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ORIGINAL ARTICLE

Clinical impact of the CONUT score and mogamulizumab in adult T cell leukemia/lymphoma

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Abstract

Accurate risk assessment to determine the eligibility for allogeneic hematopoietic stem cell transplantation (allo-HCT) in patients with adult T cell leukemia (ATL) is necessary to improve survival outcomes. The controlling nutritional status (CONUT) score predicts prognosis in several tumors; however, the prognostic significance of the CONUT score in ATL remains unclear. The present study investigated the correlation between the CONUT score and the survival outcomes of transplant-eligible ATL patients. Mogamulizumab, a humanized monoclonal antibody against C-C chemokine receptor 4, was recently identified as a promising salvage chemotherapy agent for transplant-ineligible ATL patients. We therefore evaluated the efficacy of mogamulizumab in transplant-ineligible ATL patients. Patients diagnosed with aggressive ATL (acute lymphoma of unfavorable chronic type) between January 2008 and March 2017 at Saga University Hospital, Japan, were retrospectively enrolled. Of 54 patients, 25 were < 70 years of age and 14 received allo-HCT. The median overall survival (OS) and non-relapse mortality (NRM) rate at 1 year among patients receiving allo-HCT were 1685.5 days and 30% in those with a CONUT score 0–3 ($n = 10$) and 184.5 days and 100% in those with a score ≥ 4 ($n = 4$) ($p = 0.017$, OS; $p = 0.064$, NRM). Older patients who received mogamulizumab had a significantly longer OS ($n = 12$, median 432 days) than those who did not receive mogamulizumab ($n = 17$, median 199 days) ($p = 0.018$). The CONUT score was identified as a prognostic tool for transplant-eligible ATL patients, and mogamulizumab improved OS in transplant-ineligible ATL patients.

Keywords Adult T cell leukemia/lymphoma · The controlling nutritional status score · Allogenic stem cell transplantation · Mogamulizumab · Transplant-eligibility

Introduction

Adult T cell leukemia/lymphoma (ATL) is a mature T cell neoplasm caused by human T cell lymphotropic virus type I (HTLV-I) [1]. Patients with ATL have extremely poor survival outcomes despite intensive chemotherapy [2]. Although allogeneic hematopoietic stem cell transplantation (allo-HCT) is a curative treatment for patients with ATL [3, 4], the overall survival (OS) rate remains at 30–40% [3, 4] with a high rate of non-relapse mortality (NRM) [3, 4]. An accurate prediction

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of the risk of NRM in patients receiving allo-HCT is necessary to decrease the rate of NRM; furthermore, risk assessment methods to determine transplant eligibility in ATL patients remain to be defined [5–8].

Poor nutritional status is correlated with the response to chemotherapy and the severity of chemotherapy-related toxicity [9], and anorexia and cachexia are poor prognostic markers in several cancers [10]. Despite its prognostic value, nutritional status is not routinely evaluated in most oncology treatment settings. The controlling nutritional status (CONUT) score, which is calculated from the serum albumin concentration, total peripheral lymphocyte count, and total cholesterol (TC), is a screening tool for the early detection of poor nutritional status [11] and is correlated with prognosis in many cancers [12–14]. We hypothesized that the CONUT score could be used to determine transplant eligibility in ATL patients.

Mogamulizumab, a defucosylated humanized monoclonal antibody against C-C chemokine receptor 4 (CCR4), is a promising salvage chemotherapy agent for patients with relapsed/refractory ATL [15]; however, the impact of the addition of mogamulizumab to conventional chemotherapy on survival has not been fully determined [16, 17]. Depletion of effector regulatory T cells (eTregs) [18] by mogamulizumab can increase the incidence of graft-versus-host disease (GVHD) and NRM in ATL recipients [19]; therefore, pretransplant administration of mogamulizumab is not recommended in transplant-eligible patients, although mogamulizumab may be suitable for transplant-ineligible patients. We hypothesized that mogamulizumab may improve the survival of transplant-ineligible patients.

The present study evaluated the correlation between the CONUT score and the prognosis of patients with ATL and examined the efficacy of mogamulizumab.

Material and methods

Patients

Patients diagnosed with aggressive ATL (acute, lymphoma, unfavorable chronic type, $n = 54$) [20] between January 2008 and March 2017 at Saga University Hospital, Japan, were retrospectively enrolled. Patients who received only palliative care, those lost to follow-up, and those enrolled in other clinical trials were excluded. The final follow-up date was November 2017. All clinical data were reviewed by two expert hematologists. This retrospective study was approved by the institutional review board of Saga University. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committees and with the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the data collection.

