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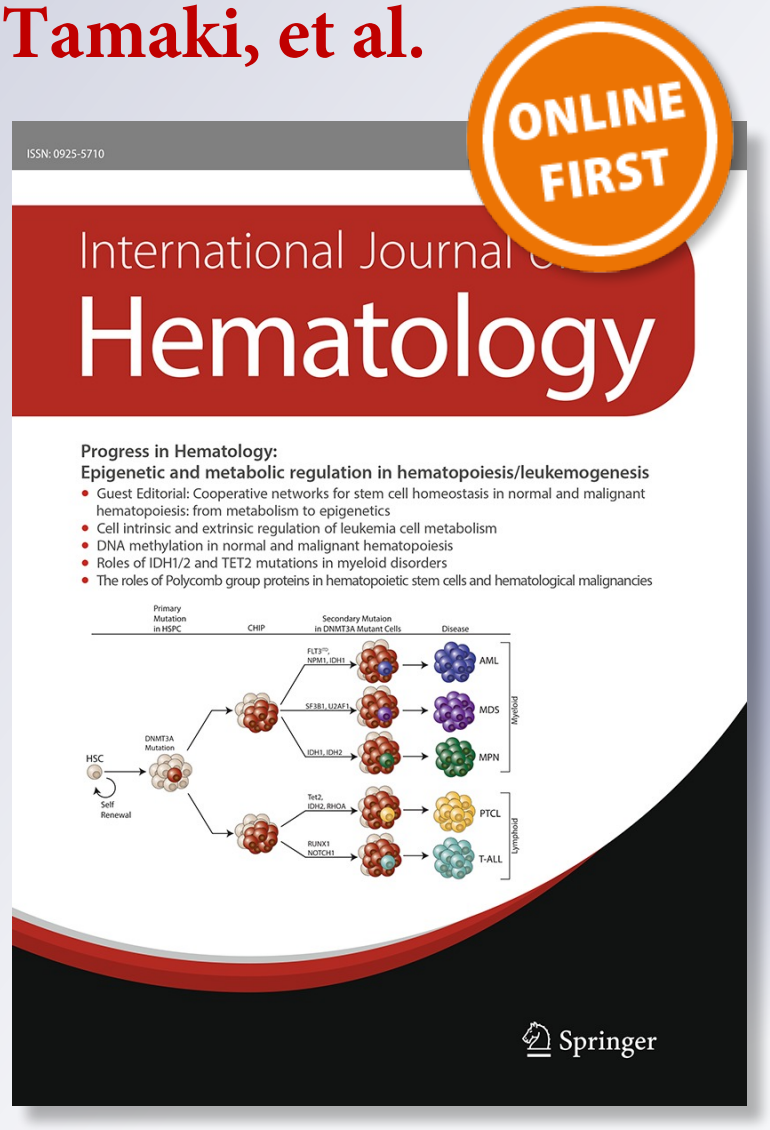

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ORIGINAL ARTICLE

Characterization of patients with aggressive adult T-cell leukemia–lymphoma in Okinawa, Japan: a retrospective analysis of a large cohort

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Abstract Okinawa Prefecture, located in the subtropics, is an area of endemic adult T-cell leukemia–lymphoma (ATL) in Japan. We retrospectively analyzed 659 patients with aggressive ATL in seven institutions in Okinawa between 2002 and 2011. The median patient age was 68 years. More patients were aged ≥90 years (2.6 %), in this study, than in a nationwide survey (<1 %). The median survival time (MST) of the entire cohort was 6.5 months. Of the 217 patients who had a clinical status similar to that stated in the eligibility criteria of JCOG9801 (a randomized phase III study comparing VCAP-AMP-VECP with CHOP-14), 147 who received the CHOP regimen had a poorer MST than those in the CHOP-14 arm of JCOG9801 (8 vs 11 months). The prevalence of strongyloidiasis in the ATL patients was much higher (12.4 %) than in the historical cohort who visited the University of the Ryukyus Hospital (3.4 %). Furthermore, strongyloidiasis may be associated with ATL-related deaths. These findings suggest that, compared with other areas in Japan, in Okinawa, the proportion of patients aged ≥90 years with clinical features of aggressive ATL is higher, outcomes are poorer, and the disease is associated with a higher prevalence of strongyloidiasis.

