Outcomes of patients with relapsed aggressive adult T-cell leukemia-lymphoma: clinical effectiveness of anti-CCR4 antibody and allogeneic hematopoietic stem cell transplantation

Adult T-cell leukemia-lymphoma (ATL) is a distinct type of peripheral T-cell lymphoma (PTCL) caused by human T-cell lymphotropic virus type I with poor outcomes.[1] To improve these results, up-front allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered in transplant-eligible patients.[1,2] Once disease progression occurs in the absence of allo-HSCT, we would expect the prognosis to be dismal, as in other types of PTCL.[3-5] However, no large studies have previously assessed the prognosis of relapsed ATL. Thus, the clinical impact of treatment choices such as initial salvage chemotherapy and subsequent allo-HSCT is unclear.

Recently, mogamulizumab, an anti-CCR4 antibody, was approved in Japan.[6,7] The high response rate with anti-CCR4 antibody is promising in this setting. However, there are no available data comparing its efficacy with other chemotherapeutic regimens in patients with relapsed ATL. Thus, we retrospectively analyzed the clinical outcomes of patients with relapsed ATL using a database of 723 patients with relapsed ATL as previously reported.[1,8] That study was approved by the institutional review board of the National Cancer Center in Tokyo, Japan (No. 2014-179). In our current study, we included only patients who suffered from relapsed ATL without prior allo-HSCT.

The probability of overall survival (OS) was calculated using the Kaplan-Meier method from the introduction of first salvage chemotherapy to the date of death. A Cox proportional hazards regression model was used to analyze OS. Variables included in the analysis were sex, age (60 years or younger *vs.* 61 years or older), modified ATL-prognostic index (PI, low *vs.* intermediate *vs.* high), chemosensitivity to first-line chemotherapy (sensitive *vs.* refractory), year of diagnosis (2000 to 2006 *vs.* 2007 to 2013), and use of anti-CCR4 antibody as first salvage chemotherapy (vs. other therapeutic drugs). Modified ATL-PI was defined as previously reported.[1] Patients with complete remission (CR) or partial remission (PR) were considered chemosensitive, and those with stable disease (SD) or progressive disease (PD) were considered chemorefractory. Allo-HSCT was included as a time-dependent variable. Factors that were associated with a two-sided *P* value of <0.10 in the univariate analysis were included in a multivariate analysis. We used a backward stepwise selection algorithm and retained only statistically significant variables in the final model. The statistical analyses were carried out using the EZR software package (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0).[9]

A total of 723 patients with relapsed ATL were included, as shown in Table 1. The median age was 61 years (range, 25-70 years), and the median follow up of surviving patients after the introduction of salvage chemotherapy was 537.5 days. The median OS after salvage chemotherapy was 125 days (range, 115-140), and the 1-year OS rate was 17.8% (95% CI, 15.0-20.8), as shown in Figure 1A. Out of 723 patients, 132 (18.3%) subsequently received allo-HSCT. The probabilities of 1-year OS were 37.9% (95% CI, 29.6-46.1) in transplanted patients and 13.1% (95% CI, 10.4-16.0) in non-transplanted patients, as shown in Figure 1B. Stratified according to the modified ATL prognostic index (ATL-PI) at diagnosis, the probabilities of 1-year OS were 25.4% (95% CI, 19.1-32.1) in the low-risk group, 18.0% (95% CI, 14.4-21.9) in the intermediate-risk group, and 6.2% (95% CI, 2.7-11.6) in the high-risk group, as shown in Figure 1C. Stratified according to the modified ATL-PI at diagnosis and subsequent allo-HSCT, the probabilities of 1-year OS were as follows: in the low-risk group, 21.5% (95% CI, 14.9-28.9) in non-transplanted patients and 38.5% (95% CI, 23.5-53.2) in transplanted patients (Figure 1D); in the intermediate-risk group, 12.3% (95% CI, 9.0-16.2) in non-transplanted patients and 42.7% (95% CI, 31.4-53.5) in transplanted patients (Figure 1E); and in the high-risk group, 4.2% (95% CI, 1.4-9.6) in non-transplanted patients and 16.7% (95% CI, 4.1-36.5) in transplanted patients (Figure 1F).

