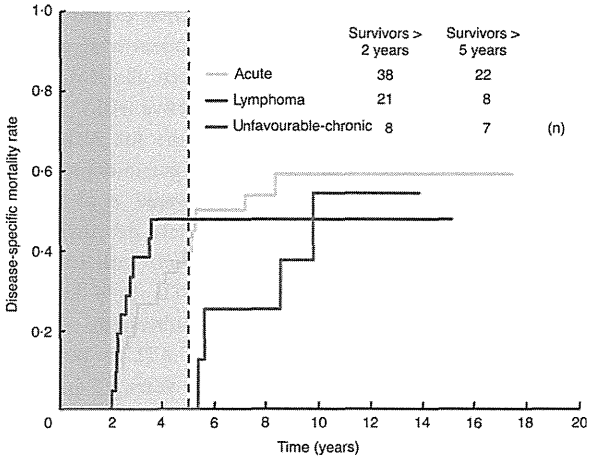

Fig 3. ATL-related deaths of patients who survived >2 years according to subtype. Among the 37 patients who survived >5 years, there were no ATL-related deaths in lymphoma type in contrast to the 10 ATL-related deaths in other types after 5 years.

external validation set than in the training set, possibly reflecting recent advances in treatment, including chemotherapy and allogeneic haematopoietic stem cell transplantation (allo-HSCT).

In our analysis of patients who survived >5 years, no ATL-related deaths occurred in those with lymphoma type, which is in contrast to the ATL-related deaths seen among patients with acute or unfavourable chronic type (Fig 3). This suggests that about 10% of patients with lymphoma type survived >5 years, most of whom might have been cured. Although abnormalities of comparative genomic hybridization might differ between acute and lymphoma types (Oshiro *et al*, 2006), the difference in clinical course between lymphoma type and acute or unfavourable chronic type remains unclear, and further analyses on the molecular and biological features of these types are needed.

Of the 276 patients studied, 20 received an allo-HSCT. The 5-year OS rate of these patients was 40%, compared with 12% in patients who did not undergo transplantation

Table II. Results of univariate and multivariate analyses in the training set (n = 193).

Factor		Univariate analysis HR (95%CI)	*P* value	Pre-planned multivariate analysis (AIC = 1545·6) HR (95%CI)	*P* value	Model used for constructing JCOG-PI (AIC = 1537·8) HR (95%CI)	*P* value
Ca, mmol/l	<2·75	Ref		Ref		Ref	
	≥2·75	1·742 (1·214–2·498)	0·002	1·688 (1·156–2·466)	0·007	1·574 (1·088–2·277)	0·016
ECOG PS	0–1	Ref		Ref		Ref	
	2–4	1·680 (1·219–2·314)	0·001	1·493 (1·073–2·078)	0·018	1·554 (1·120–2·157)	0·008
B symptoms	–	Ref		Ref			
	+	1·249 (0·926–1·685)	0·145	1·288 (0·945–1·755)	0·109		
Sex	Male	Ref					
	Female	0·999 (0·743–1·342)	0·994				
Age, years	<60	Ref					
	≥60	1·108 (0·818–1·502)	0·504				
Stage	I–II	Ref					
	III–IV	1·293 (0·682–2·451)	0·429				
Liver invasion	–	Ref					
	+	1·238 (0·867–1·768)	0·241				
LDH, iu/l	≤ULN	Ref					
	>1 × ULN	1·325 (0·840–2·091)	0·226				
BUN, mmol/l	≤ULN	Ref					
	>1 × ULN	1·332 (0·871–2·036)	0·184				
Serum protein, g/l	<60	Ref					
	≥60	0·642 (0·457–0·901)	0·010				
Lymphocytes, $\times 10^9$/l	<4	Ref					
	4–14·9 (vs. <4)	1·110 (0·785–1·570)	0·553				
	≥15 (vs. <4)	1·102 (0·747–1·626)	0·626				
Neutrophils, $\times 10^9$/l	<8	Ref					
	≥8	1·271 (0·888–1·817)	0·189				
Platelets, $\times 10^9$/l	<150	Ref					
	≥150	0·900 (0·626–1·294)	0·569				

AIC, Akaike's Information Criteria; JCOG, Japan Clinical Oncology Group; PI, Prognostic index; HR, hazard ratio; CI, confidence interval; Ref, reference; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; BUN, blood urea nitrogen.