Keywords Adult T-cell leukemia–lymphoma · Okinawa · Retrospective analysis · Subtropics · Strongyloidiasis

Introduction

Adult T-cell leukemia–lymphoma (ATL) is a distinct peripheral T-cell neoplasm associated with human T-lymphotropic virus type-I (HTLV-1) [1–5]. Classification of clinical subtypes into acute, lymphoma, chronic, and smoldering was proposed based on prognostic factors,

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clinical features, and natural history of the disease [6]. Patients with aggressive ATL (i.e., acute, lymphoma, and unfavorable chronic types) have frequently been treated as a subtype of aggressive non-Hodgkin lymphoma (NHL), whereas those with indolent ATL (i.e., favorable chronic and smoldering types) have been managed as a subtype of chronic lymphoid leukemia [7, 8]. Multicenter clinical trials for patients with aggressive ATL run by the Japan Clinical Oncology Group (JCOG) have revealed that aggressive ATL has a very poor prognosis compared with other types of aggressive NHL [9–12]. The best chemotherapy results for those patients were seen in the phase II and III trials evaluating the chemotherapy regimen of VCAP-AMP-VECP for aggressive ATL. This dose-intensified, multi-agent chemotherapy consisted of vincristine (VCR), cyclophosphamide (CPA), doxorubicin (DXR), and prednisone (PSL) (=VCAP); DXR, ranimustine, and PSL (=AMP); and vindesine, etoposide, carboplatin, and PSL (=VECP). Based on the promising results of the phase II trial JCOG9303 [13], the phase III trial JCOG9801 was conducted to compare the VCAP-AMP-VECP and CHOP (VCR, CPA, DXR, and PSL)-14 regimens [14]. The complete response (CR) and 3-year overall survival (OS) were higher in the VCAP-AMP-VECP arm than in the CHOP-14 arm (40 vs 25 %, and 24 vs 13 %, respectively), suggesting that the former is a more effective regimen for patients with newly diagnosed aggressive ATL. Recently, allogeneic hematopoietic stem cell transplantation (allo-SCT) using myeloablative and reduced intensity conditioning for some patients with aggressive ATL has been reported to cure the disease associated the graft-versus-ATL effect, despite its high transplant-related mortality [15–17]. The 3-year OS rate was about 40 % in allo-SCT from human leukocyte antigen (HLA)-matched related and unrelated donor [15].

In Japan, nationwide surveys have been conducting intermittently since the 1980s. The 4th Japan nationwide survey of 657 patients with all subtypes of ATL from 1986 to 1987 at 191 institutions (including 2 institutions in Okinawa) demonstrated that among all ATL patients registered, 5 % were from Kyushu, and no sex difference in the average age of ATL patients was observed (i.e., average age of 358 men and 295 women was 57.5 and 57.8 years, respectively) [18]. The 9th Japan nationwide survey of all ATL subtypes in 910 patients from 2006 to 2007 at 156 institutions (including 2 institutions in Okinawa) [19] demonstrated that median age was higher at 67 years and that the peak number of patients was in the 1970s age group, which was a shift from the previous peak in the 1950s age group in the 4th nationwide survey [18].

Okinawa Prefecture, located in the only subtropical area in Japan (Fig. 1), is an area endemic for ATL [18]. However, no large-scale retrospective analysis of ATL in Okinawa has been conducted to date, and therefore, differences in the clinical features of ATL between Okinawa and other areas of Japan as well as distinguishing characteristics related to the subtropics are yet to be elucidated. In this study, we aimed to characterize the clinical features by retrospectively examining a large number of patients ($n = 659$) with aggressive ATL in 7 institutions in Okinawa Prefecture.

