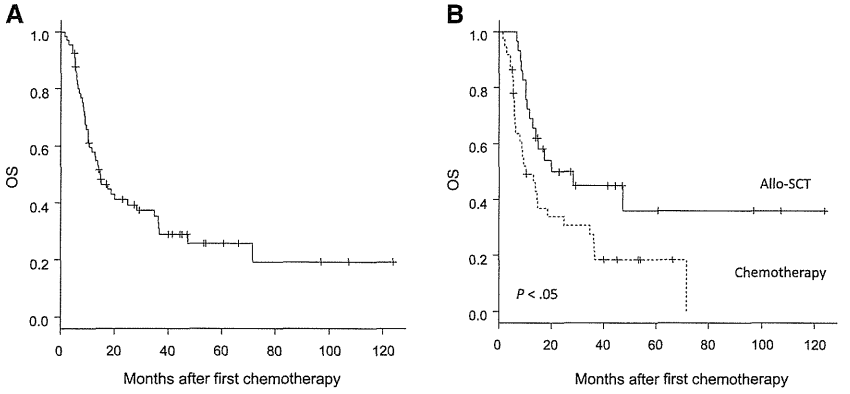

Figure 2. (A) OS after the first chemotherapy in patients with ATL. (B) OS in patients receiving either HSCT or chemotherapy only.

oligoclonal integration of HTLV-1 provirus, and all 3 donors were confirmed as HTLV-1 carriers.

Induction chemotherapy consisted primarily of the VCAP/AMP/VECP regimen, OPEC/MPEC regimen, or mogamulizumab salvage therapy [6-8] in the allo-HSCT patients, and the VCAP/AMP/VECP regimen was also the chemotherapy primarily administered in ATL patients who received only chemotherapy. All but 4 patients received the VCAP/AMP/VECP regimen [6], administered between 1 and 6 times. Before the VCAP/AMP/VECP regimen was administered, 21 patients received a CHOP-like regimen [8].

Twenty-seven patients (93.1%) received reduced-intensity conditioning that consisted of fludarabine with either busulfan or cyclophosphamide ± total body irradiation. The conditioning regimen was chosen by the physician in each case. Because many of the ATL patients and their siblings were relatively old, our institute previously conducted clinical trials testing alternative donors from their sons or daughters [9]; therefore, the percentage of mismatched donor selection was high.

Outcomes

The median follow-up period for survivors was 41 months (range, 5 to 125) from the first chemotherapy. The 3-year OS rate and median survival time for the entire cohort (with/without allo-HSCT) were 35.2% (95% CI, 24.3% to 47.3%) and 437 days (95% CI, 305 to 853 days), respectively (Figure 2A). The 3-year OS rate for the allo-HSCT and chemotherapy-only groups were 44.9% (95% CI, 25.4% to 62.6%) and 27.7% (95% CI, 14.0% to 43.2%), respectively ($P < .05$) (Figure 2B). The 3-year OS rate for the allo-HSCT group from the time of allo-HSCT was 39.9% (95% CI, 20.8% to 58.4%). Three patients with PD at the time of allo-HSCT who received transplantation from an HTLV-1–seropositive donor died on days 63, 112, and 375, respectively. Twenty-four patients who achieved neutrophil engraftment and survived 100 days after allo-HSCT were assessed for acute GVHD. Overall, grades II to IV or grades III to IV acute GVHD occurred in 16 (57.1%), 14 (50.0%), and 4 (14.3%) assessable patients. Landmark analysis at day 60 after allo-HSCT showed the effects of grades II to IV acute GVHD compared with grades 0 to I acute GVHD on OS ($P < .01$).

A high sIL-2R level just before preconditioning (≥2000 U/mL, $P < .01$) (Figure 3A) and PD at allo-HSCT ($P < .01$) (Figure 3B) were identified as significant risk factors for OS by univariate analyses. Male sex ($P = .10$), disease subtype, a high sIL-2R level at the first chemotherapy regimen, ATL prognostic index ≥ 2 [10], HLA mismatch, and the time before transplantation from first chemotherapy were not risk factors for OS in the allo-HSCT group in the univariate analyses. The multivariate analysis results showed the PD state at allo-HSCT was a risk factor for OS in PD patients (hazard ratio, 4.11; 95% CI, 1.41 to 12.0, $P < .01$). In patients with PD after allo-HSCT, 6 patients died of ATL, and 5 patients with disease progression of ATL died of a transplantation-related complication. Five other patients died of a transplantation-related complication while in remission.

Of the 37 patients who received only chemotherapy, 12 patients refused the allo-HSCT even though they were medically fit, 3 patients had an active infection, 4 patients had a concurrent or recent solid tumor, 3 patients had other severe comorbidities, and 15 patients experienced primary induction failure to conventional chemotherapy. Of the latter

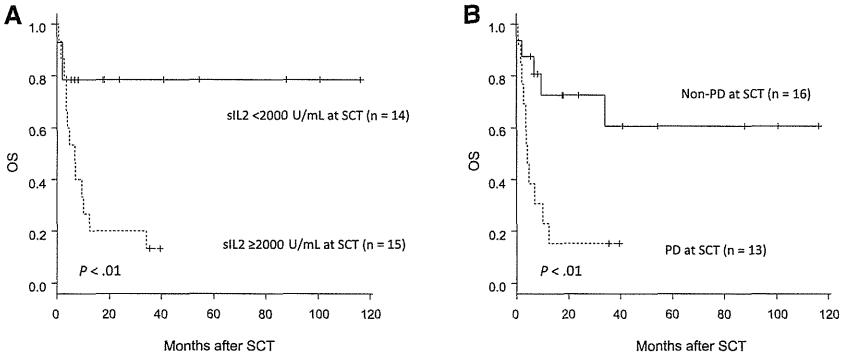

Figure 3. (A) OS according to sIL-2R levels in patients with ATL. (B) OS after HSCT, according to disease status (PD versus non-PD at HSCT).

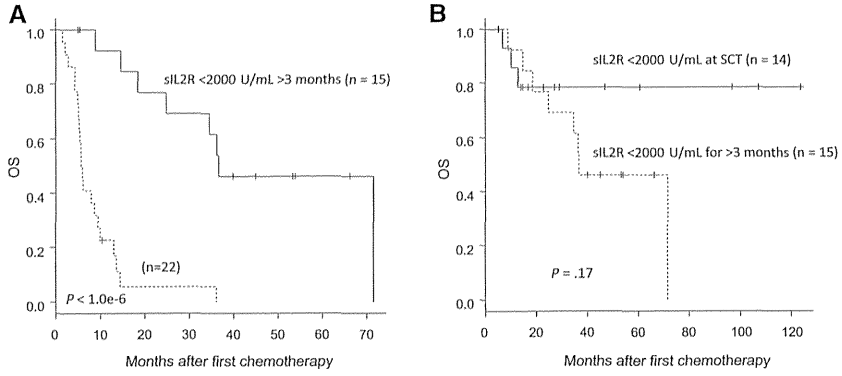

Figure 4. (A) OS according to sIL-2R < 2000 U/ml for >3 months in patients with ATL receiving only chemotherapy. (B) OS in chemosensitive patients with or without HSCT.

15 patients, 6 patients initially desired to receive HSCT and started the coordination of a donor, but the treating physician decided against allo-HSCT. Of the 37 patients who received only chemotherapy, only 15 patients (40.5%) (median age, 62 years; range, 50 to 68 years) reached serum sIL-2R levels < 2000 U/mL for >3 months, and the 3-year OS was 61.5% (95% CI, 30.8% to 81.8%) (Figure 4). The other 22 patients had a 3-year OS of 5.7% (95% CI, .4% to 22.4%) (Figure 4A). The patients in the allo-HSCT group with sIL-2R levels < 2000 U/mL at HSCT tended to have better OS rates than the patients in the chemotherapy-only group with sIL-2R levels < 2000 U/mL for >3 months (Figure 4B, $P = .17$).

DISCUSSION

The 3-year OS rate with allo-HSCT in the present study was 39.9%. Comparatively, the 3-year OS rate was 33.0% in a nationwide retrospective study on allo-HSCT for 386 ATL patients in Japan [2], and a small retrospective analysis on allo-HSCT for 15 ATL patients reported a 3-year OS rate of 73.3% [11]. Of these 15 patients, only 1 patient had PD at the time of allo-HSCT, compared with 13 of 29 patients in the present study. Of the non-PD patients receiving allo-HSCT, the 3-year OS rate was 60.6% in the present study.

Another nationwide retrospective study on allo-HSCT for 586 ATL patients in Japan demonstrated that disease status at the time of allo-HSCT (non–complete remission) was a significant predictor for poorer OS (hazard ratio, 1.94) [12], indicating that treatment outcome is greatly influenced by patient selection. In the present study, a high sIL-2R level just before preconditioning and PD at HSCT were significant risk factors for OS in the univariate analysis. At the same time, a 3-year OS rate of 78.6% was observed in ATL patients who received allo-HSCT with low sIL-2R levels just before preconditioning (<2000 U/mL). These results agree with those of a recent report indicating that high sIL-2R levels at allo-HSCT are an important risk factor for survival [13]. The multivariate analysis in the present study confirmed that patients with non-PD at HSCT were at risk for poorer OS. Because the sIL-2R levels are strongly correlated with disease status, we did not include sIL-2R levels at allo-HSCT in the multivariate analysis. However, a high sIL-2R level at allo-HSCT was determined to be a prognostic factor when used as an alternative variable for disease status at HSCT in the multivariate analysis. Thus, sIL-2R levels at allo-HSCT could be a useful surrogate marker for disease status.

