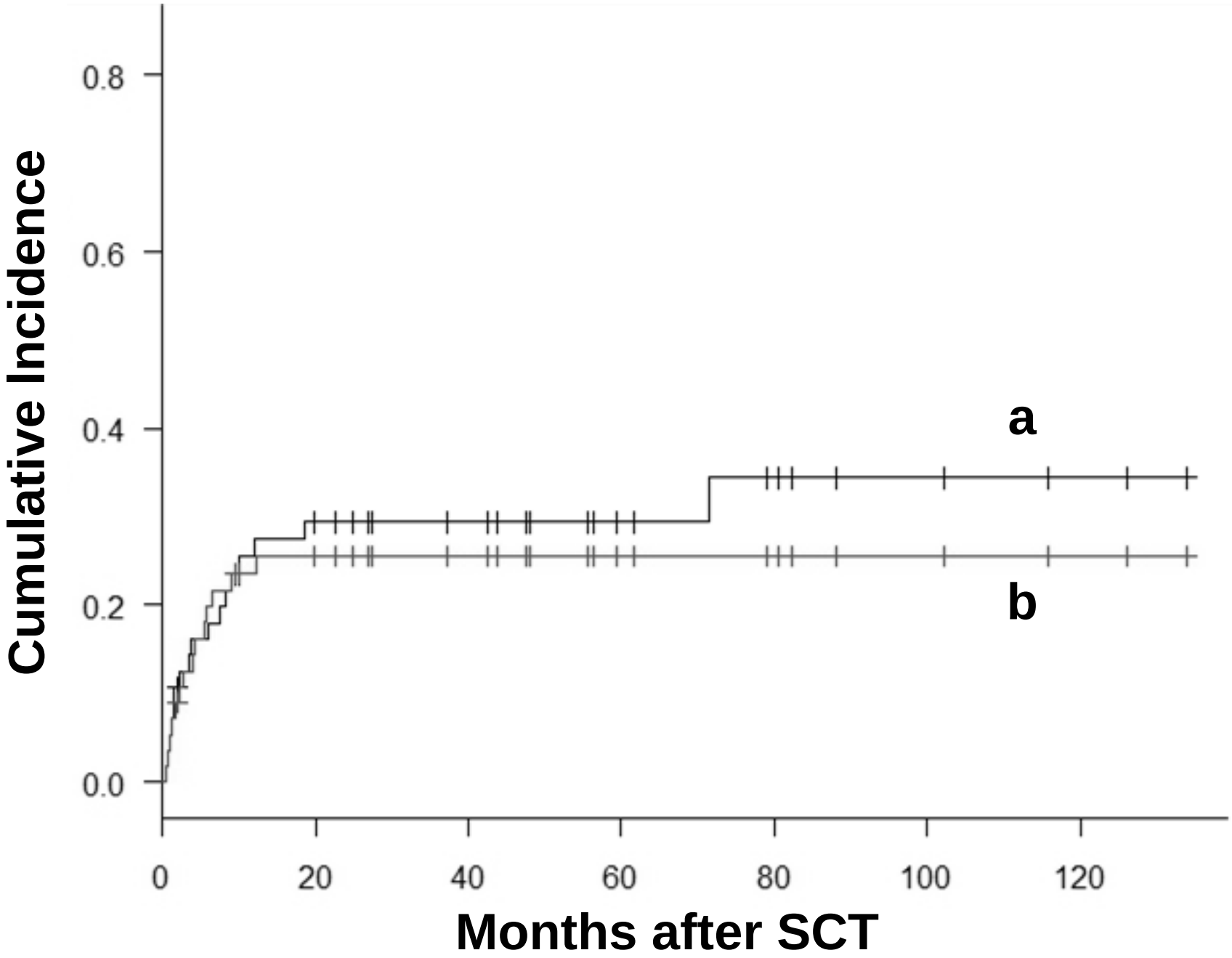
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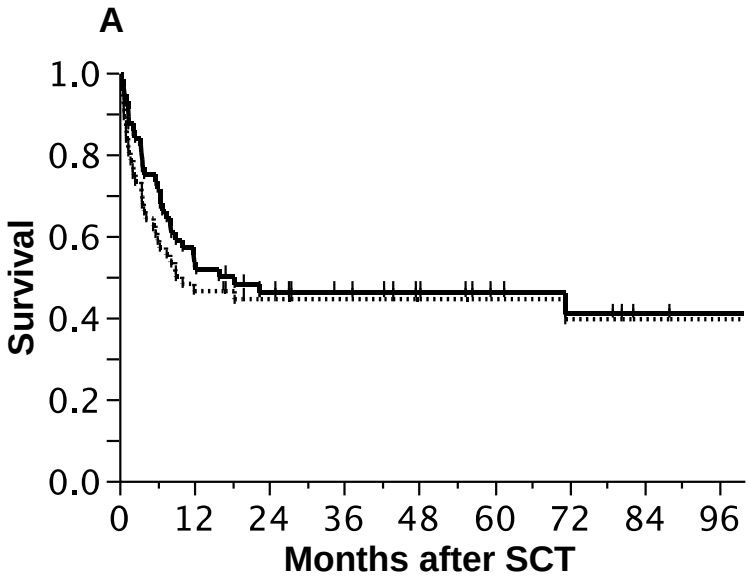
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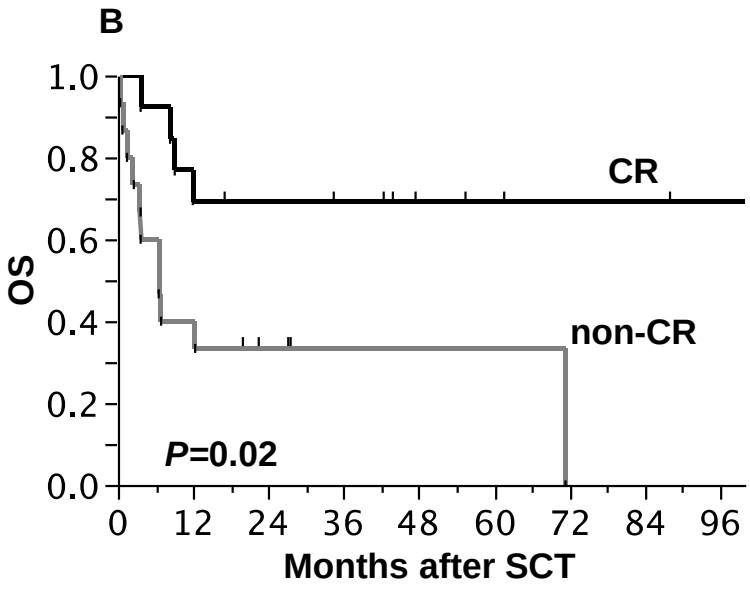
Figure 1. Cumulative incidence analyses of disease progression and TRM after SCT.
Cumulative incidences of (a) TRM and (b) disease progression after allo-SCT. Disease progression and TRM were considered as competing risks.