Fig. 1 Location of Okinawa Prefecture (*black*) in East Asia

Patients and methods

Study design and data collection

This was a retrospective analysis of patients with aggressive ATL from 7 institutions (University of the Ryukyus Hospital, Okinawa Prefecture Chubu Hospital, Heartlife Hospital, Nakagami Hospital, Naha City Hospital, Nambu Medical Center, and Okinawa Red Cross Hospital) in Okinawa Prefecture from January 2002 to December 2011. The ethics committee at each center reviewed and approved the protocol. A standardized clinical data form was distributed to each participating center in the registry (2012–2013). The collected data were reviewed and checked by expert hematologists (T.F., T.T., N.T., K.T., M.H., J.U., K.O., and Y.A.) and data manager (M.K.M). The latest data associated with prognosis were collected at the time of the investigation. The inclusion criteria were based on seropositivity for the anti-HTLV-1 antibody and histologically and/or cytologically proven peripheral T-cell malignancy.

The examination of *Strongyloides stercoralis* infection was routinely checked by microscopic stool analysis on admission in each hospital.

Definitions of clinical endpoint and responses

The endpoint of this study was OS, defined as the duration between diagnosis and death from any cause or censored at the last follow-up in living patients. The response criteria used in this report followed those established by JCOG [13, 14]. CR was defined as the disappearance of all clinical and radiographic evidences of disease and the normalization of lactate dehydrogenase (LDH). Partial response (PR) was defined as ≥50 % reduction of measurable disease with more than 75 % reduction in the absolute abnormal lymphocyte count. LDH had to be decreased to <1.5 of the normal upper limit. Progressive disease (PD) was defined as ≥25 % increase of the measurable disease or the appearance of new lesions during treatment. Stable disease (SD) was defined as an intermediate response between PR and PD.

Statistical analysis

Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The effect of infection with strongyloidiasis and the cause of death were summarized by cross tabulation.

To compare the prognosis of patients with aggressive ATL in Okinawa Prefecture with the JCOG9801 result [14], we extracted patients who had met almost the same eligibility criteria as those of JCOG9801: <70 years old, Eastern Cooperative Oncology Group (ECOG) performance status 0–3, platelet count ≥100,000/μL, creatinine levels ≤2.0 mg/dL, and aspartate aminotransferase and alanine aminotransferace <100 IU/L. Then, we evaluated prognosis by chemotherapeutic regimen (VCAP-AMP-VECP, CHOP, or others).

All statistical analyses were performed using SAS Release 9.3 (SAS institute, Inc, Cary, NC) and STATA software Release 13 (Stata Corporation, College Station, TX).

Results

This study involved 659 patients with acute, lymphoma, and unfavorable chronic and smoldering types with skin lesions treated with chemotherapy. The clinical characteristics of patients are summarized in Table 1. There were missing data on the cause of death in 2 cases. The median age was 68 years, and the age of onset group with the largest patient number for both men and women was the 70–79 group. Surprisingly, the highest age of onset was 102 years and the ≥90 age group constituted 2.6 % ($n = 17$) of all 659 patients (Table 2). The most common treatment employed was a CHOP-like regimen ($n = 366$ in total; CHOP, $n = 360$; CHOP + etoposide, $n = 6$). Only 44 patients received VCAP-AMP-VECP. Of 548 patients who received chemotherapy, 302 patients (49 %: 134 CR and 168 PR) responded to treatment, and 310 patients (50 %; 141 SD and 169 PD) were resistant to initial chemotherapy. Forty-one patients did not receive any treatment.