The complex nature of ATL creates challenges for response assessment. Response criteria for ATL were proposed at an international consensus meeting [4]; however, this criteria required a 4-week observation period. In the present study, 9 of 29 patients received HSCT within 4 weeks after the last chemotherapy, which categorizes the response criteria as "not assessable." Objective and less complex response criteria are required to ensure uniform interpretation of the results from clinical trials. Because sIL-2R levels are a good indicator of tumor burden, sIL-2R levels just before the conditioning regimen could be a better objective marker for comparing patient backgrounds between different clinical trials.

Allo-HSCT for those who are chemosensitive (IL-2R < 2000 U/mL at allo-HSCT) has been well established as a curative therapeutic modality for aggressive ATL; however, these patients represent only 21% of ATL patients aged <70 years in clinical practice in an ATL-endemic area. Based on the results of the present study, allo-HSCT might be introduced for patients with serum sIL-2R < 2000 U/mL. The outcomes of allo-HSCT might be improved with earlier administration of allo-HSCT in patients with sIL-2R levels < 2000 U/mL even with alternative donors [9] or mogamulizumab [7] administration before allo-HSCT in patients with high sIL-2R levels; however, this hypothesis requires testing in well-designed, prospective trials. Several clinical trials have investigated the applications of the blocking immune checkpoint protein, PD-1, by human antibodies; this interaction has been validated as an important target for therapeutic intervention, termed "immune checkpoint therapy," which aims to recover antitumor cytotoxic T lymphocyte function in advanced cancer patients. We have reported that HTLV-1–specific cytotoxic T lymphocyte is exhausted with expression of the immune checkpoint receptors PD-1, 2B4, and CD160 but was reinvigorated by the blockade of those receptors [14-16]. These therapies might represent an alternative approach to the treatment of ATL in the future.

In clinical practice in an endemic area, allo-HSCT may not benefit most patients with ATL. Therefore, alternative strategies need to be explored for chemorefractory ATL patients.

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bjh research paper

Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study

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Summary

This multicentre, randomized, phase II study was conducted to examine whether the addition of mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, to mLSG15, a dose-intensified chemotherapy, further increases efficacy without compromising safety of patients with newly diagnosed aggressive adult T-cell leukaemia-lymphoma (ATL). Patients were assigned 1:1 to receive mLSG15 plus mogamulizumab or mLSG15 alone. The primary endpoint was the complete response rate (%CR); secondary endpoints included the overall response rate (ORR) and safety. The %CR and ORR in the mLSG15-plus-mogamulizumab arm ($n = 29$) were 52% [95% confidence interval (CI), 33–71%] and 86%, respectively; the corresponding values in the mLSG15 arm ($n = 24$) were 33% (95% CI, 16–55%) and 75%, respectively. Grade ≥ 3 treatment-emergent adverse events, including anaemia, thrombocytopenia, lymphopenia, leucopenia and decreased appetite, were observed more frequently (≥10% difference) in the mLSG15-plus-mogamulizumab arm. Several adverse events, including skin disorders, cytomegalovirus infection, pyrexia, hyperglycaemia and interstitial lung disease, were observed only in the mLSG15-plus-mogamulizumab arm. Although the combination strategy showed a potentially less favourable safety profile, a higher %CR was achieved, providing the basis for further investigation of this novel treatment for newly diagnosed aggressive ATL. This study was registered at ClinicalTrials.gov, identifier: NCT01173887.

Keywords: adult T-cell leukaemia-lymphoma, CCR4, mogamulizumab, randomized phase II study, antibody therapy.

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Adult T-cell leukaemia-lymphoma (ATL) is an aggressive, peripheral T-cell neoplasm caused by human T-cell lymphotropic virus type I (Uchiyama *et al*, 1977; Matsuoka & Jeang, 2007), and is classified into four clinical subtypes: smouldering, chronic, lymphoma and acute (Shimoyama, 1991). Intensive chemotherapy has been recommended for patients with newly diagnosed acute lymphoma or with unfavourable chronic subtypes of ATL (i.e. aggressive ATL) (Tsukasaki *et al*, 2009). A phase III trial was performed in previously untreated patients with aggressive ATL to compare the effects of a dose-intensified multidrug regimen, namely the modified LSG15 (mLSG15) regimen (VCAP-AMP-VECP: vincristine, cyclophosphamide, doxorubicin and prednisolone; doxorubicin, ranimustine and prednisolone; vindesine, etoposide, carboplatin and prednisolone) (Yamada *et al*, 2001) with the effects of CHOP-14 (cyclophosphamide, doxorubicin, vincristine and prednisolone). The complete response rate (% CR) was higher in the mLSG15 arm (40%) than in the CHOP-14 arm (25%; $P = 0{\cdot}020$). The overall survival (OS) rates at 3 years were 24% and 13% in the mLSG15 and CHOP-14 arms, respectively, with a significant difference ($P = 0{\cdot}028$) observed between the two arms after adjustment for imbalances in baseline prognostic factors (Tsukasaki *et al*, 2007). However, the median survival time of 12·7 months in the mLSG15 arm (CHOP-14 arm, 10·9 months) was lower than that observed for other haematological malignancies. Moreover, allogeneic haematopoietic cell transplantation (allo-HCT) has been explored as a promising treatment for ATL, and it has been reported that allo-HCT can potentially provide cures for 30–40% of transplant recipients. However, only few ATL patients benefit from transplantation, such as those who are younger, achieve sufficient disease control and have an appropriate stem cell source (Hishizawa *et al*, 2010; Ishida *et al*, 2012a).

Because CC chemokine receptor 4 (CCR4) is expressed on the surface of the tumour cells of most patients with ATL (Yoshie *et al*, 2002; Ishida *et al*, 2003), it has been postulated to represent a novel molecular target for immunotherapy for ATL. Therefore, a humanized anti-CCR4 monoclonal antibody with a defucosylated Fc region, mogamulizumab (KW-0761) was developed, and has been shown to markedly enhance antibody-dependent cellular cytotoxicity (Shinkawa *et al*, 2003; Ishii *et al*, 2010). A phase I clinical study of mogamulizumab was performed in patients with relapsed CCR4-positive peripheral T-cell lymphoma (PTCL), including ATL (Yamamoto *et al*, 2010). This study showed good tolerability, predictable pharmacokinetics and preliminary evidence of the antitumour activity of mogamulizumab, and the recommended dose was determined to be 1·0 mg/kg (Yamamoto *et al*, 2010). In the subsequent phase II study, mogamulizumab monotherapy showed an overall response rate (ORR) of 50% in patients with relapsed ATL, with an acceptable toxicity profile (Ishida *et al*, 2012b). Accordingly, mogamulizumab was approved in Japan in 2012 for patients with CCR4-positive relapsed/refractory ATL.

Herein, we report the results of a multicentre, randomized phase II study, the aim of which was to evaluate whether or not the addition of mogamulizumab to mLSG15 increases efficacy without compromising safety for patients with newly diagnosed aggressive ATL.

Patients and methods

Patients

Eligible patients included those newly diagnosed with CCR4-positive aggressive ATL who were aged ≥20 years. CCR4 expression was determined by using immunohistochemistry or flow cytometry with a mouse anti-CCR4 monoclonal antibody (KM2160) (Ishida *et al*, 2003; Yamamoto *et al*, 2010) and confirmed by a central review committee. All patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2. Furthermore, the eligibility criteria included the following laboratory parameters: abso-

lute neutrophil count $\geq 1{\cdot}5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, haemoglobin level ≥80 g/l, aspartate aminotransferase level ≤2·5 × the upper limit of the normal range (ULN), alanine aminotransferase level ≤2·5 × ULN, total bilirubin level ≤2·0 mg/dl, serum creatinine level ≤ 1·3 mg/dl, and arterial partial oxygen pressure ≥65 mmHg or arterial blood oxygen saturation ≥93%. Patients were excluded if they had a severe infection, a history of organ transplantation, active concurrent cancer, central nervous system involvement, a bulky mass requiring emergent radiotherapy, or seropositivity for hepatitis B virus surface antigen, hepatitis C virus antibody or human immunodeficiency virus antibody.

Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to the two treatment groups based on dynamic allocation and minimization (Pocock & Simon, 1975) by a central randomization centre (Bell Medical Solutions, Inc., Tokyo, Japan). For randomization, the first stratification factor was clinical subtype, and the second was age (<56 or ≥56 years). The study had an open-label design.

Procedures

This was a multicentre, randomized, phase II study to compare the efficacy and safety of mLSG15 plus mogamulizumab with that of mLSG15 alone. Subjects assigned to the mLSG15-plus-mogamulizumab arm received eight intravenous 1·0 mg/kg mogamulizumab infusions during four mLSG15 cycles. Typically, mogamulizumab was administered the day before VCAP and VECP administration except for the first VCAP administration (Fig 1). When VCAP or VECP administration was delayed for any reason, mogamulizumab administration was delayed accordingly.