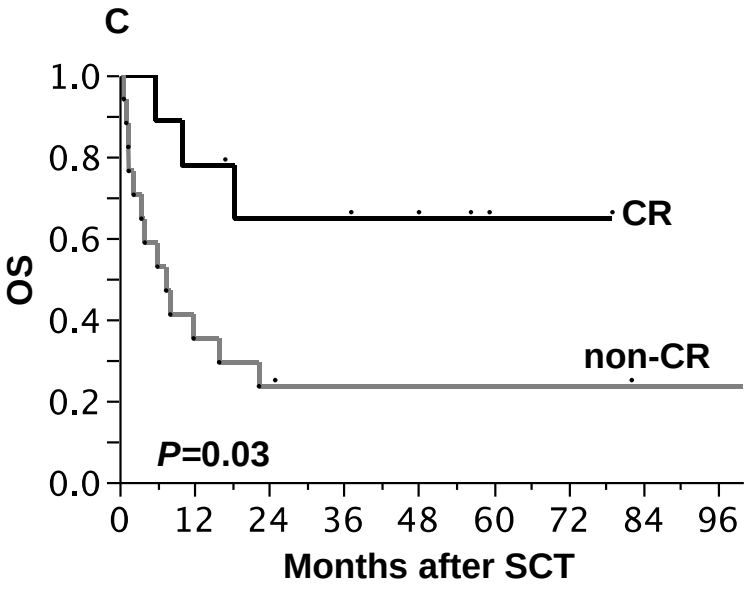
Figure 2. Survival after SCT
2A. Overall survival and progression-free survival after SCT in all patients. The solid line shows the overall survival curve and the dotted line shows the progression-free survival curve.
2B. Overall survival in patients with acute type according to disease status at SCT.
2C. Overall survival in patients with lymphoma type according to disease status at SCT.
2D. Progression-free survival in patients with acute type according to disease status at SCT.
2E. Progression-free survival in patients with lymphoma type according to disease status at SCT.