Survival analysis and its comparison with JCOG9801

The median follow-up period was 12.5 (range 0–125) months. At the time of the last follow-up, 110 patients, including 12 patients who received allo-SCT, were alive and 548 patients had died [453 had disease progression, 7 had an adverse reaction to chemotherapy, 18 had transplant-related toxicity, and 68 died from other causes (1 not evaluable)]. The MST and 2-year OS of the entire cohort were 6.5 months and 19 %, respectively (Fig. 2a). The MST and 2-year OS rate by treatment regimen were 7 months and 19 % with the CHOP regimen, 10 months and 29 % with the VCAP-AMP-VECP regimen, and 6 months and 16 % with other regimens, respectively (Fig. 2b).

Patients who roughly met the same eligibility criteria as those of JCOG9801 were extracted ($n = 217$, including 8 patients without therapy). The characteristics of the 217 patients in our study and the 118 patients in JCOG9801 are listed in Table 3. The MST was 8 months in the 147 patients who received the CHOP regimen and 9.6 months in the 22 patients who received the VCAP-AMP-VECP regimen (Fig. 3), compared with 11 and 13 months in the CHOP-14 arm and VCAP-AMP-VECP arm of the JCOG9801, respectively.

Allo-SCT

Of the 659 patients studied, 46 patients received allo-SCT with myeloablative ($n = 20$) and reduced intensity ($n = 26$) conditioning. The clinical characteristics of the patients are summarized in Table 4. At the time of the last follow-up, 12 patients were alive and 34 had died (14 PD, 18 transplant-related toxicity, and 2 deaths from other causes). MST and 3-year OS after diagnosis were 1.5 years and 29.3 % in patients who received allo-SCT, and 0.5 years and 11.5 % in those who did not (Fig. 4).

Strongyloidiasis

Okinawa Prefecture, a subtropical region of Japan, is known as an endemic area for *S. stercoralis* infection. The prevalence rate of the entire cohort was 12.4 %, which is higher than the rate of 3.4 % in the 3,992 patients,

Table 1 Clinical characteristics of all 659 patients

Sex (male/female)	341/318
Median age (range)	68 (26–102)
Subtype of ATL	
Acute	366 (56 %)
Lymphoma	233 (35 %)
Unfavorable chronic	56 (8 %)
Smoldering (skin type)	4 (1 %)
PS	
0	51 (8 %)
1	284 (43 %)
2	151 (23 %)
3	119 (18 %)
4	50 (8 %)
NE	4 (<1 %)
Corrected Ca (mg/dL)	
≥11.0 mg	168 (25 %)
<11.0	346 (53 %)
NE[a]	145 (22 %)
Chemotherapy regimen	
CHOP or CHOP-like	366 (56 %)
VCAP-AMP-VECP	44 (7 %)
ETP with or without PSL	131 (20 %)
THP-COP	19 (3 %)
Other	55 (8 %)
No therapy	41 (6 %)
NE	3 (<1 %)
Response to the initial chemotherapy	
CR	134 (20 %)
PR	168 (25 %)
SD	141 (21 %)
PD	169 (26 %)
NE	47 (7 %)
Cause of death (total 548)	
Disease progression	453 (83 %)
Chemotherapy-related AEs	7 (1 %)
Transplant-related toxicity	18 (3 %)
Other	68 (12 %)
NE	2 (<1 %)

ATL adult T-cell leukemia–lymphoma, *PS* performance status, *NE* not evaluated, *Ca* calcium, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *VCAP-AMP-VECP* cyclophosphamide, doxorubicin, vincristine, ranimustine, vindesine, carboplatin, etoposide, prednisone, *ETP* etoposide, *PSL* prednisone, *THP-COP* pirarubicin, cyclophosphamide, vincristine, prednisone, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *AE* adverse event

[a] Because of missing data on Ca ($n = 39$) and albumin ($n = 106$)

Table 2 Distribution of patients with aggressive ATL according to age group

Age group	Male	Female	Total
≥20, <30	1 (0.2 %)	1 (0.3 %)	2 (0.3 %)
≥30, <40	1 (0.2 %)	5 (2 %)	6 (0.9 %)
≥40, <50	25 (0.2 %)	10 (3 %)	35 (5.3 %)
≥50, <60	75 (22 %)	72 (20 %)	147 (22.3 %)
≥60, <70	99 (29 %)	78 (23 %)	177 (26.9 %)
≥70, <80	103 (30 %)	94 (27 %)	197 (30.0 %)
≥80, <90	30 (9 %)	48 (15 %)	78 (11.8 %)
≥90	7 (2 %)	10 (3 %)	17 (2.6 %)

ATL adult T-cell leukemia–lymphoma

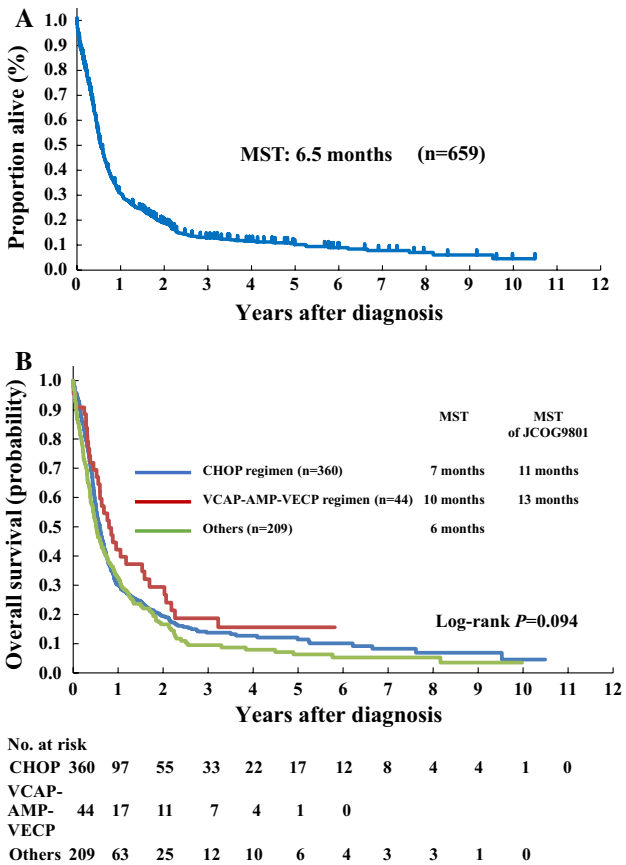

Fig. 2 Overall survival (OS) of the entire cohort and according to treatment regimens. **a** OS of all 659 patients with aggressive ATL. Median survival time (MST) was 6.5 months. **b** OS according to different treatment regimens. MST was 7 months with CHOP, 10 months with VCAP-AMP-VECP, and 6 months with others

including a few patients in the present study, who visited the University of the Ryukyus Hospital from January 2004 to November 2006 [20]. In each age group, the prevalence rate was higher in the present study than in the previous study (Fig. 5). Among 81 patients with strongyloidiasis and 574 patients without strongyloidiasis, 12 (15 %) and 97 (17 %) survived, and 63 (78 %) and 390 (68 %) died of ATL, respectively (Table 5).

Table 3 Characteristics of 217 patients who had clinical characteristics similar to the eligibility criteria of JCOG9801 and the 118 patients of JCOG9801