The primary endpoint was %CR, and the secondary endpoints included ORR, %CR and response rate according to disease site; progression-free survival (PFS); OS and safety. We estimated that 22 patients per arm would be required to achieve an 80% probability of detecting a higher %CR in the mLSG15-plus-mogamulizumab arm than in the mLSG15 arm, based on the selection design (Simon *et al*, 1985). We assumed that an increased %CR of 15% achieved upon adding mogamulizumab would imply clinical significance. This 15% increase in the %CR corresponded to the difference observed between mLSG15 and CHOP-14, with a previous phase III study showing that the former treatment prolonged OS (Tsukasaki *et al*, 2007). Thus, if the true difference is 15%, there is an 80% chance of selecting the right treatment when one chooses the treatment with the higher CR rate. Objective responses were assessed after the second and fourth chemotherapy cycles in each arm by an independent efficacy assessment committee according to the modified response criteria for ATL (Tsukasaki *et al*, 2009). Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for AEs version 4·0 (http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf), and were summarized according to the Medical Dictionary for Regulatory Activities System Organ Class and preferred terms. The presence of human anti-mogamulizumab antibodies in plasma was also determined. Blood samples were collected from

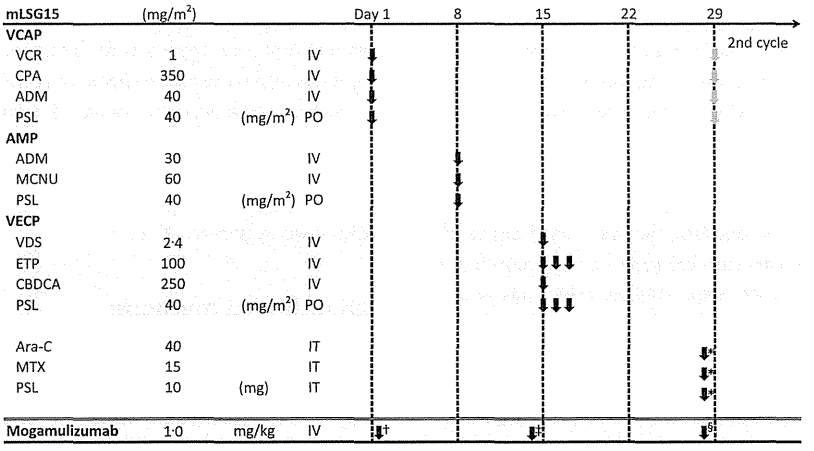

Fig 1. Treatment protocol. The mLSG15 protocol consists of three chemotherapeutic regimens, namely VCAP, AMP and VECP. Subjects assigned to the mLSG15-plus-mogamulizumab arm received up to eight infusions of mogamulizumab during four cycles of mLSG15. Cytarabine, methotrexate and prednisolone were intrathecally injected before initiation of VCAP administration in cycles 2 and 4. VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisolone; AMP: doxorubicin, ranimustine, and prednisolone; VECP: vindesine, etoposide, carboplatin, and prednisolone; IV, intravenous; PO, per os (oral administration); IT, intrathecal; VCR, vincristine; CPA, cyclophosphamide; ADM, doxorubicin; PSL, prednisolone; MCNU, ranimustine; VDS, vindesine; ETP, etoposide; CBDCA, carboplatin; Ara-C, cytarabine; MTX, methotrexate. *Before cycles 2 and 4 (Days −2 to −1). †After VCAP in Cycle 1 (Days 2 to 5). ‡Preceding VECP in Cycles 1–4 (Days 12 to 14). §Preceding VCAP in Cycles 2–4 (Days −3 to −1).

patients who had received at least one dose of mogamulizumab at time points determined by the protocol for the pharmacokinetic analysis. The maximum drug concentration (C_{max}) and trough drug concentration (C_{trough}) for each mogamulizumab administration were calculated. We also investigated the distributions of blood T-cell subsets (CD4/CD25/CCR4-positive cells and CD4/CD25/FOXP3-positive cells) during and after treatment in each arm.

Statistical analysis

Survival estimates were calculated by using the Kaplan–Meier method. PFS was defined as the time from the day of starting the protocol treatment to progression, relapse, or death from any cause. OS was measured from the day of starting the protocol treatment to death from any cause. The numbers of T-cell subsets in the two arms were compared by employing the Wilcoxon signed-rank test for each sampling point at a significance level of 0·05.

Study oversight

The study was sponsored by Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan. The academic investigators and the sponsor were jointly responsible for the study design. The protocol was approved by the institutional review boards at each participating site and all patients provided written informed consent before enrolment, in accordance with the Declaration of Helsinki.

Results

Patients

Between August 2010 and September 2011, 54 patients with newly diagnosed aggressive ATL were enrolled at 18 institutions. Of these 54 patients, 29 in the mLSG15-plus-mogamulizumab arm and 24 in the mLSG15 arm received treatment according to our study protocol. One patient assigned to the mLSG15 arm was withdrawn from the study, owing to the patient's treatment having to be deferred due to abnormal laboratory values that met the protocol criteria, and the patient was unable to wait for the protocol treatment due to deterioration of his/her general condition. The demographics and characteristics of the remaining 53 patients are summarized in Table I. Fifteen patients in the mLSG15-plus-mogamulizumab arm did not complete the planned treatment; of these, seven dropped out because of AEs, including infectious diseases; four dropped out because of progressive disease (PD); and the remaining four dropped out for different reasons, including withdrawal of consent and start of an alternative treatment. Thirteen patients in the mLSG15 arm did not complete the planned treatment; among these, four had AEs, four had PD, and the remaining five dropped out for other reasons (Fig 2).

Table I. Demographics and clinical characteristics.

	mLSG15 + mogamulizumab (n = 29)	mLSG15 (n = 24)*
ATL subtype		
Acute	20 (69%)	17 (71%)
Lymphoma	6 (21%)	7 (29%)
Chronic†	3 (10%)	0 (0%)
Age, years		
Median	61	64
Range	49–81	37–74
<56	11 (38%)	6 (25%)
≥56	18 (62%)	18 (75%)
Sex		
Male	12 (41%)	16 (67%)
Female	17 (59%)	8 (33%)
ECOG PS		
0	16 (55%)	13 (54%)
1	10 (35%)	9 (38%)
2	3 (10%)	2 (8%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*25 patients were randomized; 24 were treated.
†Chronic type with poor prognostic factors.

Efficacy

Of the 29 and 24 patients evaluable for efficacy in the mLSG15-plus-mogamulizumab and the mLSG15 arms, 25 patients [ORR, 86%; 95% confidence interval (CI), 68–96%] and 18 patients (ORR, 75%; 95% CI, 53–90%), respectively, had objective responses. The %CR, including unconfirmed CR, was higher in the mLSG15-plus-mogamulizumab arm (52%; 95% CI, 33–71%) than in the mLSG15 arm (33%; 95% CI, 16–55%), with a between-group difference of 18·4% (95% CI, −8·9 to 43·8%; Table II). The %CR according to the disease site in the mLSG15-plus-mogamulizumab and mLSG15 arms were 100% (14/14) and 43% (3/7) for blood, 92% (24/26) and 73% (16/22) for nodal and extranodal lesions and 50% (4/8) and 60% (3/5) for skin lesions, respectively. The response rate according to the disease site in the mLSG15-plus-mogamulizumab and mLSG15 arms were 100% (14/14) and 100% (7/7) for blood, 92% (24/26) and 77% (17/22) for nodal and extranodal lesions and 75% (6/8) and 80% (4/5) for skin lesions, respectively. The median PFS in the mLSG15-plus-mogamulizumab and mLSG15 arms were 8·5 months and 6·3 months, respectively (Fig 3A). The median OS was not reached in either arm (Fig 3B).

AEs

The treatment-emergent AEs (TEAEs) of ≥grade 3 that occurred in at least two patients are listed in Table III. The most common TEAEs of any grade in the mLSG15-plus-mogamulizumab arm were neutropenia (100%), thrombocytopenia (100%), leucopenia (100%), lymphopenia (97%),

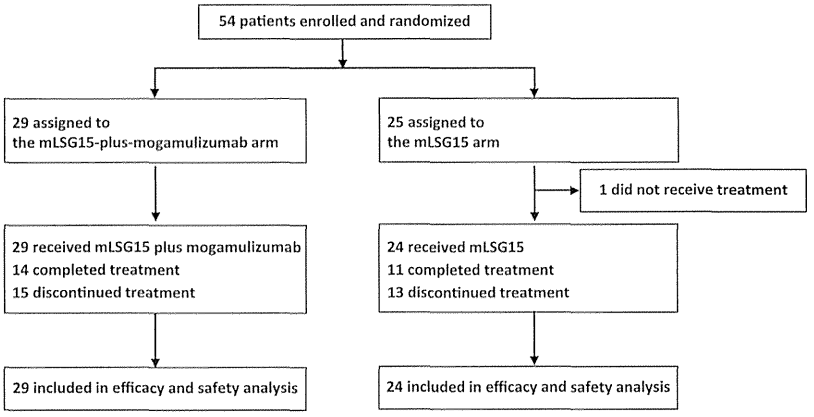

Fig 2. CONSORT diagram. Patients with newly diagnosed CC chemokine receptor 4 - positive aggressive adult T-cell leukaemia-lymphoma were assigned in a 1:1 ratio to receive treatment with mLSG15 plus mogamulizumab or mLSG15 alone. One patient assigned to the mLSG15 arm was withdrawn from the study, owing to the patient's treatment having to be deferred due to abnormal laboratory values that met the protocol criteria, and the patient was unable to wait for the protocol treatment due to deterioration of their general condition.