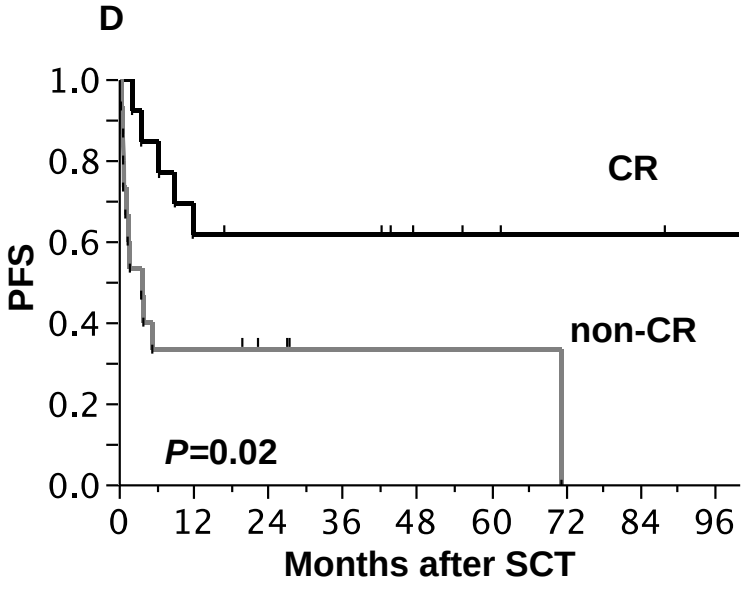
Figure 3. Overall survival according to level of serum sIL-2R at SCT.
High level of serum sIL-2R at SCT was defined as 2,000 U/mL or higher.
3A. In all patients.
3B. In patients who were in non-CR at SCT.
3C. In patients with acute type of ATL.
3D. In patients with lymphoma type of ATL.