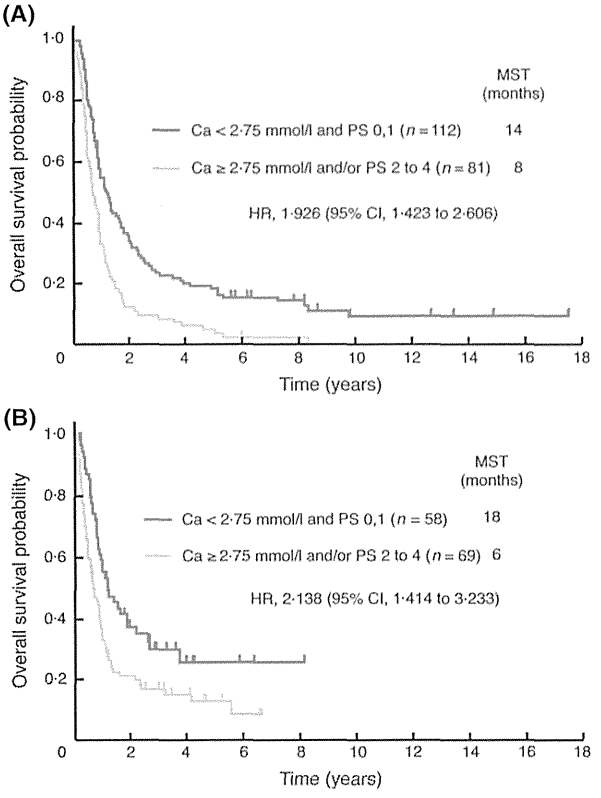

Fig 4. Overall survival of the patients in the training set and in the external validation set according to the JCOG-PI. (A) OS in the training set. The median survival time (MST) and 5-year OS were 14 months and 18% in moderate-risk group (blue line) and were 8 months and 4% in high-risk group (yellow line), respectively (B) OS in the validation set. The MST of 18 months and 6 months in the moderate- (blue line) and high-risk (yellow line) groups, respectively, and JCOG-PI showed good reproducibility.

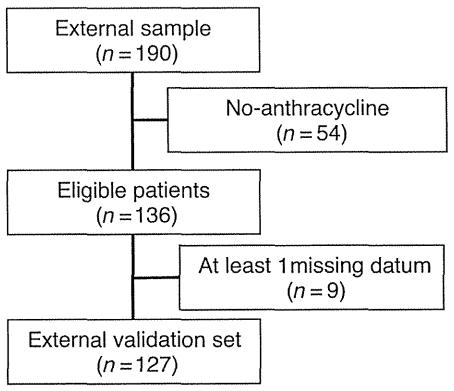

Fig 5. Patient disposition of the external validation set.

(data not shown). However, it was too difficult to evaluate the efficacy of allo-HSCT in our cohort because the disease status at transplantation and the duration from registration to transplantation were rather heterogeneous and the transition to allo-HSCT was time-dependent. To adjust this time-dependent causality, periodical data collection of, for example, indicators of treatment and time-dependent confounders, is necessary. The causal relationship between allo-HSCT and OS should be evaluated in a future prospective trial.

Several reports have revealed risk factors for ATL. In a prospective randomized trial against NHL parsimonious conducted between 1981 and 1983, Shimoyama *et al* (1988) demonstrated that poor PS and high lactate dehydrogenase levels were poor prognostic factors in patients with advanced T-cell lymphoma/leukaemia, including ATL. In a Japanese nationwide survey of 854 patients, a multivariate analysis identified major prognostic indicators of ATL as poor PS, high lactate dehydrogenase levels, age ≥40 years, >3 involved lesions and hypercalcaemia (Lymphoma Study Group, 1991). These factors were then used to construct a risk model. Additional factors reportedly associated with poor prognosis, as determined by multivariate analyses, include thrombocytopenia (Yamada *et al*, 1997), eosinophilia (Utsunomiya *et al*, 2007), bone marrow involvement (Takasaki *et al*, 2007), high interleukin (IL)5 and IL10 serum levels (Inagaki *et al*, 2006), C-C chemokine receptor 4 (CCR4) expression (Ishida *et al*, 2003), lung resistance-related protein (Ohno *et al*, 2001), *TP53* mutation (Tawara *et al*, 2006) and *CDKN2A* deletion (Yamada *et al*, 1997). Specific to chronic-type ATL, multivariate analysis has identified high lactate dehydrogenase levels, high blood urea nitrogen levels and low albumin levels as poor prognostic factors in several retrospective analyses (Shimoyama, 1994).