The CONUT score

The CONUT score is calculated from the serum albumin concentration, total peripheral lymphocyte count, and TC concentration and is used as a screening tool for the early detection of poor nutritional status. Patients are divided into four categories according to the degree of undernutrition as follows: normal (0–1), mild (2–4), moderate (5–8), and severe (9–12) (Table S1).

Statistical analyses

The cumulative incidence probability of OS and NRM was calculated using the Kaplan-Meier method. Factors involved in survival from the univariate analysis were assessed using the Cox proportional hazards model, which was used to analyze OS. Variables included in the analysis were sex; age; disease subtype (acute or lymphoma type); laboratory data at diagnosis including the levels of serum albumin, lactate dehydrogenase (LDH), adjusted serum calcium (Ca), and soluble interleukin-2 receptor (sIL-2R); presence or absence of mogamulizumab administration; presence or absence of allo-HCT; and the CONUT score. Two-sided p values of < 0.05 were considered statistically significant. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University) [21].

Results

Characteristics of the patients

The study analyzed 54 patients with aggressive ATL, including 28 men and 26 women. The disease subtypes were acute in 39 patients, lymphoma in 14 patients, and unfavorable chronic subtype in 1 patient. All patients received intensive chemotherapy as initial treatment, including CHOP-like ($n = 25$), mLSG15 ($n = 24$), and others ($n = 5$). The median OS was 326 days [1-year OS, 41.4%; 95% confidence interval (CI), 28.1–54.2; Fig. 1a]. The clinical characteristics of the patients are summarized in Table 1.

Older age (≥ 70 years) is a poor prognostic factor in ATL patients

Twenty-nine patients (53.7%) were ≥ 70 years old (older patients), and these patients had a worse survival outcome (median OS, 287 days; HR, 2.006; 95% CI, 1.06–3.799; $p = 0.033$) than younger patients (median OS, 342.5 days) (Table 2; Fig. 1b). No other factors were associated with OS in the present cohort (Table 2). None of the patients in the older group received allo-HCT, whereas 14 younger patients received allo-HCT ($p < 0.001$) (Table 3), indicating that

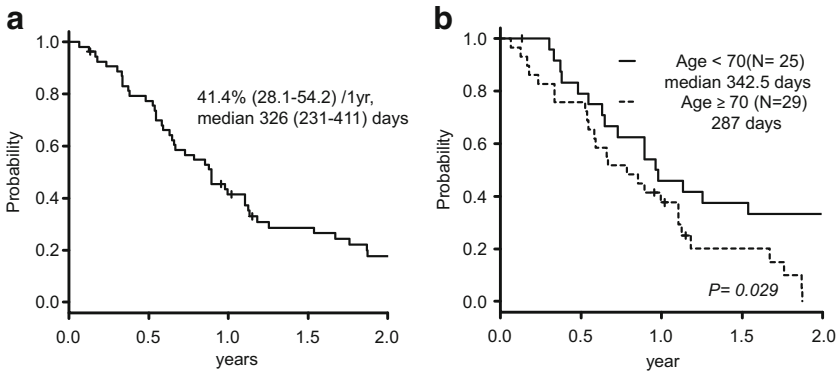

Fig. 1 **a** Kaplan-Meier curve of estimated overall survival (OS) in the cohort. The median OS was 326 days. **b** Kaplan-Meier curve estimates of OS in elderly patients ≥ 70 years and in younger patients < 70 years; the median OS was 287 days and 342.5 days, respectively

treatment strategies, especially the absence or presence of allo-HCT, can vary depending on age. Next, we assessed the prognostic variables after dividing the patients into an older group (≥ 70 years) and a younger group (< 70 years).

A lower CONUT score (0–3) is correlated with favorable OS in younger but not in older ATL patients

Among younger patients, 17 (17/25) had a CONUT score of 0–3 (lower CONUT score group) and a significantly longer OS than those with a CONUT score ≥ 4 (higher CONUT score group) (median OS, 562 days and 321 days, respectively; HR, 0.33; 95% CI, 0.117–0.932; $p = 0.036$) (Fig. 2a; Table 3). Among older patients, 14 (14/29) were in the lower CONUT score group, and there were no significant differences in OS between the lower and higher CONUT score groups (HR, 1.056; 95% CI, 0.48–2.32; $p = 0.893$) (Fig. 2b; Table 3). Allo-HCT is critical for inducing long-term remission in younger patients, and a low incidence of NRM can contribute to long-term survival [3, 4]. We hypothesized that younger patients in the lower CONUT score group show favorable treatment outcomes of allo-HCT.

Table 1 Patients' characteristics

Variable	No.
Age	Median 70.5 (47–88)
Sex Male/female	28/26
Disease subtype Acute/lymphoma/unfavorable chronic	39/14/1
Initial treatment CHOP like/mLSG15/other	25/24/5
White cell count × 10^9/L	9.0 (2.7–150)
Lymphocytes count × 10^9/L	0.9 (0–3.5)
Abnormal lymphocytes %	6 (0–95.5)
Serum albumin mg/dL	3.6 (1.8–4.3)
Lactate dehydrogenase U/mL	560 (172–4926)
Adjusted serum Ca mg/dL	9.75(7.3–16.8)
Hypercalcemia	15
Total cholesterol mg/dL	173 (103–321)
Soluble interleukin-2 receptor U/mL	25,597 (1114–191,800)
The CONUT score	3 (0–10)
Received HCT	14
Administration of moga	17

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; *mLSG15*, modified LSG (VCAP-AMP-VECP: vincristine, cyclophosphamide, doxorubicin, and prednisolone; doxorubicin, ranimustine, and prednisolone; vindesine, etoposide, carboplatin, and prednisolone); *Ca*, calcium; *CONUT* score, controlling nutritional status score; *moga*, mogamulizumab

The CONUT score, but not the HCT-specific comorbidity index, can predict OS and NRM in patients receiving allo-HCT

Of 14 younger patients who received allo-HCT, 10 were in the lower CONUT score group. The median OS of patients who received allo-HCT in the lower and higher CONUT score groups was 1685.5 and 184.5 days (Fig. 2c; $p = 0.017$), respectively, whereas NRM at 1 year was 30% and 100%

Table 2 Univariate analysis of overall survival in all patients

Variable	*N*	HR	95% CI	*p* value
Age 70 years or older	29/54	2.006	1.06–3.799	0.033
Sex male	28/54	1.072	0.584–1.971	0.822
Disease subtype Acute vs lymphoma	39/53	0.872	0.444–1.71	0.69
Alb < 3.5 mg/dL	23/54	0.929	0.502–1.722	0.816
sIL-2R over 20,000 U/mL	31/54	1.146	0.618–2.126	0.666
Hypercalcemia	24/54	1.303	0.71–2.392	0.392
LDH > 500 U/mL	29/54	1.336	0.725–2.463	0.352
Received HCT	14/54	0.608	0.288–1.281	0.191
Administration of moga	17/54	0.979	0.51–1.876	0.948
CONUT score 0–4	35/54	0.576	0.307–1.078	0.085
CONUT score 0–3	31/54	0.56	0.30–1.047	0.069

Alb, albumin; *sIL-2R*, soluble interleukin receptor-2; *LDH*, lactate dehydrogenase; *HCT*, hematopoietic stem cell transplantation; *moga*, mogamulizumab; *CONUT* score, controlling nutritional status score

Table 3 Univariate analysis of overall survival in patients 70 years and older or younger

Variable Age	*N* Age < 70	HR	95% CI	*p* value	*N* Age ≥ 70	HR	95% CI	*p* value
Alb < 3.5 mg/dL	9/25	0.525	0.169–1.621	0.266	14/29	1.443	0.642–3.245	0.375
sIL-2R over 20,000 U/mL	12/25	0.92	0.342–2.474	0.869	19/29	0.951	0.397–2.282	0.911
Hypercalcemia	11/25	1.327	0.496–3.549	0.573	11/29	1.238	0.558–2.747	0.599
LDH > 500 IU/mL	15/25	1.336	0.725–2.463	0.352	14/29	2.409	0.981–5.921	0.052
Received HCT	14/25	1.026	0.380–2.766	0.96	0/29			
Administration of moga	5/25	2.551	0.860–7.567	0.092	12/29	0.377	0.163–0.873	0.023
CONUT score 0–4	21/25	0.501	0.141–1.781	0.285	15/29	0.845	0.383–1.867	0.678
CONUT score 0–3	17/25	0.33	0.117–0.932	0.036	14/29	1.056	0.480–2.32	0.893

Alb, albumin; *sIL-2R*, soluble interleukin receptor-2; *LDH*, lactate dehydrogenase; *HCT*, hematopoietic stem cell transplantation; *moga*, mogamulizumab; *CONUT* score, controlling nutritional status score