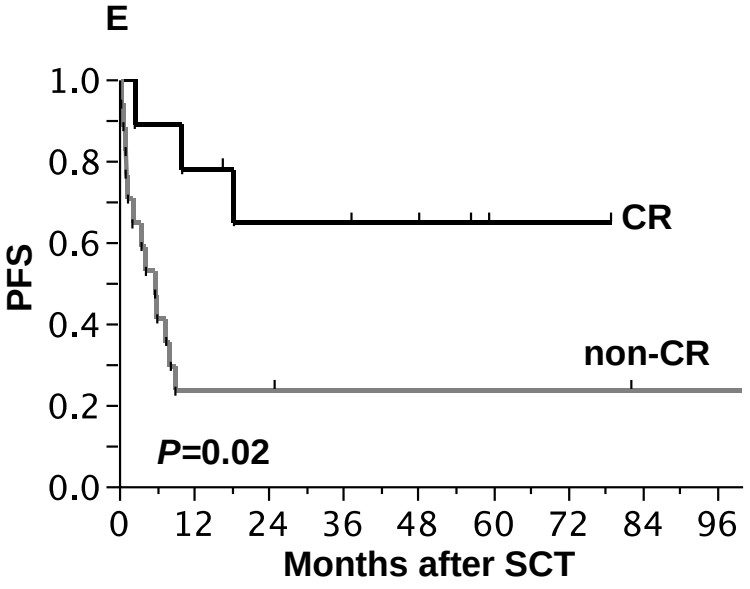

Cumulative Incidence
0.8
0.6
0.4
0.2
0.0
a
b
0
20
40
60
80
100
120
Months after SCT