	Our study ($n = 217$)	JCOG9801	
		VCAP-AMP-VECP ($n = 57$)	Biweekly CHOP ($n = 61$)
Age			
Median	59	56	58
Range	28–69	36–69	33–69
Sex			
Male	102 (47 %)	27 (47 %)	34 (56 %)
Female	115 (53 %)	30 (53 %)	27 (44 %)
Subtype			
Acute	117 (54 %)	40 (70 %)	41 (67 %)
Lymphoma	77 (35 %)	12 (21 %)	14 (23 %)
Unfavorable chronic	22 (10 %)	5 (9 %)	6 (10 %)
Smoldering	1 (0.5 %)	0 (0 %)	0 (0 %)
PS			
0	20 (9 %)	19 (33 %)	30 (49 %)
1	131 (60 %)	27 (47 %)	19 (31 %)
2	45 (21 %)	8 (14 %)	10 (16 %)
3	21 (10 %)	2 (4 %)	2 (3 %)
4	0 (0 %)	1 (2 %)	0 (0 %)
Regimen			
CHOP	147		
VCAP-AMP-VECP	22		
Other	40		
No therapy	8		

ATL adult T-cell leukemia–lymphoma, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *VCAP-AMP-VECP* cyclophosphamide, doxorubicin, vincristine, ranimustine, vindesine, carboplatin, etoposide, prednisone, *PS* performance status

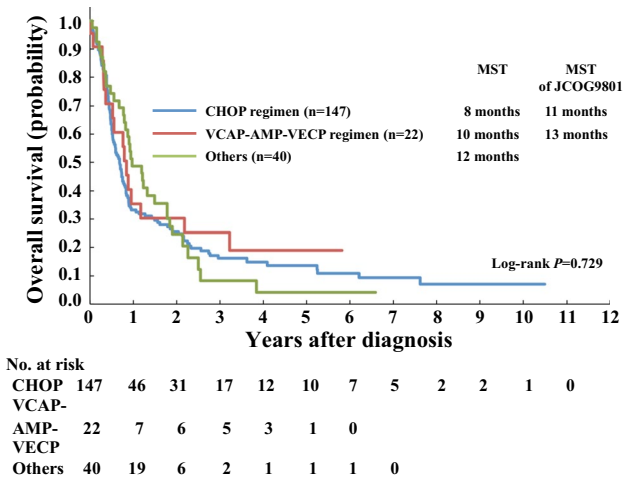

Fig. 3 OS of patients who roughly met the same eligibility criteria as patients in the JCOG9801 study. MST was 8 months with CHOP, 10 months with VCAP-AMP-VECP, and 12 months with others

Discussion

This was the first retrospective analysis of a large cohort of patients with aggressive ATL in Okinawa Prefecture, and it revealed the clinical features of the disease, namely, more patients aged ≥90 years, possibly poorer outcome compared with that of other areas in Japan, and association with a high frequency of *S. stercoralis* infection. In particular, we clarified for the first time that strongyloidiasis could be an important issue for patients with aggressive ATL in the subtropics.

In this analysis, the median age of all 659 patients with aggressive ATL was 68 years, which was almost the same as the age of 67 years of the 910 patients in the nationwide survey of all ATL subtypes from 2006 to 2007 in Japan (including some patients in two institutions in the present study) [19]. However, the proportion of patients aged ≥90 years was 2.6 %, compared with <1 % in the

Table 4 Clinical characteristics of 46 patients who received all-SCT

Sex (male/female)	19/27
Median age (range)	51 (26–68)
Subtype of ATL	
Acute	29
Lymphoma	16
Unfavorable chronic	1
Disease status at transplantation	
CR	16
PR	19
SD	5
PD	5
NE	1
PS at transplantation	
1	2
2	32
3	5
4	5
NE	2
Conditioning regimen	
Myeloablative	20
Reduced intensity	26
Donor	
Related	30
Unrelated	13
Cord blood	3
Cause of death (total 34)	
Disease progression	4
Transplant-related toxicity	18
Other	2

ATL adult T-cell leukemia–lymphoma, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated, *PS* performance status