Recently, an ATL-PI consisting of Ann Arbour clinical stage, PS, age, serum albumin level and soluble IL2 receptor level was used to identify three risk groups for patients with acute and lymphoma types of ATL (Katsuya *et al*, 2012). However, in that study, both the ATL-PI and the risk grouping in the 1980's were constructed based on the results of questionnaires collected retrospectively; hence the treatments used were diverse and the prognostic factors might not have been evaluated homogeneously, in contrast to present study based on the three prospective trials (Lymphoma Study Group, 1991; Katsuya *et al*, 2012).

In the present study, monoclonal integration of HTLV-1 was not detected in four of 104 patients analysed. It was previously demonstrated that about 20% of patients with lymphoma-type ATL did not have monoclonal integration of HTLV-1, by Southern blot analysis, when investigating lymph node specimens (Ohshima *et al*, 1998). From this aspect, the possibility that a fraction of patients with the lymphoma type in the present study had non-ATL-peripheral T-cell lymphoma cannot be completely excluded. Further studies are required to differentiate lymphoma-type ATL from non-ATL-peripheral T-cell lymphoma by analysing monoclonal integration of the HTLV-1 provirus by Southern blot analysis or integration site-specific polymerase chain reaction.

In this study, the median age of 56 years in the training set was notably younger than that in other recent reports and that of the average population of patients with ATL. The

population investigated in the present study represents a selection of fairly young and physically fit patients with preserved organ functions. Although we expected to define a favourable prognosis group in the international PI for aggressive NHL, which consists mostly of diffuse large B-cell lymphoma, the difference in the OS between the two risk groups was small. This finding was similar to a recent retrospective nationwide survey in Japan of all patients with acute or lymphoma type at each institute (Katsuya *et al*, 2012). Therefore, the JCOG-PI could not be used to identify patients with aggressive ATL who could be treated with intensive chemotherapy alone and spared from more intensive therapy, such as allo-HSCT, as is the case with the ATL-PI (Katsuya *et al*, 2012). However, we did manage to identify patients with extremely poor prognosis despite undergoing intensive chemotherapy in clinical trials. These patients might be candidates for future trials that combine new agents or investigational strategies.

Recently, the results of several phase I and II trials using a defucosylated anti-CCR4 antibody for relapsed patients with aggressive ATL have demonstrated clinically meaningful antitumour activity and an acceptable toxicity profile (Yamamoto *et al*, 2010; Ishida *et al*, 2012a). Moreover, allo-HSCT with myeloablative and reduced intensity conditioning for patients with aggressive ATL has been reported to cure diseases associated with the graft-*versus*-ATL effect, despite the high transplant-related mortality (Hishizawa *et al*, 2010; Ishida *et al*, 2012b; Kanda *et al*, 2012). To further improve patient outcomes, two trials are ongoing in Japan: a phase II trial of VCAP-AMP-VECP followed by allo-HSCT with myeloablative conditioning for patients aged <55 years with aggressive ATL (JCOG 0907), and a randomized phase II trial of VCAP-AMP-VECP with or without anti-CCR4 antibody (Jo *et al*, 2013).

In conclusion, patients with lymphoma-type ATL who survived >5 years might have been cured, which is in contrast to long-term survivors with acute or unfavourable chronic type. The JCOG-PI, based on corrected calcium levels and PS, is a simple and valuable tool for identifying patients with aggressive ATL having extremely poor prognosis in clinical trials, and it will be useful for the design of future studies combining new drugs or investigational strategies.

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Authorship

T.F., M.S, H.F., K. T. and K.T. designed the study and wrote the paper. T.H. designed the study. S.N. and T.S. designed the study, analysed data and wrote the paper. Y.I., Y.M., T.T., K.U., Y.K., N.F., A.U., M.T., K.N., M.H., N.U., S.Y., K.T., K.I., M.K. and M.N. collected data and reviewed the paper.

Disclosure

The authors report no potential conflict of interest.