Table II. Response to treatment.

	mLSG15 + mogamulizumab (n = 29)	mLSG15 (n = 24)
CR	9	5
CRu	6	3
PR	10	10
CR + CRu	15	8
% CR (95% CI)	52% (33–71)	33% (16–55)
Between-group difference (95% CI)	18·4% (−8·9 to 43·8)	
CR + CRu + PR	25	18
ORR (95% CI)	86% (68–96)	75% (53–90)

CR, complete response; CRu, uncertified complete response; PR, partial response; %CR, complete response rate; CI, confidence interval; ORR, overall response rate.

anaemia (97%) and febrile neutropenia (90%). The corresponding percentages in the mLSG15 arm were 96%, 96%, 92%, 96%, 92% and 88%, respectively. The following TEAEs of grade ≥ 3 were more frequently observed (≥10% difference) in the mLSG15-plus-mogamulizumab arm than in the mLSG15 arm: anaemia (97% vs. 79%), thrombocytopenia (90% vs. 71%), lymphopenia (97% vs. 75%), leucopenia (100% vs. 88%) and decreased appetite (28% vs. 13%). Papular rash (21%), hyperglycaemia (14%), pyrexia (14%), interstitial lung disease (10%), erythematous rash (7%), cytomegalovirus infection (7%) cytomegaloviral pneumonia (7%) and oxygen saturation decreased (7%) occurred only in the mLSG15-plus-mogamulizumab arm.

Twenty serious AEs (SAEs) were reported in 12 patients in the mLSG15-plus-mogamulizumab arm. These included pneumonia in two patients, cytomegalovirus infection in two, interstitial lung disease in two, and the following events occurred in one patient each: febrile neutropenia, septic shock, cytomegaloviral pneumonia, pneumonitis, generalized erythema, viral encephalitis, oral disorder, bacteraemia, infection, exfoliative rash, ileus, cholecystitis, haemorrhagic cystitis and disease progression. The patient with septic shock did not recover and ultimately died. Another patient with haemorrhagic cystitis, which was suspected to be due to a viral infection, showed disease progression and died during the follow-up period due to the haemorrhagic cystitis as an SAE. The remaining 17 SAEs in the mLSG15-plus-mogamulizumab arm all improved or resolved.

Eleven SAEs were reported in nine patients in the mLSG15 arm. These included two patients with bacteraemia, and the following events in one patient each: infection, enterocolitis, pneumonia, soft tissue inflammation, myelodysplastic syndrome, ischaemic colitis, herpes zoster, neurogenic bladder and febrile neutropenia. The outcomes of all SAEs in the mLSG15 arm, with the exception of myelodysplastic syndrome, improved or resolved. There were no deaths during the treatment or follow-up period in the mLSG15 arm.

Pharmacokinetics and immunogenicity

Of the 29 patients enrolled in the mLSG15-plus-mogamulizumab arm, 16 (55%) completed the eight doses of mogamulizumab. The C_{max} (at the end of the eighth infusion) and C_{trough} (14 days after the eighth infusion) of mogamulizumab were 22·8 ± 4·6 and 94 ± 3·8 μg/ml (mean ± SD), respectively. None of the patients developed detectable levels of anti-mogamulizumab antibodies.

T-cell subset analysis

The numbers of circulating CD4/CD25/CCR4-positive cells in the blood immediately before VCAP therapy for cycle three in the mLSG15-plus-mogamulizumab arm (mean, 0·0246 × 10^9/l; median, 0·015 × 10^9/l; range, 0·004–0·094 × 10^9/l) were significantly lower than those in the mLSG15 arm (mean, 0·4693 × 10^9/l; median, 0·234 × 10^9/l; range, 0·077–3·991 × 10^9/l) ($P < 0·001$). The corresponding numbers of these cells 28 days after VECP therapy (Cycle 4) in the mLSG15-plus-mogamulizumab arm (0·0173 × 10^9/l; 0·0095 × 10^9/l; 0·001–0·133 × 10^9/l) were significantly lower

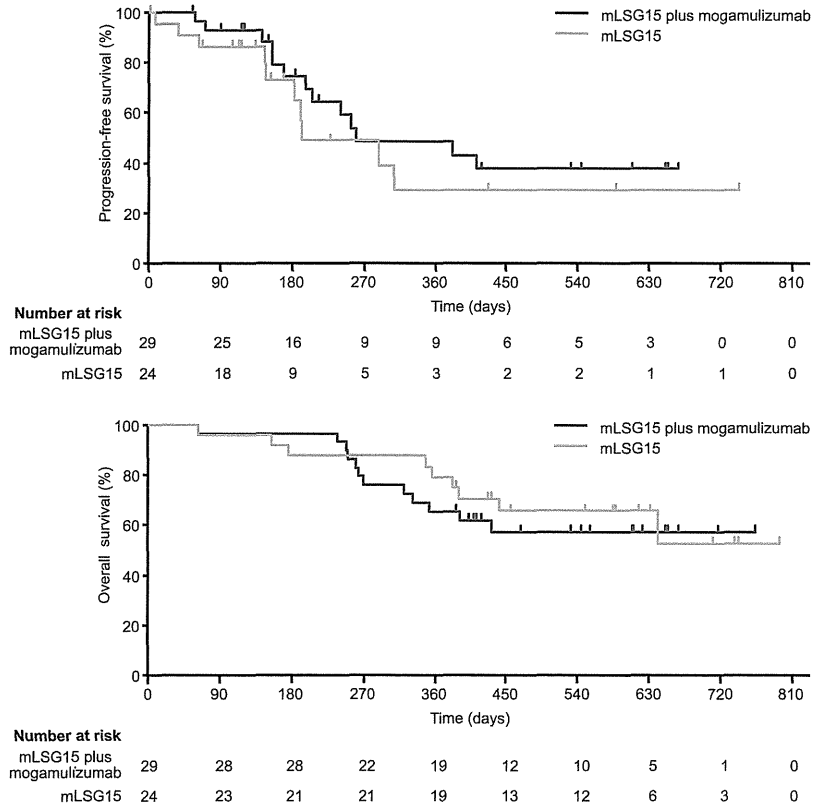

Fig 3. Progression-free survival and overall survival. (A) Kaplan–Meier curve of estimated progression-free survival (median, 8·5 months and 6·3 months in the mLSG15-plus-mogamulizumab and mLSG15 arms, respectively). (B) Kaplan–Meier curve of estimated overall survival (median, not achieved in either arm). The median follow-up periods in the mLSG15-plus-mogamulizumab and mLSG15 arms were 413 days (range, 63–764 days) and 502 days (range, 62–794 days), respectively.

than those in the mLSG15 arm ($0{\cdot}1478 \times 10^9$/l; $0{\cdot}133 \times 10^9$/l; $0{\cdot}059$–$0{\cdot}368 \times 10^9$/l) ($P < 0{\cdot}001$) (Fig 4A). Similarly, the numbers of CD4/CD25/FOXP3-positive cells in the blood immediately before VCAP therapy (Cycle 3) in the mLSG15-plus-mogamulizumab arm ($0{\cdot}0085 \times 10^9$/l; $0{\cdot}004 \times 10^9$/l; 0–$0{\cdot}048 \times 10^9$/l) were significantly lower than those in the mLSG15 arm ($0{\cdot}2432 \times 10^9$/l; $0{\cdot}074 \times 10^9$/l; $0{\cdot}018$–$2{\cdot}77 \times 10^9$/l) ($P < 0{\cdot}001$), and the numbers of these cells 28 days after VECP therapy (Cycle 4) in the mLSG15-plus-mogamulizumab arm ($0{\cdot}0054 \times 10^9$/l; $0{\cdot}003 \times 10^9$/l; 0–$0{\cdot}037 \times 10^9$/l) were significantly lower than those in the mLSG15 arm ($0{\cdot}0684 \times 10^9$/l; $0{\cdot}0435 \times 10^9$/l; $0{\cdot}016$–$0{\cdot}25 \times 10^9$/l) ($P < 0{\cdot}001$, Fig 4B).

Discussion

This study showed that the %CR in patients who received mLSG15 plus mogamulizumab was higher than that obtained in those treated with mLSG15 alone (52% vs. 33%; difference, 18·4%). The increase in the %CR with the addition of mogamulizumab observed in this study surpassed the predicted, targeted, clinically significant 15% increase in patients with ATL. Importantly, the %CR in patients with lesions in the blood compartment was higher in the combination arm, leading to the increase in overall %CR. This finding was consistent with that observed in previous studies, in which ATL lesions in the blood were found to be more sensitive to mogamulizumab monotherapy than ATL lesions at other disease sites (Yamamoto *et al*, 2010; Ishida *et al*, 2012b).

Infections were more frequent in the combination arm. In particular, cytomegalovirus infection was observed in 14% of patients in the combination arm, whereas it was not observed in the chemotherapy alone arm. Furthermore, cytomegalovirus-related SAEs occurred in three patients in the combination arm. Cytomegalovirus reactivation is observed in approximately 60% of patients with ATL during systemic chemotherapy (Ogata *et al*, 2011). Our study suggests that the addition of mogamulizumab to systemic chemotherapy might further increase the incidence of cytomegalovirus infection; therefore, careful monitoring for cytomegalovirus infection and appropriate use of antiviral therapy are recommended when systemic chemotherapy in combination with mogamulizumab is administered to patients with ATL.

In our previous study of mogamulizumab monotherapy for patients with relapsed ATL, skin rashes, including Stevens–Johnson syndrome, were the most frequently observed AEs (63%) (Ishida *et al*, 2012b, 2013). In the present study, as expected, AEs involving skin and subcutaneous tissue disorders were more frequent in the combination arm than in the chemotherapy alone arm. Even though no severe skin-related AEs, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, occurred in the present study, special attention should be paid to these skin-related AEs

Table III. Treatment-emergent adverse events in the mLSG15-plus-mogamulizumab (n = 29) and mLSG15 (n = 24) arms.

	All grades		≥Grade3	
	mLSG15 + mogamulizumab n = 29	mLSG15 n = 24	mLSG15 + mogamulizumab n = 29	mLSG15 n = 24
Blood and lymphatic system disorders	29 (100%)	22 (92%)	29 (100%)	22 (92%)
Anaemia	28 (97%)	22 (92%)	28 (97%)	19 (79%)
Febrile neutropenia	26 (90%)	21 (88%)	26 (90%)	21 (88%)
Gastrointestinal disorders	29 (100%)	23 (96%)	7 (24%)	7 (29%)
Stomatitis	16 (55%)	13 (54%)	4 (14%)	4 (17%)
General disorders and administration site conditions	29 (100%)	21 (88%)	6 (21%)	0 (0%)
Pyrexia	24 (83%)	15 (63%)	4 (14%)	0 (0%)
Infections and infestations	19 (66%)	16 (67%)	10 (34%)	7 (29%)
Bacteraemia	4 (14%)	3 (13%)	3 (10%)	3 (13%)
Pneumonia	4 (14%)	2 (8%)	3 (10%)	1 (4%)
Cytomegalovirus infection	4 (14%)	0 (0%)	2 (7%)	0 (0%)
Cytomegaloviral pneumonia	2 (7%)	0 (0%)	2 (7%)	0 (0%)
Investigations	29 (100%)	24 (100%)	29 (100%)	24 (100%)
Neutropenia	29 (100%)	23 (96%)	29 (100%)	22 (92%)
Thrombocytopenia	29 (100%)	23 (96%)	26 (90%)	17 (71%)
Lymphopenia	28 (97%)	23 (96%)	28 (97%)	18 (75%)
Leucopenia	29 (100%)	22 (92%)	29 (100%)	21 (88%)
Albuminaemia	12 (41%)	11 (46%)	2 (7%)	1 (4%)
Alanine transaminase increased	12 (41%)	10 (42%)	2 (7%)	2 (8%)
Aspartate transaminase increased	9 (31%)	8 (33%)	2 (7%)	1 (4%)
Potassium decreased	9 (31%)	6 (25%)	3 (10%)	1 (4%)
Sodium decreased	8 (28%)	7 (29%)	4 (14%)	2 (8%)
Phosphorus decreased	8 (28%)	3 (13%)	3 (10%)	1 (4%)
Blood pressure increased	7 (24%)	2 (8%)	5 (17%)	2 (8%)
Oxygen saturation decreased	4 (14%)	1 (4%)	2 (7%)	0 (0%)
Metabolism and nutrition disorders	27 (93%)	19 (79%)	14 (48%)	6 (25%)
Decreased appetite	23 (79%)	15 (63%)	8 (28%)	3 (13%)
Hyperglycaemia	13 (45%)	7 (29%)	4 (14%)	0 (0%)
Hyponatraemia	4 (14%)	3 (13%)	2 (7%)	2 (8%)
Hypophosphataemia	4 (14%)	3 (13%)	4 (14%)	2 (8%)
Hypokalaemia	5 (17%)	1 (4%)	2 (7%)	1 (4%)
Respiratory, thoracic and mediastinal disorders	21 (72%)	9 (38%)	4 (14%)	1 (4%)
Interstitial lung disease	3 (10%)	0 (0%)	3 (10%)	0 (0%)
Skin and subcutaneous tissue disorders	29 (100%)	20 (83%)	15 (52%)	1 (4%)
Papular rash	12 (41%)	0 (0%)	6 (21%)	0 (0%)
Erythematous rash	8 (28%)	0 (0%)	2 (7%)	0 (0%)

when mogamulizumab is administered to patients with ATL.

Adult T-cell leukaemia-lymphoma cells constitutively express CD25 (Waldmann *et al*, 1984), and the present study had an eligibility criterion of CCR4 positivity. Hence, most of the CD4/CD25/CCR4-positive cells were considered ATL cells. Compared to the chemotherapy alone arm, the combination arm showed a significant reduction in the number of CD4/CD25/CCR4-positive cells. This finding is consistent with the proposed antitumour mechanism of mogamulizumab, in that mogamulizumab kills CCR4-expressing ATL cells by increasing antibody-dependent cellular cytotoxicity (Shinkawa *et al*, 2003; Ishii *et al*, 2010; Yamamoto *et al*, 2010). In humans, CCR4 is expressed on CD45RO-positive, CD45RA-negative, FOXP3-positive activated regulatory T (Treg) cells (Miyara *et al*,

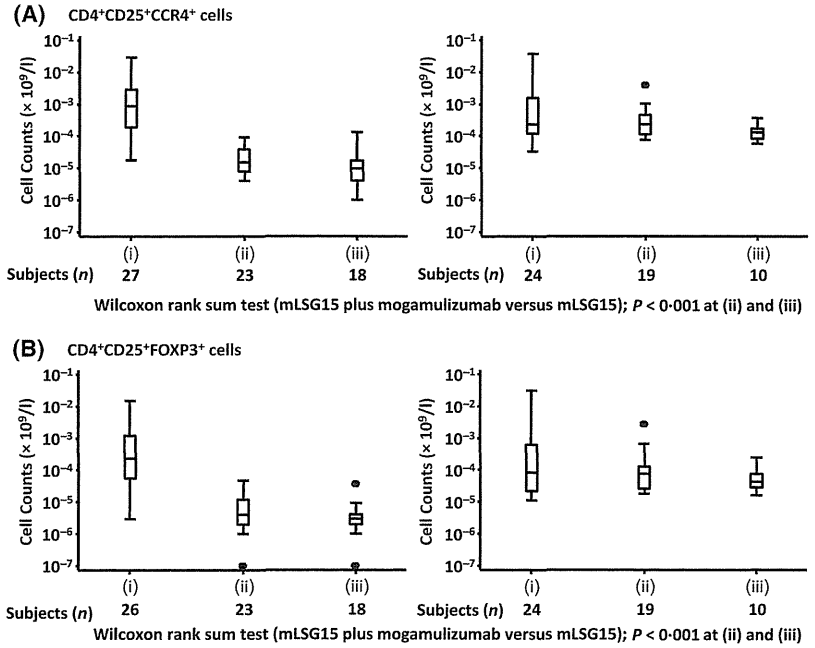

Fig 4. T-cell subset analysis. Blood samples were taken (i) immediately before the initiation of treatment, (ii) immediately before VCAP therapy for cycle three, and (iii) 28 days after VECP therapy for cycle four. The numbers of CD4/CD25/CC chemokine receptor 4 (CCR4)-positive cells (A) and CD4/CD25/FOXP3-positive cells (B) are shown as box and whisker plots indicating the minimum, lower, median, upper quartile, and maximum values. The number of samples used for analysis at each point is indicated below the graph. The differences of each point [(ii) & (iii)] between the mLSG15-plus-mogamulizumab and mLSG15 arms are indicated as p-values (Wilcoxon signed-rank test) below the graphs. CCR4 was detected by using a monoclonal antibody (clone 1G1), with its binding to CCR4 being unaffected by the presence of mogamulizumab. VCAP: vincristine, cyclophosphamide, doxorubicin, and prednisolone; VECP: vindesine, etoposide, carboplatin, and prednisolone.

2009; Ishida & Ueda, 2011; Sugiyama *et al*, 2013). In addition, ATL cells from a subset of patients express FOXP3 and function as Treg cells (Yano *et al*, 2007). Thus, the CD4/CD25/FOXP3-positive cells included not only endogenous activated Treg cells, but also ATL cells, in some patients. Our study indicated that compared to the chemotherapy alone arm, the combination arm showed a significant reduction in the number of CD4/CD25/FOXP3-positive cells, which is consistent with the findings from our previous study of mogamulizumab monotherapy. In general, decreasing the number of Treg cells is considered a promising strategy for boosting antitumour immunity in patients with cancer, because the numbers of these cells increase in the tumour microenvironment, and they may play an important role in the ability of the tumour to escape host immunity in several different types of cancer (Ishida & Ueda, 2011; Jacobs *et al*, 2012). On the other hand, because alterations in Treg cell frequencies and/or function may contribute to various autoimmune diseases (Michels-van Amelsfort *et al*, 2011), immune-related AEs, such as skin disorders, which were also observed in our study, should be carefully monitored.

The present study was conducted according to the premise that mLSG15 is the most recommended chemotherapeutic regimen for patients with newly diagnosed aggressive ATL. We found higher rates of treatment-related toxicities with mLSG15 compared to what has been reported for CHOP-14 (Tsukasaki *et al*, 2007). In the context of this scenario, this study suggests that a younger patient population, particularly those aged <56 years, will benefit from VCAP-AMP-VECP, while an older population consisting of those aged 56–69 years will not; there are no data regarding mLSG15 therapy for patients with ATL aged >69 years (Tsukasaki *et al*, 2007). In the present study, the median ages in the mLSG15-plus-mogamulizumab and mLSG15 arms were 61 years and 64 years, respectively; patients potentially benefiting from mLSG15 (<56 years) accounted for only 38% of the patients in the mLSG15-plus-mogamulizumab arm and 25% of those in the mLSG15 arm. Adult T-cell leukaemia-lymphoma generally occurs in older individuals, with a median age at diagnosis of approximately 66 years (Iwanaga *et al*, 2012); therefore, further investigations are needed to determine whether mLSG15 is indeed the most suitable systemic chemotherapeutic regimen when combined with mogamulizumab.