Out of 638 evaluable patients, the overall response rate (ORR) to salvage therapy was 24.8% with a CR rate of 5.8%. Various salvage treatment regimens were used, as shown in *Online Supplementary Table S1*. The response rate of anti-CCR4 antibody (ORR, 47.9%) was significantly higher than that of other drugs (ORR, 23.1% using other drugs; odds ratio 3.06, 95% CI 1.61–5.82, *P*<0.001). In terms of OS after the introduction of salvage therapy, the probability of OS in patients who received anti-CCR4 antibody (1-y OS 32.7%, 95% CI, 20.8–45.1) was significantly higher than that in those who did not receive anti-CCR4 antibody as the first salvage chemotherapy (1-y OS 16.5%, 95% CI, 13.7-19.5, *P*=0.012), as shown in Figure 2A. In multivariate analysis, age, modified ATL-PI, chemosensitivity to first-line chemotherapy, year of diagnosis, allo-HSCT, and use of anti-CCR4 antibody remained significant, as shown in *Online Supplementary Table S2*. In a subgroup analysis of non-transplanted patients (n = 591), the probability of 1-year OS in patients who received anti-CCR4 antibody as the first

Table 1. Patient characteristics (n=723).

Factor		N (%)
Total number of patients		723
Age at diagnosis		
Median (range)		61 (25-70)
Sex (%)	Female	315 (43.6)
	Male	408 (56.4)
ATL subtype	Acute	500 (69.2)
	Lymphoma	223 (30.8)
Modified ATL-PI at diagnosis	Low	177 (24.5)
	Intermediate	422 (58.4)
	High	124 (17.2)
Induction chemotherapy	mLSG15	332 (49.1)
	CHOP	254 (37.6)
	THP-COP	38 (5.6)
	Others	99 (13.7)
Chemosensitivity to induction chemotherapy	No	456 (64.6)
	Yes	250 (35.4)
Allogeneic transplant performed after relapse	No	591 (81.7)
	Yes	132 (18.3)

ATL: adult T-cell leukemia-lymphoma; ATL-PI: ATL-prognostic index; mLSG15: vincristine (VCR), cyclophosphamide (CY), doxorubicin (DOX) and prednisone (PSL), DOX, ranimustine (MCNU), and PSL-vindesine (VDS), etoposide (ETO), carboplatin (CBDCA), and PSL; CHOP: CY, DOX, VCR, and PSL; THP-COP: pirarubicin, CY, VCR, and PSL; EPOCH: ETO, PSL, VCR, CY, and DOX; mEPOCH: ETO, DOX, VCR, PSL, and CBDCA.[13]

salvage therapy (29.7%, 95% CI, 16.1-44.6) was significantly higher than in those who did not (11.9%, 95% CI, 9.3-14.9), as shown in Figure 2B (P=0.011).

We also performed a subgroup analysis of transplanted patients (n=132). In addition to 18 patients who received anti-CCR4 antibody as the first salvage chemotherapy, 6 patients subsequently received anti-CCR4 antibody before allo-HSCT and 1 patient received it as a part of the first-line chemotherapy. Thus, a total of 25 patients received anti-CCR4 antibody before allo-HSCT. Pretransplant disease status is shown in *Online Supplementary Table S3*. The median interval between the last anti-CCR4 antibody administration and allo-HSCT was 49 days in this cohort (range, 10–1077). The cumulative incidences of relapse after allo-HSCT at 1 year were 54.0% (95% CI, 30.6-72.6) in patients who