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LETTER TO THE EDITOR

Molecular analysis of loss of CCR4 expression during mogamulizumab monotherapy in an adult T cell leukemia/lymphoma patient

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Dear Editor,

A 63-year-old male was admitted to our hospital with relapsed CC chemokine receptor 4 (CCR4)-positive adult T cell leukemia/lymphoma (ATL) (Fig. 1a). He received intravenous infusions of mogamulizumab (Moga), a defucosylated, humanized anti-CCR4 monoclonal antibody [1], once a week at a dose of 1.0 mg/kg. After the third infusion of Moga, morphologically abnormal lymphocyte count and human T cell leukemia virus type 1 (HTLV-1) proviral load [2] decreased from 4.8×10^9/L (32 % of white blood cell (WBC)) and 60.3 copies/100 peripheral blood mononuclear cells (PBMCs) to 0.33×10^9/L (4 % of WBC) and 17.0 copies/100 PBMCs, respectively. However, serum lactate dehydrogenase and soluble interleukin-2 receptor levels rose from 475 and 4,627 U/ml to 596 and 56,092 U/ml, respectively. His mediastinal and intra-abdominal lymph nodes also increased in size. Flow cytometric analysis (FCM) of his PB revealed that the majority of the remaining ATL cells were negative for CCR4 (Fig. 1a). It should be noted that the anti-CCR4 antibody used for FCM was clone lG1, which binds to a different epitope from Moga [3]; thus, epitope masking by Moga was unlikely. Southern blot hybridization analysis showed the same monoclonal integration of the HTLV-1 provirus as before (Fig. 1b), which indicated that ATL cells from the pre- and post-Moga monotherapies were of the same clonal origin.

To elucidate the molecular mechanisms underlying the loss of CCR4 antigen expression, we analyzed the messenger RNA (mRNA) expression of *CCR4* and other related genes in his PBMCs using reverse transcriptase–polymerase chain reaction analysis [4, 5] (Fig. 1c). The expression of *CCR4* mRNA markedly decreased following Moga monotherapy. On the other hand, the expression of *FRA-2*, the upstream transcription factor that induces the expression of *CCR4* and promotes cell growth in ATL [4], was maintained even after the treatment. Expression of the other target proto-oncogenes of *FRA-2*, such as *c-MYB*, *MDM2*, *BCL-6*, and *SOX4* [4, 5], was also maintained. We performed Sanger sequencing of the *CCR4* gene using genomic DNA from pre- and post-treatment PBMCs. No acquired mutations were detected in the post-treatment sample. These results suggested that neither genetic mutations nor the reduced expression of upstream transcription factors may be the cause of the loss of CCR4 expression. Epigenetic mechanisms or clonal selection may be the cause, namely a minor fraction of CCR4-negative sub-clones could have already existed and expanded during the treatment (Fig. 1a).

The loss of target molecules on tumor cells has been reported as an important mechanism of resistance to antibody-based therapies [6]. CCR4 is frequently expressed on ATL cells [7] and is a promising target molecule for therapy against ATL [1]. However, as in the case considered here, loss of CCR4 antigen expression was observed in an

