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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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 prognoses of aggressive subtypes (acute type and lymphoma type) of ATL are very poor [1]. Although only allogeneic hematopoietic stem cell transplantation (allo-SCT) has been considered to be a curative treatment for ATL [2], less than 40% of patients who have received allo-SCT have been cured [3-5]. We previously reported excellent outcomes for ATL patients who received allo-SCT from 2 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

Clinical data for 56 patients who received allo-SCT for ATL between January 2000 and March 2012 were collected from all stem cell transplantation (SCT) centers in Hokkaido, Japan. The patients included all 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 > 5 x 10^9/L and the first of 7 days with an untransfused platelet count > 50 x 10^9/L, respectively. The hematopoietic cell transplant comorbidity index was scored by the criteria previously described [8]. Acute graft-versus-host disease (ACGVHD) and chronic GVHD (CCGVHD) were graded by standard criteria [9,10]. Transplantation-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...
circularizing 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 serum soluble interleukin-2 receptor (sIL-2R) at diagnosis and SCT, disease status at SCT, disease subtypes, months from diagnosis to SCT, levels of lactate dehydrogenase (LDH) at diagnosis and at SCT, donor, stem cell source, intensity of the conditioning regimen, GVHD prophylaxis, and CGVHD. All P values were 2-sided and a P value of .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 one half of the patients were male. Twenty-eight (50.0%) patients had acute type and 22 (46.4%) patients had lymphoma type. HTLV-1 serostatus of donors were available in 47 patients, and only 2 (4.3%) donors were positive for HTLV-1. After induction chemotherapies that were mainly CHOP or VCAP-AMP-VECP regimen [12], 23 (41.1%) patients received allo-SCT in complete remission (CR) and 33 (58.9%) 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 1 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, 435 to 37,384 U/mL) in non-CR patients; P = .02. Seventeen (30.4%) patients received myeloablative conditioning, which consisted of high-dose cyclophosphamide and total body irradiation with or without VP-16, and 39 (69.6%) patients received reduced-intensity conditioning, which consisted of fludarabine with either busulfan or melphalan ± low-dose total body irradiation of 2 to 4 Gray.

**Transplantation Outcomes**

**Engraftment and GVHD**

Except for 3 patients who died before engraftment, 53 (94.6%) patients achieved neutrophil engraftment at a median of 16 (range, 9 to 31) days. Platelet engraftment could be assessed in 52 patients, and 40 (76.9%) patients achieved platelet engraftment at a median of 27 (range, 14 to 415) days. All patients who achieved neutrophil engraftment were assessed for AGVHD. Overall AGVHD, grade II to IV AGVHD, and grade III to IV AGVHD occurred in 40 (75.5%), 31 (58.5%), and 8 (15.1%) of the evaluable patients, respectively. The median onset of AGVHD was 29 (range, 8 to 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 to 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%) patients showed disease progression at a median of 74 (range, 12 to 273) days after SCT. Twelve patients with disease progression after SCT died of ATL. One of the other 2 patients with disease progression died of a transplantation-related complication in
remission and the other is alive in remission. The median time from disease progression to death was 92 (range, 32 to 399) days. Eighteen (32.1%) patients died of TRM at a median of 148 (range, 12 to 2143) days. The causes of TRM included infection (n = 6), AGVHD (n = 4), veno-occlusive 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 a high level of sIL-2R at SCT (> 2000 U/mL) was significantly associated with disease progression (P = .02), whereas male sex tended to be associated with increased risk (P = .06). Non-CR at SCT was marginally significant for TRM (P = .07).

Survival

The median follow-up period for survivors was 48 (range, 17 to 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 51.4% and 45.6%, respectively. The survival curve reached a plateau at 22 months after SCT (Figure 2). Male sex (P = .002), a high level of sIL-2R both at diagnosis (> 10,000 U/mL, 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. (A) 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. (B) Overall survival in patients with acute type according to disease status at SCT. (C) Overall survival in patients with lymphoma type according to disease status at SCT. (D) Progression-free survival in patients with acute type according to disease status at SCT. (E) Progression-free survival in patients with lymphoma type according to disease status at SCT.
$P = .02$) and at SCT ($\geq 2000$ U/mL, $P < .001$) (Figure 3), and non-CR at SCT ($P < .001$) 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 2000 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, 3.40 [95% confidence interval (CI), 1.44 to 8.02] for male patients; hazard ratio, 4.45 [95% CI, 1.82 to 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 patients in non-CR at SCT, the level of sIL-2R was significantly associated with OS ($P = .02$) (Figure 3B), regardless of disease subtype ($P = .02$ for acute type and $P = .01$ for lymphoma type) (Figure 3C,D), 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% CI, 2.14 to 17.9]). We performed multivariate analysis for non-CR patients using a 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% CI, 1.07 to 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 a reduced-intensity conditioning 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 were no differences in characteristics of the patients and SCT between male and female patients (data not shown), and the incidence of disease progression after allo-SCT was increased in male patients with marginal significance ($P = .06$). 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 the multivariate analysis because the level of sIL-2R at SCT was stringently correlated with disease status at SCT. However, 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, and a 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 transplantation 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

**Figure 3.** Overall survival according to level of serum sIL-2R at SCT. A high level of serum sIL-2R at SCT was defined as 2000 U/mL or higher. (A) All patients. (B) Patients who were in non-CR at SCT. (C) Patients with acute type of ATL. (D) Patients with lymphoma type of ATL.
novel anti-CCR4 antibody therapy [15] before 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 patients with ATL in both CR and non-CR with low levels of sIL-2R at SCT.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES