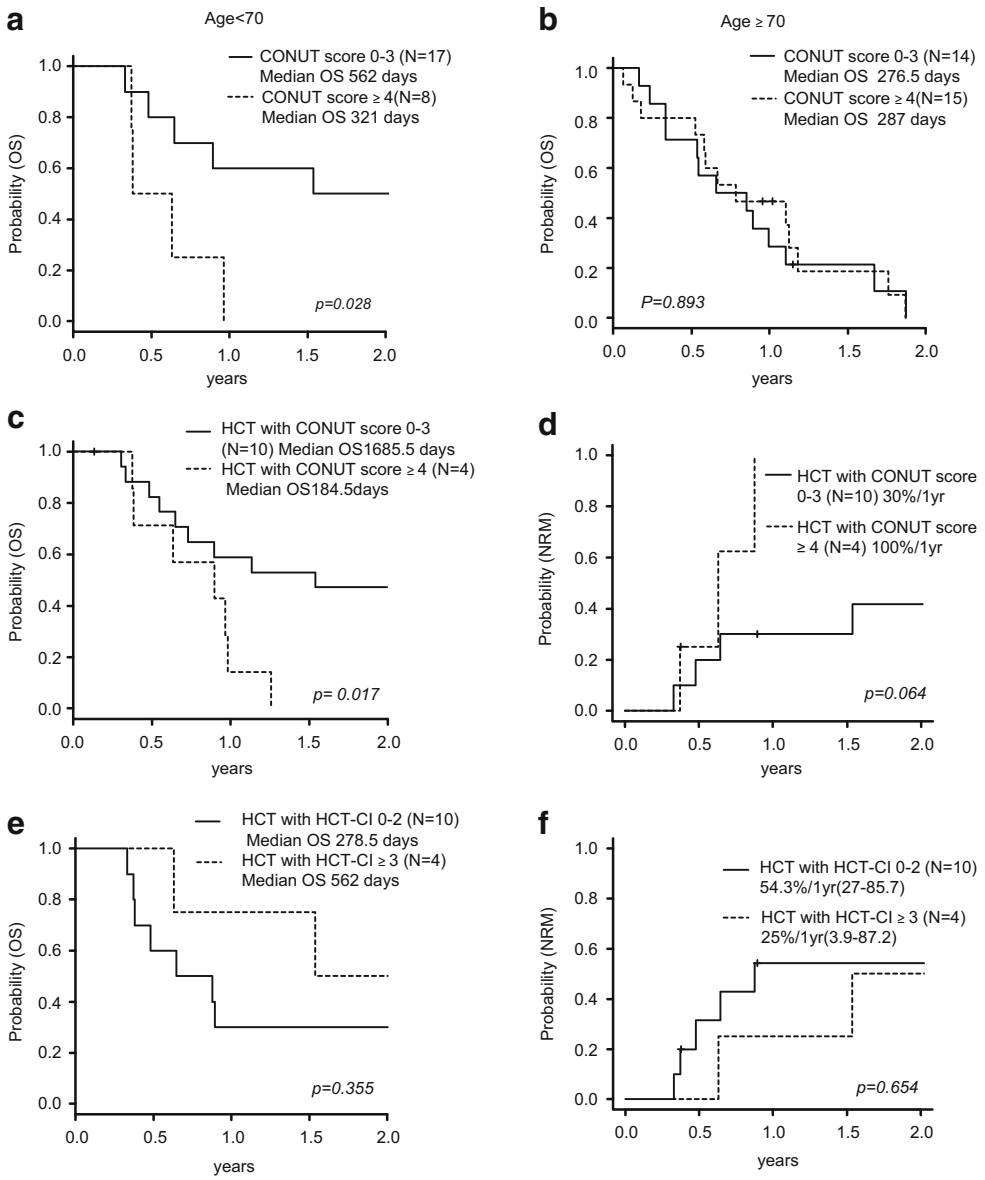

Fig. 2 **a** Kaplan-Meier survival curves of overall survival (OS) in younger patients (< 70 years). The median OS was 562 days in the 0–3 CONUT score group and 321 days in the ≥ 4 CONUT score group. **b** Kaplan-Meier survival curves of OS in older patients (≥ 70 years). The median OS was 276.5 days in the 0–3 CONUT score group and 287 days in the ≥ 4 CONUT score group. **c** Kaplan-Meier survival curves of OS in patients who received hematopoietic stem cell transplantation (HCT). The median OS was 1685.5 days in the 0–3 CONUT score group and 184.5 days in the ≥ 4 CONUT score group. **d** Cumulative incidence of non-relapse mortality (NRM) in patients who received HCT. The 1-year NRM rates were 30% in the 0–3 CONUT score group and 100% in the ≥ 4 CONUT score group. **e** Kaplan-Meier survival curves of OS in patients who received HCT. The median OS was 278.5 days in the 0–2 HCT-comorbidity index (HCT-CI) group and 562 days in the ≥ 3 HCT-CI group. **f** Cumulative incidence of NRM in patients who received HCT. The 1-year NRM rates were 54.3% in the 0–2 HCT-CI group and 25% in the ≥ 3 HCT-CI group