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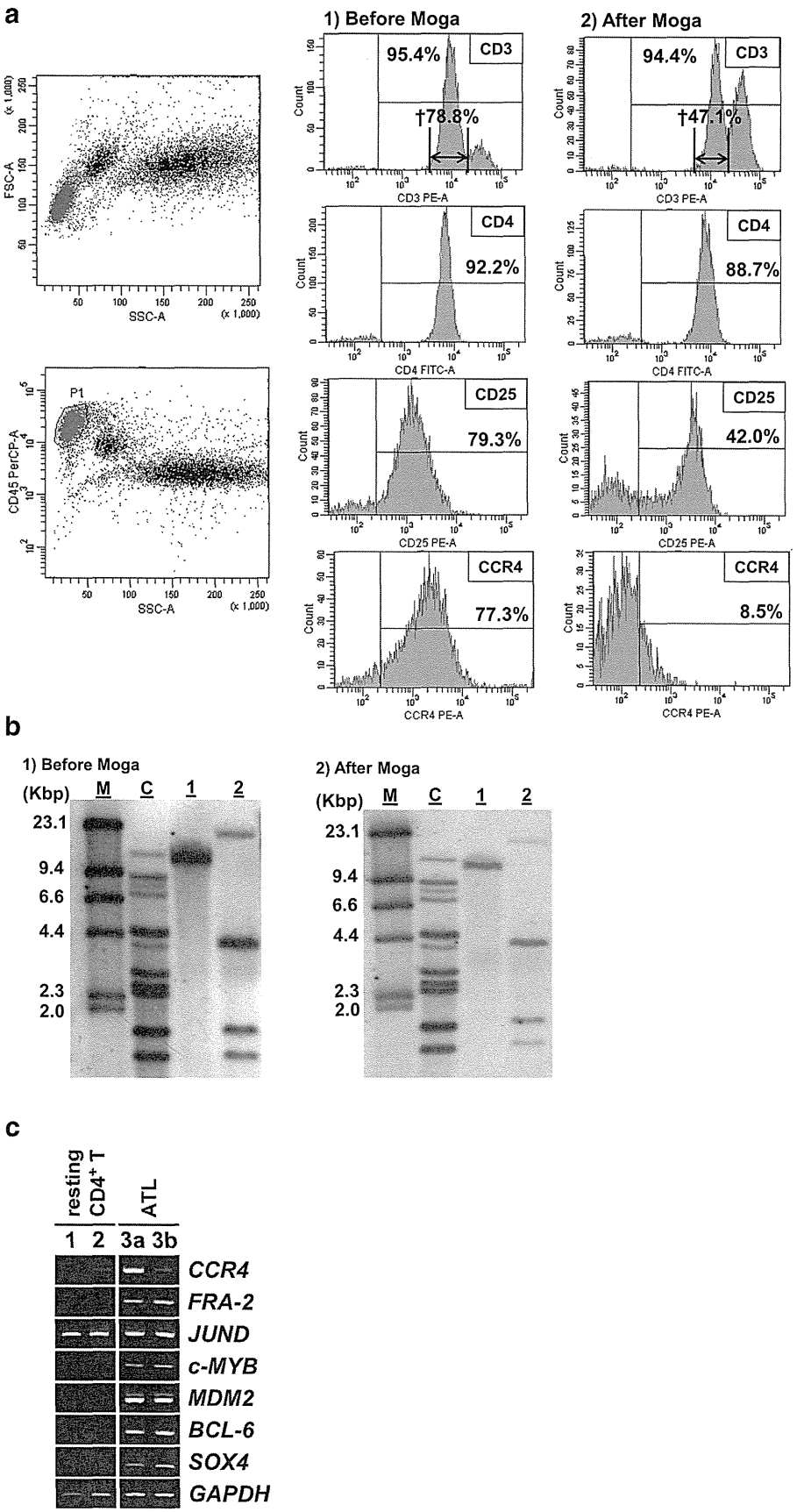

Fig. 1 **a** FCM. Lymphocytes were gated in FSC/SSC and CD45/SSC cytograms. Each histogram was conditioned on the lymphocyte gate: *1*) Before Moga monotherapy and *2*) after Moga monotherapy. Most tumor cells that accumulated in the $CD3^{dim}$ sub-population (dagger) seemed to have lost the expression of the CCR4 antigen following Moga monotherapy. **b** Southern blot hybridization analysis. The same monoclonal integration of HTLV-1 provirus was observed in PBMCs from *1*) pre- and *2*) post-Moga monotherapies. *M* size marker (λDNA/*Hind*III), *C* positive control, *lane 1* patient's DNA digested with *EcoRI*, *lane 2* patient's DNA digested with *PstI*. **c** Reverse transcriptase–polymerase chain reaction analysis. The mRNA expression of the indicated genes was examined for normal resting $CD4^+$ T cells from two healthy donors (*lanes 1* and *2*) and the patient's PBMCs before (*lane 3a*) and after (*lane 3b*) Moga monotherapy. While the expression of *CCR4* mRNA was markedly decreased following Moga monotherapy, the expression of the upstream transcription factor, *FRA-2*, as well as its downstream target proto-oncogenes, *c-MYB*, *MDM2*, *BCL-6*, and *SOX4*, remained unchanged. *GAPDH* was used as a loading control

ATL patient at relapse following Moga monotherapy [8]. Thus, the loss of CCR4 expression on ATL cells may not be a rare phenomenon and may be critically involved in resistance to Moga. Further analyses are needed to fully understand the mechanisms underlying the loss of CCR4 expression to overcome resistance to Moga.

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Conflict of interest The authors declare no competing financial interests.