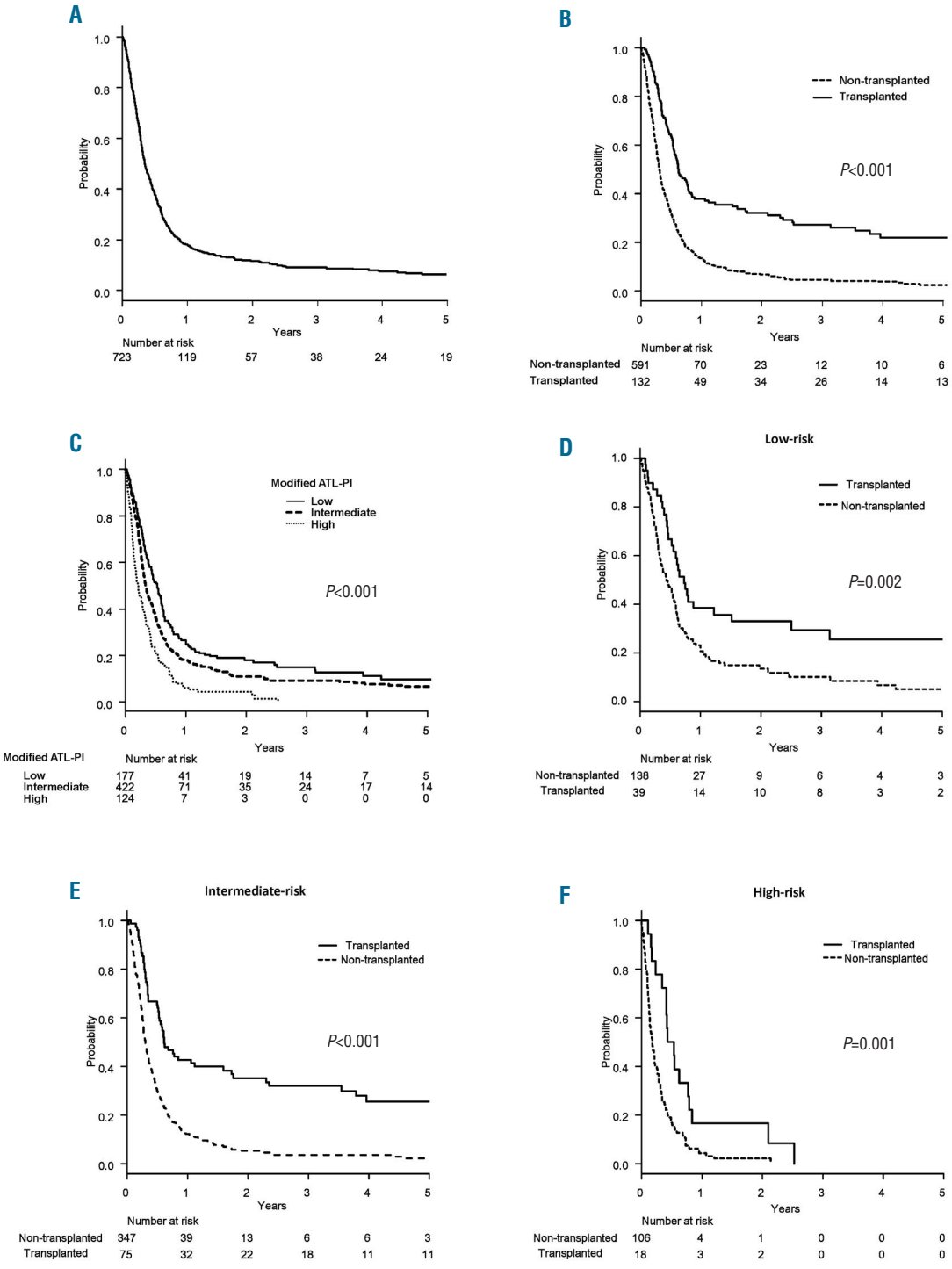

Figure 1. Overall survival rate after the introduction of salvage chemotherapy. Overall survival rate after the introduction of salvage chemotherapy in the entire cohort (A). Overall survival rate by transplantation status (B) and by modified ATL-PI (C). Overall survival rate by transplantation status in a subgroup analysis of patients in the low-risk group (D), in the intermediate-risk group (E), and in the high-risk group (F).