(Fig. 2d; $p = 0.064$), respectively. A previous report suggested that HCT-specific comorbidity index (HCT-CI) can predict OS and NRM in patients who received HCT [22]. Patients with a HCT-CI score of 0–2 ($n = 4$) were defined as the lower HCT-CI group, whereas those with a HCT-CI score ≥ 3 were defined as the higher HCT-CI group ($n = 4$) based on a report suggesting that the higher HCT-CI group had significantly shorter OS and higher NRM [22]. The median OS of patients in the lower and higher HCT-CI groups was 278.5 and 562 days (Fig. 2e; $p = 0.355$), respectively, and NRM at 1 year was 54.3% and 25% (Fig. 2f; $p = 0.654$), respectively. These results of HCT-CI were inconsistent with those of previous reports, and the CONUT score was therefore considered more suitable as a predictive tool for the prognosis of patients who received allo-HCT than the HCT-CI.

Mogamulizumab can improve OS in older patients (≥ 70 years)

Of 29 older patients, 12 received mogamulizumab as salvage chemotherapy. Patients who received mogamulizumab had a significantly longer OS (432 days) than those who were not treated with mogamulizumab (199 days) (Fig. 3a; Table 3; HR, 0.377; 95% CI, 0.163–0.873; $p = 0.023$). No other factors had an effect on OS in older ATL patients (Table 3), indicating that administration of mogamulizumab may improve OS in older ATL patients. Five younger ATL patients received mogamulizumab as salvage chemotherapy and showed a tendency towards a worse prognosis (Fig. 3b; Table 3; HR, 2.551; 95% CI, 0.860–7.567; $p = 0.092$). One patient who received pretransplant mogamulizumab developed severe GVHD, resulting in early death.

Discussion

The present study identified a new prognostic index for allo-HCT recipients in ATL. The median OS in the present study was 326 days (10.9 months). The JCOG9801 study, which compared the efficacy of mLSG15 and bi-weekly CHOP, reported a median OS of 13 months and 11 months, respectively [2]. These findings indicate that despite its small size ($n = 54$), the present cohort was representative.

The CONUT score is used to grade poor nutritional status and is useful for predicting prognosis in many cancers [12, 13, 23] because poor nutritional status is correlated with the response to chemotherapy and the severity of therapy-related toxicity [9]. Allo-HCT is a promising treatment to induce long-term remission [3, 4], and allo-HCT recipients in the lower CONUT score group achieved long-term remission with a lower NRM rate. However, the CONUT score was not correlated with prognosis in older patients, indicating that the CONUT score may be more suitable for evaluating the prognosis of transplant-eligible ATL patients. In the present study, variables such as low serum albumin concentration (a well-known poor prognostic factor in ATL), low total peripheral lymphocyte count (lymphocyte count differences were not observed according to disease subtypes: median, acute, 975/μL; lymphoma, 886.8/μL; $p = 0.739$), and low TC concentration were not predictors of prognosis in transplant-eligible ATL patients (data not shown), whereas the CONUT score predicted prognosis. The HCT-CI, which is reported as a predictive tool for OS and NRM in allo-HCT recipients [22], was not a predictor of OS and NRM in the present cohort. In addition, the CONUT score is determined in the setting of first diagnosis, whereas the HCT-CI is determined at the pretransplant setting; therefore, the CONUT score may be useful as an early assessment tool in clinical practice. Chemosensitivity is important for the success of allo-HCT in ATL [24], as the early administration of induction chemotherapy to control ATL is necessary for transplant-eligible patients [25]. Early prediction of transplant eligibility based on the CONUT score is beneficial in ATL. This result suggests that nutritional status can affect the prognosis of transplant-recipients, and this tool may be applicable to other hematological malignancies.

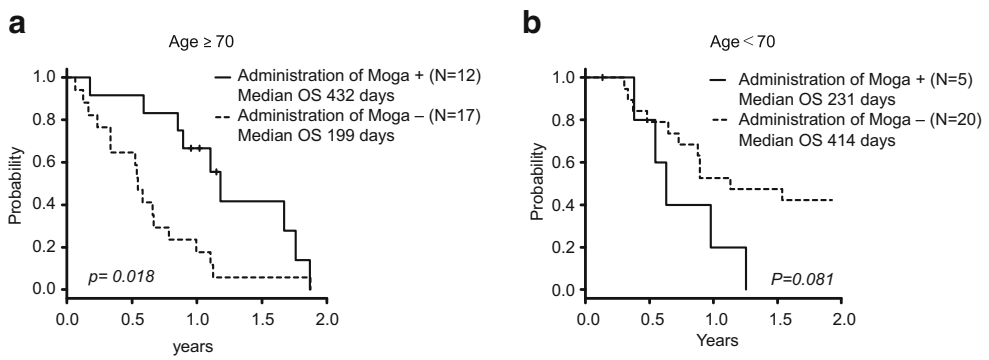

Fig. 3 **a** Kaplan-Meier curve estimates of OS in elderly patients (≥ 70 years) who received or did not receive moga; the median OS was 432 days and 199 days, respectively. **b** Kaplan-Meier curve estimates of OS in younger patients (< 70 years) who received or did not receive moga; the median OS was 231 days and 414 days, respectively. Abbreviation: Moga, mogamulizumab