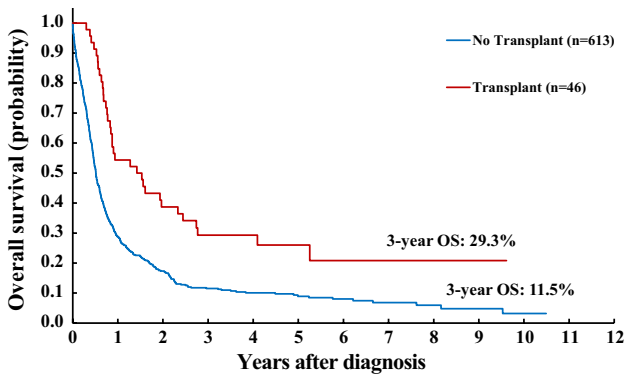

Fig. 4 OS of patients who received (transplant) or did not receive (no transplant) allogeneic hematopoietic stem cell transplantation. Three-year OS was 29.3 % with transplant and 115 % with no transplant

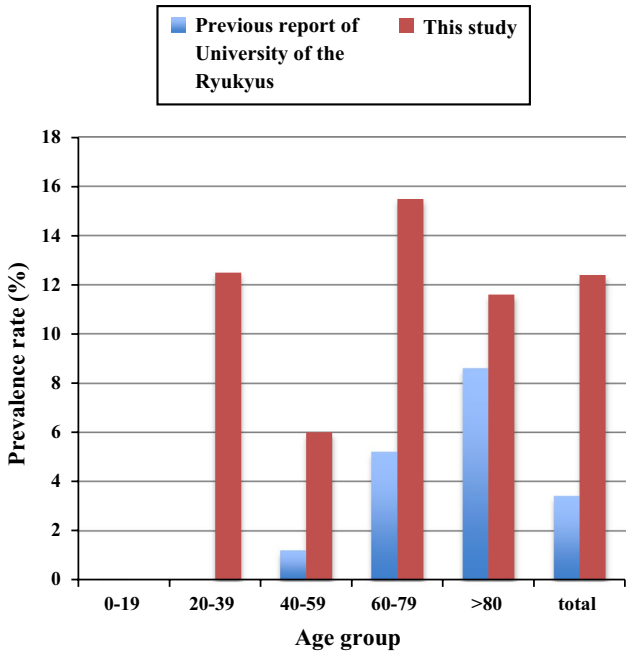

Fig. 5 Comparison of the prevalence rate of strongyloidiasis in each age group between the present study and the previous study at the University of the Ryukyus Hospital. The prevalence rate in the present study was higher than that in the previous study, which was most notable in the 1920s and 1930s age groups

Table 5 Association between strongyloidiasis and cause of death ($n = 655$)

Strongyloidiasis	Yes ($n = 81$)	No ($n = 574$)
Survival	12 (15 %)	97 (18 %)
ATL-related death	63 (78 %)	390 (68 %)
Other cause of death	5 (6 %)	63 (11 %)
Treatment-related death	1 (1 %)	6 (1 %)
Transplant-related death	0	18 (3 %)

ATL adult T-cell leukemia–lymphoma

nationwide survey. Moreover, there were 2 patients aged ≥100 years, and a 102-year-old patient was the oldest in this analysis. There were more patients in the ≥90 age group in Okinawa Prefecture than in the other areas in Japan.

The MST of the entire cohort in this study was 6.5 months, which is a poorer outcome compared with approximately 8 months in the previous reports [6–11]. Furthermore, in 217 patients who had clinical conditions similar to those in the eligibility criteria of JCOG9801, the MST was poorer in both patients who received the CHOP regimen and those who received the VCAP-AMP-VECP

regimen than in the CHOP-14 arm and VCAP-AMP-VECP arm of JCOG9801 [14] (Fig. 3). These findings suggest that patients with aggressive ATL in Okinawa might have a poorer response to chemotherapy than those in other areas in Japan. The MST of other regimens in the comparison set was superior to that of the CHOP and VCAP-AMP-VECP regimens. However, the regimens were heterogeneous, and also, the long-term survival rate was extremely poor (Fig. 3). When considering these points, it is not so important to evaluate the reason for the better outcome in the other regimen group.