received anti-CCR4 antibody before allo-HSCT and 46.9% (95% CI, 37.1-56.0) in those who did not (Figure 2C). The cumulative incidences of non-relapse mortality after allo-HSCT at 1 year tended to be higher in patients who received anti-CCR4 antibody before allo-HSCT (40.0%, 95% CI, 20.6-58.7) than in those who did not (29.0%, 95% CI, 20.7-37.8), although there was no statistically significant difference (P=0.379, Figure 2D). The probabilities of OS after allo-HSCT at 1 year were 32.0% in patients who received anti-CCR4 antibody before allo-HSCT (95% CI, 15.2-50.2) and 33.6% in those who did not (95% CI, 24.9-42.6, Figure 2E). In evaluable patients with data on acute GvHD (n=127), grade 3 to 4 acute GvHD occurred in 6 (25.0%) patients who received anti-CCR4 antibody and in 19 (18.4%) patients who did not.

This study used a large database of aggressive ATL patients and demonstrated for the first time the very poor survival outcome of this population after relapse. The median OS after the first salvage chemotherapy was only 125 days, with a low response rate to salvage chemotherapy (ORR 24.8%). This indirectly emphasizes the importance of treatment strategies incorporating up-front allo-HSCT while ATL is under control with first-line chemotherapy. However, a significant proportion of patients did suffer from relapse or progressive disease before a planned up-front allo-HSCT. In this study, a