CCR4 is expressed on the surface of tumour cells of patients from a subgroup of PTCL other than ATL, which also has an unfavourable prognosis (Ishida *et al*, 2004; Nakagawa *et al*, 2009). We have already completed a multicentre phase II study of mogamulizumab monotherapy for patients with relapsed CCR4-positive PTCL in Japan (Clinicaltrials.gov: NCT01192984) (Ogura *et al*, 2014). Furthermore, other clinical trials of mogamulizumab for PTCL (Clinicaltrials.gov: NCT01611142) or cutaneous T-cell lymphoma (Clinicaltrials.gov: NCT01728805) are currently underway worldwide. Further studies are expected to allow the determination of the efficacy of combining mogamulizumab with chemotherapy or other novel molecular target therapies for PTCL subtypes other than ATL.

Although this study offers a novel treatment option for newly diagnosed aggressive ATL, some limitations should be discussed. First, this study was designed to set the %CR as a primary endpoint; as a result, this study does not have enough power or a long enough follow-up period to detect

PFS and OS differences between the two arms. Thus, although a tendency towards prolongation of PFS in the combination arm was observed in the present study, this was not confirmed. Second, the treatment after the study protocol, including allo-HCT and mogamulizumab, varied among the patients. Because the use of mogamulizumab for relapsed/refractory ATL was approved in Japan during the study period, the patients, including those in the chemotherapy alone arm, may have a chance to receive this drug. Both of these factors may affect the OS (Chihara *et al*, 2013).

In conclusion, although mLSG15 plus mogamulizumab was found to be associated with a potentially less favourable safety profile, particularly for infectious and skin-related events, the majority of the AEs were manageable. The %CR was higher with combination therapy. Accordingly, this combination treatment appears to be a better option for managing patients with newly diagnosed aggressive ATL. Further clinical studies are necessary to evaluate the survival parameters in patients treated with chemotherapy plus mogamulizumab and to determine a more suitable combination regimen.

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Author contributions

T.I., K.U., K.Y., N.U., A.U., K.T., S.A. and R.U. contributed to the conception and design of the study; T.I., T.J., S.T., H.S., K.U., K.Y., N.U., Y.S., K.N., A.U., K.T., H.F., K. Ishitsuka, S.Y., N.T., Y.M., K. Imada and T.M. contributed to the acquisition of data; T.I., K.T., S.A., M.T. and R.U. analysed and interpreted the data; all authors drafted and reviewed the manuscript and approved the final version for submission.

Conflicts of interest

T.I. has received honoraria and travel grants from Kyowa Hakko Kirin, and research funding from Kyowa Hakko Kirin, Chugai, Bayer and Celgene, and has served on the speakers bureau for Kyowa Hakko Kirin. T.J. has received honoraria and travel grants from Kyowa Hakko Kirin. S.T. has received travel grants and research funding from Kyowa Hakko Kirin. H.S. has served on the speakers bureau for Kyowa Hakko Kirin. K.Y. has a consultancy/advisory role with Kyowa Hakko Kirin and Novartis, has received honoraria from Kyowa Hakko Kirin, Novartis, Takeda and Janssen, and has received research funding from Kyowa Hakko Kirin, Novartis, Pfizer and ARIAD. Y.S. has received honoraria and research funding from Kyowa Hakko Kirin. K.N. has received honoraria from Kyowa Hakko Kirin. A.U. has received honoraria and research funding from Kyowa Hakko Kirin. K.T. has received honoraria from Kyowa Hakko Kirin and research funding from Kyowa Hakko Kirin, Celgene, Eisai, Solasia Pharma and Mundipharma. S.Y. has received honoraria and research funding from Kyowa Hakko Kirin. Y.M. has received honoraria, travel grants and research funding from Kyowa Hakko Kirin. K. Imada has received research funding from Kyowa Hakko Kirin. S.A. is employed by Kyowa Hakko Kirin, and is a stock owner. M.T. has a consultancy/advisory role with Kyowa Hakko Kirin, and has received honoraria from Kyowa Hakko Kirin. R.U. has a consultancy/advisory role with Mundipharma, and has received honoraria, travel grants and research funding from Kyowa Hakko Kirin and Chugai, and has served on the speakers bureau for Kyowa Hakko Kirin. The remaining authors declare no competing financial interests.

Appendix I

List of the review committees and medical experts who participated in this trial:

1 Junji Suzumiya, Shimane University Hospital
2 Takashi Terauchi, Research Centre for Cancer Prevention and Screening National Cancer Centre
3 Ukihide Tateishi, Yokohama City University Graduate School of Medicine
4 Junichi Tsukada, University of Occupational and Environmental Health
5 Koichi Nakata, University of Occupational and Environmental Health
6 Shigeo Nakamura, Nagoya University Graduate School of Medicine
7 Hiroshi Inagaki, Nagoya City University Graduate School of Medical Sciences
8 Koichi Ohshima, Kurume University School of Medicine
9 Michinori Ogura, Nagoya Daini Red Cross Hospital
10 Tetsuo Nagatani, Hachioji Medical Centre of Tokyo Medical University
11 Akimichi Morita, Nagoya City University Graduate School of Medical Sciences
12 Kazunari Yamaguchi, Institute of Molecular Embryology and Genetics, Kumamoto University
13 Yasuaki Yamada, Nagasaki University Graduate School of Biomedical Sciences
14 Shuichi Hanada, National Hospital Organization Kagoshima Medical Centre.

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ORIGINAL ARTICLE

Treatment outcome of elderly patients with aggressive adult T cell leukemia-lymphoma: Nagasaki University Hospital experience

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Abstract VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone)-AMP (doxorubicin, ranimustine, and prednisone)-VECP (vindesine, etoposide, carboplatin, and prednisone) is a standard regimen for aggressive adult T cell leukemia-lymphoma (ATL). However, the efficacy of this regimen has not been fully elucidated for patients aged 70 years or older. Here, we retrospectively analyzed elderly patients with aggressive ATL at Nagasaki University Hospital between 1994 and 2010 to assess treatment outcomes. Of 148 evaluable patients, 54 were aged 70 years or older at diagnosis. The median survival time (MST) and overall survival (OS) at 2 years in elderly patients were 10.6 months and 22.1 %, respectively. Thirty-four patients received VCAP-AMP-VECP as the initial treatment, although the doses were reduced for most patients. In these patients, MST and OS at 2 years were 13.4 months and 26.6 %, respectively. Eleven of 34 patients (32 %) received maintenance oral chemotherapy after two or three cycles of VCAP-AMP-VECP, and MST and OS at 2 years were 16.7 months and 32.7 %, respectively. Our results suggest that the VCAP-AMP-VECP regimen may be effective and that maintenance oral chemotherapy may be considered as a therapeutic option for elderly patients with aggressive ATL.

Keywords Adult T cell leukemia-lymphoma (ATL) · Elderly patients · Chemotherapy

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Introduction

Adult T cell leukemia-lymphoma (ATL) is a distinct peripheral T cell malignancy associated with human T-lymphotropic virus type I (HTLV-1) [1–4]. Aggressive ATL (i.e., acute, lymphoma, or unfavorable chronic type) generally has a poor prognosis and has been considered a target of chemotherapy [5–7]. However, a poor treatment outcome has been reported with chemotherapy for aggressive ATL. The VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone)-AMP (doxorubicin, ranimustine, and prednisone)-VECP (vindesine, etoposide, carboplatin, and prednisone) regimen was developed as an intensified regimen and efficacy has been reported for aggressive ATL [8, 9]. In the regimen, the interval between courses of chemotherapy was shortened to increase the dose intensity with administration of

granulocyte colony stimulating factor, and ranimustine and carboplatin were incorporated because the activity of these agents is not affected by the expression of P-glycoprotein, a possible mechanism of therapy resistance in ATL. The longer overall survival (OS) at 3 years and higher complete remission (CR) rate with VCAP-AMP-VECP compared with CHOP (cyclophosphamide, doxorubicine, vincristine, and prednisone)-14 have been reported for previously untreated aggressive ATL in a prospective randomized study [9]. The median survival time (MST) was reported to be 13 months, and the OS at 3 years was 24 % for patients treated with VCAP-AMP-VECP. Thus, this regimen is considered a standard treatment for patients with aggressive ATL. However, patients older than 70 years were not included in the clinical trial. Thus, the efficacy of this regimen in elderly ATL patients has not been elucidated.

In Western countries, the efficacy of antiviral therapy (combination of the antiretroviral agents, interferon alpha, and zidovudine) has been reported and adopted for the treatment of ATL [10]. However, the outcome of this treatment was not sufficient for aggressive ATL. The outcome of antiviral therapy for lymphoma-type ATL was reported to be inferior to that of chemotherapy. Furthermore, the reported result of antiviral therapy for acute-type ATL was not superior to the outcome of VCAP-AMP-VECP [9, 10]. In addition, these drugs are not approved for the treatment of ATL in Japan.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been adopted for the treatment of aggressive ATL, and its efficacy has been reported [11–13]. However, the high therapy-related mortality remains a problem, and generally, allo-HSCT cannot be used in patients older than 70 years. Thus, the optimal treatment of elderly patients has not been established.

A nationwide survey of ATL was carried out in Japan between 2006 and 2007 [14]. According to this survey, the age of ATL patients shifted toward older ages compared to previous nationwide studies, and the mean age gradually increased from 52.7 years in the first survey (cases before 1980) to 61.1 years in the ninth survey (1996–1997), and finally to 66.0 years in the current survey (median 67 years, range 19–94 years). Therefore, establishment of the optimal treatment strategy for elderly ATL patients is an important issue. However, the treatment outcome of elderly patients with aggressive ATL has not been evaluated.

In this study, we retrospectively investigated the outcome of patients 70 years or older with aggressive ATL in our hospital. The purpose of this study was to evaluate the treatment outcome in clinical practice and to provide baseline data for treatment of elderly ATL patients.

Patients and methods

Patients

We evaluated a total of 196 previously untreated patients with aggressive ATL (i.e., acute, lymphoma, or unfavorable chronic type) who were admitted to the Nagasaki University Hospital between January 1994 and December 2010. Clinical subtypes of ATL were classified based on Shimoyama criteria [5]. The unfavorable chronic type of ATL was defined by the presence of at least one of the following three factors: low serum albumin (Alb), high serum lactate dehydrogenase (LDH), or high blood urea nitrogen (BUN) concentration [6]. Diagnosis of ATL was made based on clinical features, the presence of anti-HTLV-1 antibody, histologically and/or cytologically proven mature T cell malignancy, and monoclonal integration of HTLV-1 proviral DNA into tumor cells in the evaluable cases. Of the 196 patients, 48 patients were excluded: 13 patients were excluded due to missing data at diagnosis, and 35 patients who had undergone allo-HSCT were also excluded (Fig. 1). We conducted the study with the remaining 148 eligible patients. Of these patients, 54 patients were 70 years or older (elderly group). The remaining 94 patients who were under 70 years old were designated as the younger group. Data were collected and updated by October 2012.

Clinical data

We collected information regarding age, sex, clinical subtype, white blood cell (WBC) count, neutrophil count, total lymphocyte count, platelet count, serum total protein,

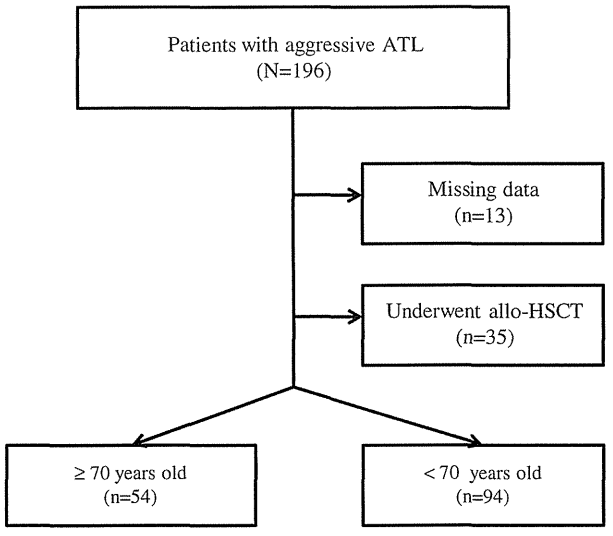


Fig. 1 Flowchart of patients. Allo-HSCT, allogeneic hematopoietic stem cell transplantation

serum Alb, LDH, BUN, soluble interleukin-2 receptor (sIL-2R), serum corrected calcium, serum calcium + (4 − Alb), Ann Arbor stage, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG), B symptoms (i.e., fever of unknown origin, loss of weight, or nocturnal sweating), and initial treatment. We defined leukemic stage IV disease as the presence of more than 1 % abnormal lymphocytes in peripheral blood [15]. This retrospective, nonrandomized, observational study that used existing data was granted exemption from the institutional review board, and the requirement for written informed consent was waived.

Treatment and response

Basically, patients with aggressive ATL were treated with the VCAP-AMP-VECP regimen, if their general condition was adequate. Patients who were not candidates for the full dose treatment received a dose-reduced VCAP-AMP-VECP regimen, which became the second treatment option. Patients with a worse condition were treated with other less-toxic regimens. Our study had no strict criteria for the selection of the treatment regimen or for the degree of the dose reduction. The final decision of the choice of the treatment regimen was made by each attending physician. Patients who received at least one cycle of the full dose or dose-adjusted VCAP-AMP-VECP as the initial treatment were assigned to the VCAP-AMP-VECP group, because it was difficult to distinguish the patient treated with VCAP regimen from those treated with dose-reduced CHOP-like regimen for the initial treatment in the retrospective analysis. The remaining patients were assigned to the other treatment group. In the elderly group, no patient was treated with mogamulizumab, an anti-CC chemokine receptor 4 monoclonal antibody, at the point of final analysis of this study. In some elderly patients treated with the VCAP-AMP-VECP regimen, the treatment was stopped after two or three cycles of the regimen, and maintenance oral chemotherapy was administered that was mainly composed of etoposide and/or sobuzoxane and/or prednisone. The response criteria were divided into four categories: CR, partial remission (PR), stable disease (SD), and progressive disease (PD). Responses were defined as follows: CR, disappearance of all disease; PR, $\geq$50 % reduction of measurable disease; SD, failure to attain CR or PR, but not PD; and PD, new or increased lesions according to the Response Criteria for ATL [16]. In this study, the best response was assessed regardless of the duration of the response.

Statistical analysis

Comparison among groups was performed with the chi-square statistic or Fisher's exact test as appropriate for categorical variables, and the Mann–Whitney U test for continuous variables. OS was calculated from the time of diagnosis to the date of death from any cause or to the last follow-up date. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The 95 % confidence interval (CI) of OS at 2 years was calculated. All tests were two-sided, and $P < 0.05$ was considered significant in all analyses. All statistical analyses were performed with Prism 6.0 software (GraphPad Software, San Diego, CA).

Results

Patient characteristics

We conducted the study with the 148 eligible patients (Fig. 1). The clinical characteristics of all patients by age are summarized in Table 1. Ninety-four patients were in the younger group, and 54 patients were in the elderly group. WBC count, neutrophil count, and total lymphocyte count were significantly increased in the younger patients compared with those in the elderly group. The initial treatment was also different in the two groups. In the elderly group, the doses of VCAP-AMP-VECP were reduced in most patients. We found no difference in other clinical parameters between the groups. The median follow-up time for the survivors was 12.9 months (range 0.2–201.5 months). Ninety-seven of 148 patients (65.5 %) received VCAP-AMP-VECP as the initial treatment, 45 patients (30.4 %) received other treatments, and six patients (4.1 %) received only supportive care.

Survival of the patients

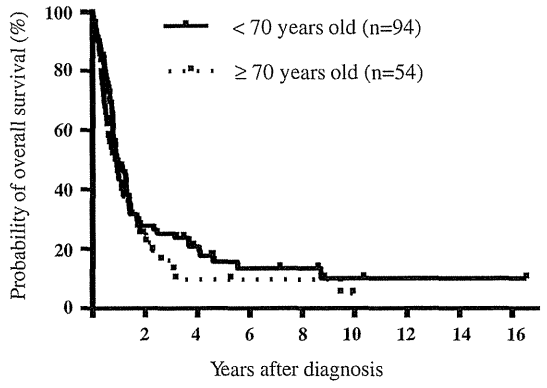
In the younger group, MST and OS at 2 years were 11.7 months and 26.4 % (95 % CI 17.2–36.6 %), respectively, whereas in the elderly group, MST and OS at 2 years were 10.6 months and 22.1 % (95 % CI 11.6–34.8 %), respectively (Fig. 2). Although MST and OS at 2 years in the younger group tended to be better than those in the elderly group, no significant difference was observed between the two groups ($P = 0.28$; log-rank test).

Survival and response of the elderly patients

The clinical characteristics of the elderly patients by initial treatment are summarized in Table 2. The median follow-up time for the survivors was 22.2 months (range 0.2–121.1 months). Thirty-four out of 54 patients (63.0 %) received the VCAP-AMP-VECP regimen as the initial treatment, whereas 16 patients (30.0 %) received other treatments. Four patients received only supportive care. We

Table 1 Characteristics of all patients with aggressive ATL

	<70 years old (n = 94)	>70 years old (n = 54)	P value
Median age (range) (year)	60.5 (34–69)	74 (70–85)	
Sex			1
Male	52	30	
Female	42	24	
Subtype			0.21
Acute type	76	38	
Lymphoma type	15	15	
Unfavorable chronic type	3	1	
WBC count ($\times 10^9$/L), median (range)	9.9 (1.4–224.8)	7.2 (1.2–186.0)	0.01*
Neutrophil count ($\times 10^9$/L), median (range)	5.8 (0.2–108.5)	4.1 (0–21.6)	0.008*
Total lymphocyte count ($\times 10^9$/L), median (range)	2.9 (0.3–206.8)	1.7 (0.4–169.3)	0.04*
Platelet count ($\times 10^9$/L), median (range)	204 (18–566)	188 (58–415)	0.66
Serum total protein (g/dL), median (range)	6.3 (4.1–7.9)	6.6 (4.4–8.8)	0.21
Serum albumin (g/dL), median (range)	3.6 (2.2–4.7)	3.7 (1.3–4.5)	0.82
LDH (IU/L), median (range)	496 (151–9165)	503 (138–4425)	0.46
BUN (mg/dL), median (range)	15 (5–57)	16 (5–81)	0.43
Soluble IL-2R (U/mL), median (range)	12252.5 (397–150124)	11212 (595–117784)	0.53
Serum corrected calcium (mg/dL), median (range)	9.9 (8.4–19.4)	9.8 (8.4–18.9)	0.85
Ann Arbor stage			0.5
I–II	5	5	
III–IV	89	49	
Performance status			0.85
0–2	67	40	
3, 4	27	14	
B symptom present	32	15	0.47
Initial treatment			<0.0001*
VCAP-AMP-VECP (full dose)	47	3	
VCAP-AMP-VECP (dose modification)	16	31	
Other treatment	29	16	
Supportive care	2	4	



No. at risk

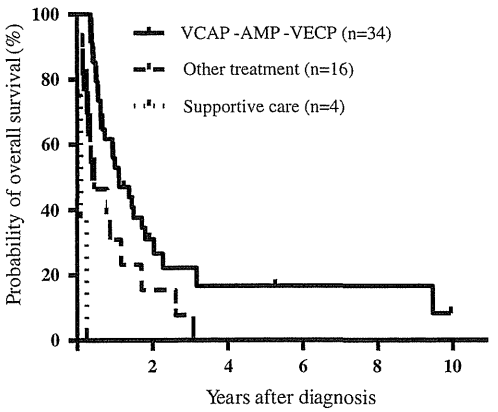
< 70 years old	94	21	13	6	5	2	1	1	1
≥ 70 years old	54	9	3	2	2	0	0	0	0

Fig. 2 Survival of patients by age

observed a statistically significant difference in age, WBC count, and total lymphocyte count between the VCAP-AMP-VECP group and the other treatment group (data not shown). The doses were reduced from the start of the chemotherapy in 31 out of 34 patients (91.2 %) treated with the VCAP-AMP-VECP regimen. Of the 16 patients who received other treatments, 7 patients had CHOP/CHOP-like treatment, 3 patients had single agent treatment, 4 patients had other combination therapy, and 2 patients had radiation therapy. In the VCAP-AMP-VECP group, MST and OS at 2 years were 13.4 months and 26.6 % (95 % CI 12.6–43.0 %), respectively, whereas in the other treatment group, MST and OS at 2 years were 5.4 months and 15.5 % (95 % CI 2.6–38.7 %), respectively (Fig. 3). In elderly patients treated with the VCAP-AMP-VECP regimen as the initial treatment, the survival curve was similar to the reported result in a clinical study

Table 2 Characteristics of elderly patients by initial treatment

	VCAP-AMP-VECP (n = 34)	Other treatment (n = 16)	Supportive care (n = 4)
Median age (range) (year)	73 (70–85)	79 (70–84)	75.5 (72–85)
Sex			
Male	20	7	3
Female	14	9	1
Subtype			
Acute type	25	12	1
Lymphoma type	9	4	2
Unfavorable chronic type	0	0	1
WBC count ($\times 10^9$/L), median (range)	6.3 (3.0–186.0)	8.0 (1.2–27.9)	12.0 (8.1–17.1)
Neutrophil count ($\times 10^9$/L), median (range)	4.0 (0.3–21.6)	4.0 (0–12.1)	5.7 (2.9–10.1)
Total lymphocyte count ($\times 10^9$/L), median (range)	1.8 (0.3–169.3)	1.4 (0.5–23.7)	4.1 (0.6–13.2)
Platelet count ($\times 10^9$/L), median (range)	189 (58–415)	189 (101–339)	166 (111–293)
Serum total protein (g/dL), median (range)	6.7 (4.9–7.8)	6.3 (4.4–8.8)	6.5 (5.7–7.3)
Serum albumin (g/dL), median (range)	3.7 (1.3–4.5)	3.4 (2.7–4.1)	3.1 (2.7–4.3)
LDH (IU/L), median (range)	527 (176–4425)	526 (182–1634)	279 (138–1306)
BUN (mg/dL), median (range)	15 (5–47)	17 (11–81)	20 (18–22)
Soluble IL-2R (U/mL), median (range)	11931 (595–117784)	10981 (1171–29533)	10277 (3580–25136)
Serum corrected calcium (mg/dL), median (range)	9.8 (8.4–13.4)	9.7 (8.7–18.9)	9.8 (9.6–10.4)
Ann Arbor stage			
I–II	4	1	1
III–IV	27	15	3
Performance status			
0–2	27	11	2
3, 4	7	5	2
B symptom present	10	4	1



No. at risk						
VCAP-AMP-VECP	34	7	3	2	2	0
Other treatment	16	2	0	0	0	0
Supportive care	4	0	0	0	0	0

Fig. 3 Survival of the elderly patients according to the initial therapy

of patients older than 56 years and younger than 70 years [9]. The overall response rate (CR + PR) was 75 % (24/32; two patients were unknown) after two or three cycles of VCAP-AMP-VECP, and the rate of completion of the six cycles of VCAP-AMP-VECP was 19 % (6/32) in the elderly group.

Maintenance oral chemotherapy

For some elderly patients treated with the VCAP-AMP-VECP regimen who had some response to the initial treatment, maintenance oral chemotherapy was administered after fewer than three cycles of the VCAP-AMP-VECP regimen, considering their quality of life and the difficulty in continuing the intensive regimen. We also evaluated the outcome of patients treated with maintenance oral chemotherapy. Eleven out of 34 (32 %) patients received maintenance oral chemotherapy.

Table 3 Characteristics of elderly patients according to maintenance oral chemotherapy

	Maintenance oral chemotherapy (+) ($n = 11$)	Maintenance oral chemotherapy (−) ($n = 21$)	P value
Median age (range) (year)	73 (70–80)	74 (70–85)	0.90
Sex			1.00
Male	6	12	
Female	5	9	
Subtype			0.09
Acute type	6	18	
Lymphoma type	5	3	
WBC count ($\times 10^9$/L), median (range)	7.0 (3.3–36.3)	6.1 (3.0–186.0)	0.84
Neutrophil count ($\times 10^9$/L), median (range)	4.3 (0.3–6.9)	3.7 (0.6–21.6)	0.61
Total lymphocyte count ($\times 10^9$/L), median (range)	1.7 (0.5–26.8)	2.1 (0.4–169.2)	0.34
Platelet count ($\times 10^9$/L), median (range)	250 (123–415)	170 (58–365)	0.0122*
Serum total protein (g/dL), median (range)	7.0 (4.9–7.5)	7.0 (4.9–7.8)	0.31
Serum albumin (g/dL), median (range)	4.0 (1.3–4.1)	4.0 (2.7–4.5)	0.43
LDH (IU/L), median (range)	488 (203–938)	635 (176–4425)	0.66
BUN (mg/dL), median (range)	15 (5–38)	14 (10–47)	0.49
Soluble IL-2R (U/mL), median (range)	5752 (940–39734)	12223 (595–117784)	0.58
Serum corrected calcium (mg/dL), median (range)	10.0 (9.0–12.8)	10.0 (8.4–13.4)	0.86
Ann Arbor stage			1.00
I–II	1	3	
III–IV	10	18	
Performance status			1.00
0–2	9	16	
3, 4	2	5	
B symptom present	5	5	0.25

The disease status at the beginning of the maintenance therapy was CR in 2 patients, PR in 8 patients, and SD in 1 patient. In patients who received maintenance therapy, MST and OS at 2 years were 16.7 months and 32.7 % (95 % CI 8.3–60.6 %), respectively. Twenty-three patients were not treated with the maintenance therapy, and the disease status was CR in 1 patient, PR in 12 patients, and PD in 3 patients, for the patients assessed after 3 cycles of VCAP-AMP-VECP, and PR in 1 patient and PD in 4 patients, for the patients who were treated no more than 2 cycles of the regimen. For the two remaining patients, it was not clear whether they were treated with maintenance therapy or not. The clinical characteristics of the patients according to the maintenance therapy are summarized in Table 3. There was no significant difference, except for the platelet count, in the background between the patients treated with the maintenance therapy and those without the treatment.

A simplified ATL-prognostic index (PI)

An ATL-PI has been proposed to develop a system for risk stratification in patients with acute- and lymphoma-type ATL [15]. A simplified ATL-PI was defined with five risk factors as follows: 2 (if stage = III or IV) + 1 (if ECOG PS > 1) + 1 (if age > 70 years) + 1 (if albumin < 3.5 g/dL) + 1 (if sIL-2R > 20,000 U/mL). Scores from 0 to 2 were categorized into the low-risk group, 3 and 4 into the intermediate-risk group, and 5 to 6 into the high-risk group. MSTs were reported to be 4.5, 7.0, and 16.2 months, and OS at 2 years were reported to be 6, 17, and 37 % for patients at high, intermediate, and low risk, respectively [15]. We evaluated the elderly patients in our study using the simplified ATL-PI. Ten patients were excluded because of missing data. The MSTs were 5.1, 12.9, and 19.5 months, and OS at 2 years were 17.8 % (95 % CI 3.4–41.4 %), 18.4 % (95 % CI 5.8–36.6 %), and 50.0 % (95 % CI 0.6–91.0 %) for patients in the high-risk ($n = 4$), intermediate-risk ($n = 23$), and low-risk groups ($n = 17$), respectively (Fig. 4a). We identified no statistically significant difference, but observed a tendency for a better prognosis in the low-risk group. The effects of the risk factors in the ATL-PI on OS in the elderly patients were analyzed with univariate analysis. The survival rate was