A
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
Months after SCT


B
OS
CR
non-CR
P=0.02
Months after SCT


C
OS
CR
non-CR
P=0.03
Months after SCT


D
PFS
CR
non-CR
P=0.02
Months after SCT


E
PFS
CR
non-CR
P=0.02
Months after SCT

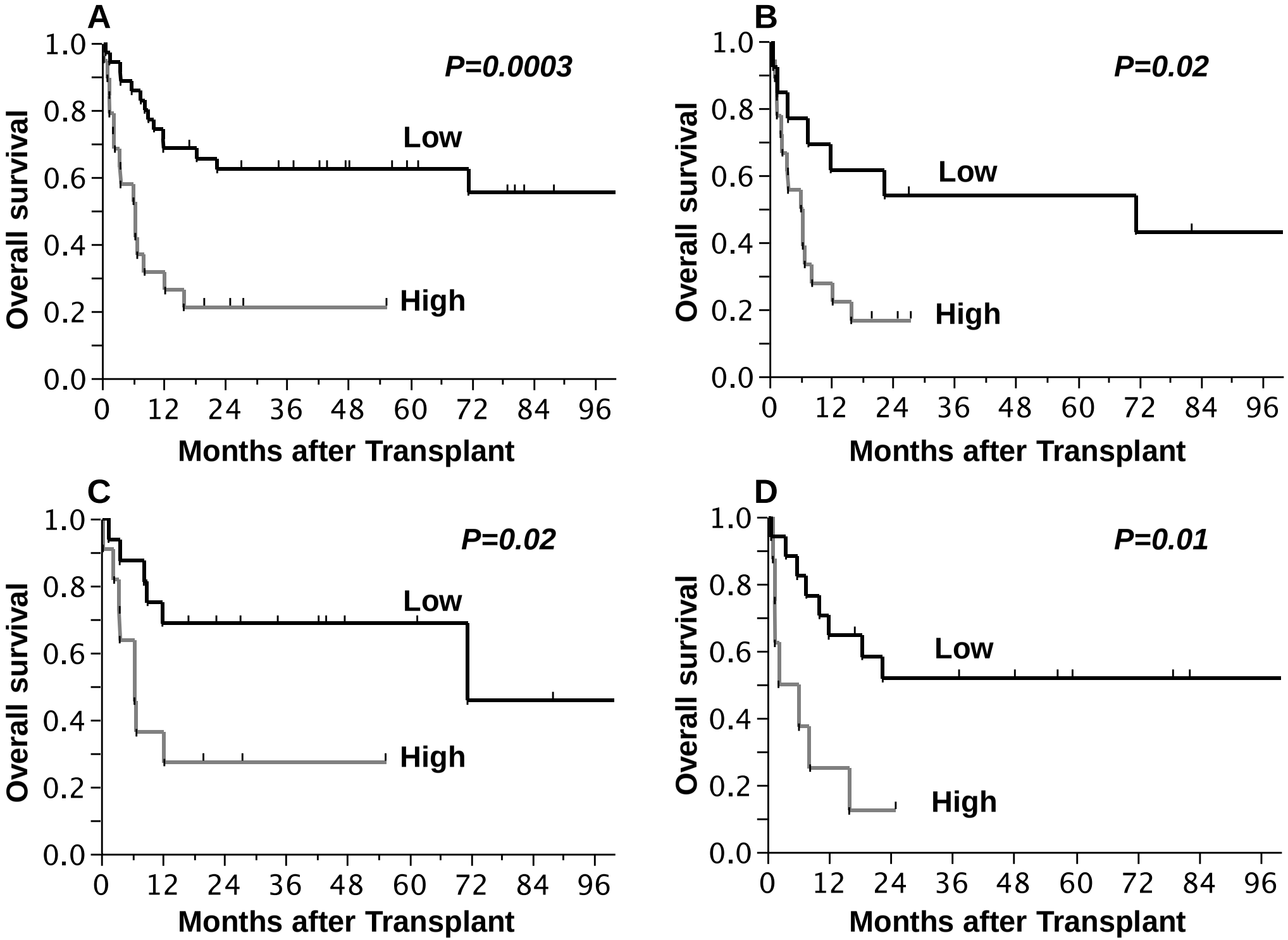

A
P=0.0003
Low
High
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
Months after Transplant
B
P=0.02
Low
High
Overall survival
Months after Transplant
C
P=0.02
Low
High
Overall survival
Months after Transplant
D
P=0.01
Low
High
Overall survival
Months after Transplant

Table 1. Patient and transplant characteristics (n=56)

		n	% or range
Age, years	Median (range)	57	37-69
	Age >=60	37	66.1%
Sex	Male	28	50.0%
	Female	28	50.0%
Disease subtype	Acute	28	50.0%
	Lymphoma	26	46.4%
	Chronic	1	1.8%
	Smoldering	1	1.8%
WBC count at diagnosis (/μL)	median (range)	10900	2500-331000
LDH level at diagnosis (IU/L)	median (range)	352	144-1736
sIL-2R level at diagnosis (U/ml)	median (range)	11153	998-116100
Months from diagnosis to SCT	median (range)	196	60-3690
	<= 3 months	7	12.5%
	3-6 months	17	30.4%
	> 6 months	32	57.1%
Disease status at SCT	CR	23	41.1%
	Non-CR	33	58.9%
	PR	19	33.9%
	REF	10	17.9%
	REL	4	7.1%
LDH level at diagnosis (IU/L)	median (range)	218	150-766
sIL-2R level at SCT (U/ml)	median (range)	1219	351-37387
HCT-CI score*	0	22	41.5%
	1	11	20.8%
	2	9	17.0%
	3	6	11.3%
	4-7	5	9.4%
Donor	MRD	20	35.7%
	MUD	22	39.3%
	MMD	14	25.0%
Sex disparity	Match	32	57.1%
	Mismatch	24	42.9%
	Male to female	15	26.8%
	Female to male	9	16.1%
Stem cell source	BM	39	69.6%
	PBSC	11	19.6%
	CB	6	10.7%
Conditioning regimen	MAC	17	30.4%
	RIC	39	69.6%
TBI	Yes	40	71.4%
	No	16	28.6%
GVHD prophylaxis	CSP+MTX	22	39.3%
	TK+MTX	25	44.6%
	CSP alone or TK alone	7	12.5%

Abbreviations; WBC indicates white blood cell; sIL-2R, soluble interleukin-2 receptor; SCT, stem cell transplantation; CR, complete remission; PR, partial remission; REF, primary refratcory; REL, relapse; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMD HLA-mismatched donor; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; HCT-CI, The Hematopoietic cell transplant co-morbidity index; TBI, Total body irradiation; GVHD, graft-versus-host disease; CSP, cyclosporin A;
*HCT-CI score was not available in 3 patients.
†PBSC were from an MRD in all cases because donation of PBSC from unrelated donors is not permitted in Japan until 2010.