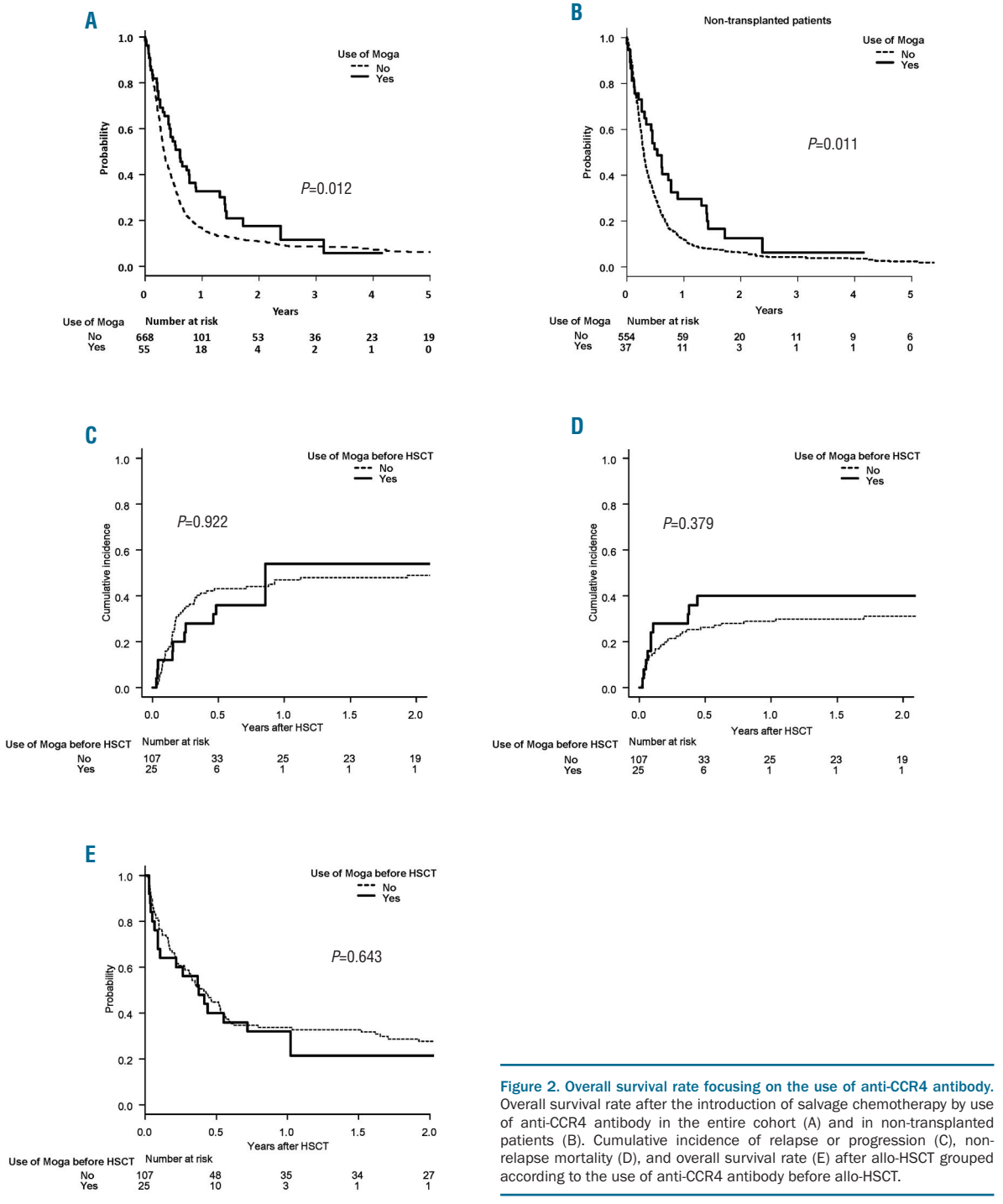

Figure 2. Overall survival rate focusing on the use of anti-CCR4 antibody. Overall survival rate after the introduction of salvage chemotherapy by use of anti-CCR4 antibody in the entire cohort (A) and in non-transplanted patients (B). Cumulative incidence of relapse or progression (C), non-relapse mortality (D), and overall survival rate (E) after allo-HSCT grouped according to the use of anti-CCR4 antibody before allo-HSCT.

large number of patients who underwent allo-HSCT after the first salvage chemotherapy achieved long-term survival. Therefore, allo-HSCT should be considered in transplant-eligible patients after relapse or progression.

There is no established salvage regimen in patients with relapsed ATL. In our study, anti-CCR4 antibody showed a promising response rate that was significantly higher than that of other regimens, suggesting that anti-CCR4 antibody is a valuable option for salvage chemotherapy, although a marginal transient improvement was observed. However, in transplant-eligible patients, there is a major concern that anti-CCR4 antibody might increase the risk of severe/refractory GvHD after allo-HSCT, and therefore the indication for anti-CCR4 antibody should be carefully determined.[8,10] In our current cohort, the cumulative incidence of NRM, and the risk of grade 3 to 4 acute GvHD were higher, though not significantly so, in patients who received anti-CCR4 antibody before allo-HSCT than in those who did not; this is consistent with our previous report.[8,11] The reason for the lack of statistical significance in these clinical outcomes is possibly the much smaller sample size of patients who received allo-HSCT following anti-CCR4 antibody in this cohort. However, the risk of severe acute GvHD does not completely preclude the possibility of administering anti-CCR4 antibody to transplant-eligible patients with relapsed ATL. Without appropriate control of ATL before allo-HSCT, the clinical outcome after allo-HSCT is unsatisfactory.[8,12] Therefore, anti-CCR4 antibody may still be an important option in transplant-eligible patients with uncontrolled ATL. When patients undergo allo-HSCT after treatment that includes anti-CCR4 antibody, the timing of HSCT and intensification of GvHD prophylaxis should be carefully determined.

In conclusion, our retrospective analysis clearly showed that the prognosis of patients with relapsed ATL was dismal, although some patients might be rescued by treatment strategies incorporating allo-HSCT. Anti-CCR4 antibody was demonstrated to be a valuable option in this setting. In the treatment of relapsed ATL patients, approaches that include anti-CCR4 antibody, novel agents, and allo-HSCT should be further explored in the future.

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