In addition to its antibody-dependent cytotoxic activity against CCR4-positive cells, mogamulizumab promotes antitumor immune responses by depleting eTregs [18] and altering T cell immune reconstitution [26], thus exerting strong antitumor effects [15]. Depletion of eTregs and alteration of T cell immune reconstitution often persist half a year or longer after initiating mogamulizumab treatment [27], promoting the development of severe GVHD [19] in the pretransplant setting. Younger patients treated with mogamulizumab had a tendency towards a worse prognosis in our cohort, and one patient who received pretransplant mogamulizumab developed severe GVHD, resulting in early death. Therefore, the indications for mogamulizumab should be carefully determined in younger patients. However, elderly patients who received mogamulizumab had significantly improved OS compared with that in patients who were not treated with this agent. Depletion of eTregs activates HTLV-I-specific cytotoxic T cells (CTLs) [18], which are involved in regulating ATL progression [28]. The presence of CTLs in the peripheral blood or bone marrow after allo-HCT has been reported [29]; therefore, Tax peptide-pulsed dendritic cell vaccination [30] or mogamulizumab [31] could provide promising antitumor effects. In clinical practice, immune-related cutaneous adverse events are a favorable prognostic factor in patients who received mogamulizumab with generally limited toxicity [32]. Because these immunological alterations can contribute to the strong antitumor effects in ATL, administration of mogamulizumab is beneficial for transplant-ineligible ATL patients.

The simplified ATL-prognostic index (sATL-PI), which includes age, serum albumin level, sIL-2R level, Ann Arbor stage, and performance status (PS), can predict the prognosis of ATL patients who did not receive allo-HCT [5]. In the current cohort, only older age had an effect on OS, whereas serum albumin and sIL-2R levels did not affect OS, even in the limited group of patients who did not receive allo-HCT (Table S2). However, Ann Arbor stage is not accurate in ATL because many ATL patients have a leukemic phase and PS can be variable depending on the evaluator [33]. Hence, it remains unclear whether sATL-PI correctly predicts OS in ATL, and a more accurate prognostic index for ATL is needed.

We identified the CONUT score as a new prognostic factor in ATL. However, we cannot conclude the association between the CONUT score and the prognosis of patients with ATL due to small sample size in our retrospective study. Further investigation with a sufficient number of cases is needed to clarify the clinical impact of the CONUT score in ATL.

Compliance with ethical standards

Disclosure of conflict of interest S. K. received a research funding from Kyowa Hakko Kirin. The other authors declare no conflicts of interest.

Ethical approval This study was approved by the Institutional Review Board of Saga University. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committees and with the Declaration of Helsinki.

Informed consent Informed consent was waived due to the retrospective design of the data collection.