In this study, 50 % of patients were resistant to the initial chemotherapy, and 83 % of patients died from disease progression. On the other hand, the overall response rate (CR and PR) in JCOG9801 was 72 and 66 % in the VCAP-AMP-VECP arm and CHOP-14 arm, respectively. This observation further supports the idea that early disease-related death could be associated with the poorer outcome in Okinawa. The results of JCOG9801 suggested that VCAP-AMP-VECP is a more effective regimen than CHOP-14 at the expense of greater toxicity in patients aged <70 years with newly diagnosed aggressive ATL [14]. In addition, the Nagasaki Group reported that the VCAP-AMP-VECP regimen might be effective for elderly patients with aggressive ATL [21]. Of all 659 registered patients in this study, 366 (56 %) received the CHOP regimen or a CHOP-like regimen, but only 44 (7 %) received the VCAP-AMP-VECP regimen. Recently, the randomized phase II study of VCAP-AMP-VECP with or without mogamulizumab, a human anti-CC chemokine receptor 4 antibody, demonstrated that %CR and overall response rate in the mogamulizumab-plus-VCAP-AMP-VECP arm (52 and 86 %, respectively) were superior to those in the VCAP-AMP-VECP arm (33 and 75 %, respectively) [22]. Further investigation of mogamulizumab-plus-VCAP-AMP-VECP is needed to improve the outcome for newly diagnosed aggressive ATL in Okinawa.

As mentioned earlier, the nationwide retrospective study of allo-SCT for ATL in Japan demonstrated that 3-year OS was 33 % for the whole cohort and approximately 40 % in HLA-matched related and unrelated graft recipients [15]. Of the 659 patients in the present study, 46 received allo-SCT. The MST and 3-year OS of these patients were 1.5 years and 29.3 %, respectively (Fig. 4). The evaluation of the efficacy of allo-SCT in Okinawa was hindered by the heterogeneity of the disease status at the time of transplantation, and variation in the duration from diagnosis to transplantation and transplant procedures.

Okinawa Prefecture is an endemic area for *S. stercoralis* infection, which frequently occurs in the subtropics. In this study, we found a higher prevalence rate of strongyloidiasis (12.4 %) in patients with aggressive ATL compared with the previous data on 3,292 patients who visited the University of the Ryukyus Hospital [20] (Fig. 4). Previous reports demonstrated that concurrent infection of *S. stercoralis* in HTLV-1 carriers was highly associated with parasite dissemination and development of severe strongyloidiasis [23–27]. In our series, it was demonstrated that strongyloidiasis might be associated with ATL-related deaths (78 % with strongyloidiasis vs 68 % without strongyloidiasis). However, it is not clear whether strongyloidiasis influences the survival of patients with aggressive ATL. Further evaluation involving a multivariate analysis, including *S. stercoralis* infection, as one of covariates is needed.

This study had an inherent limitation that some essential data may be insufficient or inaccurate, because we collected clinical data retrospectively. For example, disease subtype could not be fully evaluated, because of missing data, and information on dosing of CHOP or VCAP-AMP-VECP was limited. In addition, due to the nature of the observational study, comparison of OS across treatment regimens might have been biased, because treatment was determined by the physicians of each institution, not randomly. We addressed this limitation by extracting patients who roughly met the same eligibility criteria as those of JCOG9801 and compared their prognosis with those in the previous study.

In conclusion, patients with aggressive ATL in Okinawa might have different clinical features compared with those in other areas in Japan, namely more patients aged ≥90 years, poorer outcome, and a higher prevalence of strongyloidiasis. To investigate the cause of clinical features and to improve the treatment outcome, biological analyses using cells from patients with ATL and HTLV-1 carriers are needed in Okinawa.

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Compliance with ethical standards

Conflict of interest The authors report no potential conflict of interest.

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