References

1. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H (1977) Adult T-cell leukemia: clinical and hematologic features of 16 cases. Blood 50:481–492
2. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y, Ikeda S, Masuda M, Nagoshi H, Ueda R, Tamura K, Sano M, Momita S, Yamaguchi K, Kawano F, Hanada S, Tobinai K, Shimoyama M, Hotta T, Tomonaga M, Japan Clinical Oncology Group Study JCOG9801 (2007) VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group Study JCOG9801. J Clin Oncol 25:5458–5464
3. Hishizawa M, Kanda J (2010) Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 116:1369–1376
4. Kawada H, Yoshimitsu M, Nakamura D, Arai A, Hayashida M, Kamada Y, Maekawa K, Fujino S, Arima M, Arima N, Tabuchi T, Inoue H, Hamda H, Suzuki S, Matsushita K, Arima N (2015) A retrospective analysis of treatment outcomes in adult T cell leukemia/lymphoma patients with aggressive disease treated with or without allogeneic stem cell transplantation: a single-center experience. Biol Blood Marrow Transplant 21:696–700
5. Katsuya H, Yamanaka T, Ishitsuka K, Utsunomiya A, Sasaki H, Hanada S, Eto T, Moriuchi Y, Saburi Y, Miyahara M, Sueoka E, Uike N, Yoshida S, Yamashita K, Tsukasaki K, Suzushima H, Ohno Y, Matsuoka H, Jo T, Suzumiya J, Tamura K (2012) Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol 30:1635–1640
6. Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K (2014) Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A). Br J Haematol 166:739–748
7. Fuji S, Yamaguchi T, Inoue Y, Utsunomiya A, Moriuchi Y, Uchimaru K, Owatari S, Miyagi T, Taguchi J, Choi I, Otsuka E, Nakachi S, Yamamoto H, Kurosawa S, Tobinai K, Fukuda T (2017) Development of a modified prognostic index for patients with aggressive adult T-cell leukemia-lymphoma aged 70 years or younger: possible risk-adapted management strategies including allogeneic transplantation. Haematologica 102:1258–1265
8. Yoshimitsu M, Tanosaki R, Kato K, Ishida T, Choi I, Takatsuka Y, Fukuda T, Eto T, Hidaka M, Uchida N, Miyamoto T, Nakashima Y, Moriuchi Y, Nagafuji K, Miyazaki Y, Ichinohe T, Takanashi M, Atsuta Y, Utsunomiya A, ATL Working Group of the Japan Society for Hematopoietic Cell Transplantation (2018) Risk assessment in adult T cell leukemia/lymphoma treated with allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 24:832–839
9. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, Cohen MH, Douglass HO Jr, Engstrom PF, Ezdinli EZ, Horton J, Johnson GJ, Moertel CG, Oken MM, Perlia C, Rosenbaum C,

Silverstein MN, Skeel RT, Sponzo RW, Tormey DC (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 69:491–497

10. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, Glare P, Nabal M, Viganò A, Larkin P, de Conno F, Hanks G, Kaasa S, Steering Committee of the European Association for Palliative Care (2005) Prognostic factors in advanced cancer patients: evidence-based clinical recommendations–a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 23:6240–6248
11. Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP et al (2005) CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 20:38–45
12. Iseki Y, Shibutani M, Maeda K, Nagahara H, Ohtani H, Sugano K, Ikeya T, Muguruma K, Tanaka H, Toyokawa T, Sakurai K, Hirakawa K (2015) Impact of the preoperative controlling nutritional status (CONUT) score on the survival after curative surgery for colorectal cancer. PLoS One 10:e0132488
13. Toyokawa T, Kubo N, Tamura T, Sakurai K, Amano R, Tanaka H, Muguruma K, Yashiro M, Hirakawa K, Ohira M (2016) The pretreatment controlling nutritional status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. BMC Cancer 16:722
14. Toyokawa G, Kozuma Y, Matsubara T, Haratake N, Takamori S, Akamine T, Takada K, Katsura M, Shimokawa M, Shoji F, Okamoto T, Maehara Y (2017) Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma. J Thorac Dis 9:2942–2951
15. Ishida T, Joh T, Uike N, Yamamoto K, Utsunomiya A, Yoshida S, Saburi Y, Miyamoto T, Takemoto S, Suzushima H, Tsukasaki K, Nosaka K, Fujiwara H, Ishitsuka K, Inagaki H, Ogura M, Akinaga S, Tomonaga M, Tobinai K, Ueda R (2012) Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 30:837–842
16. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K, Fujiwara H, Ishitsuka K, Yoshida S, Taira N, Moriuchi Y, Imada K, Miyamoto T, Akinaga S, Tomonaga M, Ueda R (2015) Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol 169:672–682
17. Iyama S, Sato T, Ohnishi H, Kanisawa Y, Ohta S, Kondo T, Mori A, Tsutsumi Y, Kuroda H, Kakinoki Y, Yamamoto S, Takahashi T, Shindo M, Torimoto Y, Sato K, Iwasaki H, Haseyama Y, Kohda K, Nagamachi Y, Hirayama Y, Sakai H, Hirata Y, Fukuhara T, Ikeda H, Kobune M, Kato J, Kurosawa M (2017) A multicenter retrospective study of mogamulizumab efficacy in adult T-cell leukemia/lymphoma. Clin Lymphoma, Myeloma Leuk 17:23–30.e2
18. Sugiyama D, Nishikawa H, Maeda Y, Nishioka M, Tanemura A, Katayama I, Ezoe S, Kanakura Y, Sato E, Fukumori Y, Karbach J, Jager E, Sakaguchi S (2013) Anti-CCR4 mAb selectively depletes effector-type FoxP3+CD4+ regulatory T cells, evoking antitumor immune responses in humans. Proc Natl Acad Sci U S A 110: 17945–17950
19. Fuji S, Inoue Y, Utsunomiya A, Moriuchi Y, Uchimaru K, Choi I, Otsuka E, Henzan H, Kato K, Tomoyose T, Yamamoto H, Kurosawa S, Matsuoka KI, Yamaguchi T, Fukuda T (2016) Pretransplantation anti-CCR4 antibody mogamulizumab against adult T-cell leukemia/lymphoma is associated with significantly increased risks of severe and corticosteroid-refractory graft-versus-host disease, nonrelapse mortality, and overall mortality. J Clin Oncol 34:3426–3433
20. Shimoyama M (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the Lymphoma Study Group (1984–87). Br J Haematol 79:428–437
21. Kanda Y (2013) Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant 48:452–458
22. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912–2919
23. Kuroda D, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, Kitano Y, Yamamura K, Ouchi M, Nakamura K, Baba Y, Sakamoto Y, Yamashita Y, Yoshida N, Chikamoto A, Baba H (2018) Controlling nutritional status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. Gastric Cancer 21:204–212
24. Nakamura T, Oku E, Nomura K, Morishige S, Takata Y, Seki R, Imamura R, Osaki K, Hashiguchi M, Yakushiji K, Mouri F, Mizuno S, Yoshimoto K, Ohshima K, Nagafuji K, Okamura T (2012) Unrelated cord blood transplantation for patients with adult T-cell leukemia/lymphoma: experience at a single institute. Int J Hematol 96:657–663
25. Fuji S, Fujiwara H, Nakano N et al (2015) Early application of related SCT might improve clinical outcome in adult T-cell leukemia / lymphoma. Bone Marrow Transplant 51:205–211
26. Shindo T, Kitaura K, Ureshino H, Kamachi K, Miyahara M, Doi K, Watanabe T, Sueoka E, Shin-I T, Suzuki R, Kimura S (2018) Deep sequencing of the T cell receptor visualizes reconstitution of T cell immunity in mogamulizumab-treated adult T cell leukemia. Oncoimmunology 7:e1405204
27. Ureshino H, Shindo T, Nishikawa H, Watanabe N, Watanabe E, Satoh N, Kitaura K, Kitamura H, Doi K, Nagase K, Kimura H, Samukawa M, Kusunoki S, Miyahara M, Shin-I T, Suzuki R, Sakaguchi S, Kimura S (2016) Effector regulatory T cells reflect the equilibrium between antitumor immunity and autoimmunity in adult T-cell leukemia. Cancer Immunol Res 4:644–649
28. Takamori A, Hasegawa A, Utsunomiya A, Maeda Y, Yamano Y, Masuda M, Shimizu Y, Tamai Y, Sasada A, Zeng N, Choi I, Uike N, Okamura J, Watanabe T, Masuda T, Kannagi M (2011) Functional impairment of Tax-specific but not cytomegalovirus-specific CD8+ T lymphocytes in a minor population of asymptomatic human T-cell leukemia virus type 1-carriers. Retrovirology 8:100
29. Tanaka Y, Nakasone H, Yamazaki R, Wada H, Ishihara Y, Kawamura K, Sakamoto K, Ashizawa M, Machishima T, Sato M, Terasako K, Kimura SI, Kikuchi M, Okuda S, Kako S, Kanda J, Tanihara A, Nishida J, Kanda Y (2012) Long-term persistence of limited HTLV-I tax-specific cytotoxic T cell clones in a patient with adult t cell leukemia/lymphoma after allogeneic stem cell transplantation. J Clin Immunol 32:1340–1352
30. Suehiro Y, Hasegawa A, Iino T, Sasada A, Watanabe N, Matsuoka M, Takamori A, Tanosaki R, Utsunomiya A, Choi I, Fukuda T, Miura O, Takaishi S, Teshima T, Akashi K, Kannagi M, Uike N, Okamura J (2015) Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study. Br J Haematol 169:356–367
31. Ureshino H, Kamachi K, Miyahara M (2017) Detection of human T-cell lymphotropic virus type I-specific cytotoxic T-cells may predict treatment responses in adult T-cell leukemia/lymphoma patients. Ann Hematol 96:1587–1588
32. Ishida T, Utsunomiya A, Jo T, Yamamoto K, Kato K, Yoshida S, Takemoto S, Suzushima H, Kobayashi Y, Imaizumi Y, Yoshimura K, Kawamura K, Takahashi T, Tobinai K, Ueda R (2017) Mogamulizumab for relapsed adult T-cell leukemia–lymphoma: updated follow-up analysis of phase I and II studies. Cancer Sci 108:2022–2029
33. Schnadig ID, Fromme EK, Loprinzi CL, Sloan JA, Mori M, Li H, Beer TM (2008) Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. Cancer 113:2205–2214