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Synergy of Myc, cell cycle regulators and the Akt pathway in the development of aggressive B-cell lymphoma in a mouse model

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The accumulation of multiple genetic abnormalities can result in hematological malignancies. With regard to B-cell lymphomas, chromosomal translocations, copy number alterations and abnormal gene expression were shown to be involved in lymphomagenesis.[1] Furthermore, numerous gene mutations are being found by high-throughput sequencing.[2–4] Broad and intensive functional analyses are required to delineate the degree to which specific genetic alterations contribute to the development of lymphomas, although it is not an easy task to elucidate the synergistic effects of candidate genes employing currently available methods such as those employing transgenic or knockout mice. Moreover, additional genetic changes sometimes occur in lymphomas developing in genetically modified mice,[5] which make it difficult to determine the minimum genetic abnormalities required for tumor development.

In an effort to identify the genes required for the transformation of normal B cells into malignant cells, we have established *in vitro* culture systems that allow gene transduction into normal murine pre-B cells[6] and mature B cells.[7] These systems successfully showed the synergistic effects of deregulated translocation-associated genes on the development of lymphoma *in vivo*. In the present study, we have focused on gene mutations, and have aimed to provide direct evidence of the synergy of Myc, cell cycle regulators and the Akt pathway in the development of lymphoma in a mouse model.

As Burkitt lymphoma (BL) driven by the *IgH–Myc* translocation has recently been shown to involve gene mutations of cell cycle regulators such as *CCND3*^{T283A} and *E47*^{V557E},[2] we initially examined a combination of Myc, CCND3^{T283A} and E47^{V557E} in terms of their ability to induce lymphoma. Germinal center B (GCB) cells induced *in vitro* were retrovirally transduced with *CCND3*^{T283A}*/Myc* (using MSCV-*CCND3*^{T283A}-pgk-*Myc*-ires-*GFP retrovirus*) and *E47*^{V557E} (MSCV-*E47*^{V557E}-ires-*human* (*h*) *CD8*) (Supplementary Figures 1 and 2), and transplanted ($5–10 \times 10^6$ cells) intraperitoneally into mice, as previously described[7] (summarized in Figure 1a). Although T and NK cells could influence the development of lymphoma in a positive or negative manner, we chose NSG mice (NOD.Cg-Prkdc^{scid}Il2rg^{tm1Wjl}/SzJ; Jackson Laboratory, Bar Harbor, ME, USA) lacking T and NK cells as recipients in an effort to directly examine the tumorigenic effects of the transduced genes. All animal experiments were performed according to protocols approved by the Institutional Animal Care and Use Committee at the Aichi Cancer Center. Although transplanted mice were apparently normal with no evidence of clinical lymphoma, a population of rare GFP- and/or hCD8-positive cells was found in the spleen of primary recipient mice (data not shown). Nevertheless, secondary recipient mice transplanted with spleen cells obtained from primary mice did not show any signs of lymphoma, which suggested that this combination of genes was insufficient for the transformation of normal B cells into malignant cells under our experimental conditions. Detailed analysis of the kinetics of engraftment/proliferation awaits further study.

We therefore explored additional genetic aberrations that might operate with *Myc*, *CCND3*^{T283A} and *E47*^{V557E}, and focused on genes involved in the PI3K/AKT pathway. We previously showed the synergistic action of *Myc* and miR-17 cluster,[8] microRNAs that activate the PI3K/AKT pathway, partly through downregulation of PTEN and PHLPP2.[9,10] In addition, our investigation of the gene expression data of BL, and diffuse large B-cell lymphoma (DLBCL) made available by Hummel *et al.*[11] (GSE4475), revealed high expression of the T-cell breakpoint 1 (*TCL1A*) gene, the product of which facilitates AKT dimerization and enhances phosphorylation of the S473 residue of AKT,[12] although AKT expression was slightly lower in BL than in DLBCL (Supplementary Figure 3). Elevated expression of TCL1 has been reported in many B-cell malignancies[13] including Epstein–Barr virus-positive BL cell lines.[14] These findings as well as the recent reports[2,5] prompted us to examine the possible involvement of the AKT pathway in the development of Myc-driven lymphoma in our model system *in vivo*. We thus constructed two retroviral vectors, MSCV-*myristoylated*(*myr*)*Akt*-ires-*hCD4* and pGCDNsam-*TCL1A*-ires-*human Kusabira-Orange* (*hKO*) (Supplementary Figure 1), transduced these together with *CCND3*^{T283A}*/Myc* and *E47*^{V557E} into GCB cells (hereinafter referred to as 'MCEAT'; M = *Myc*, C = *CCND3*^{T283A}, E = *E47*^{V557E}, A = *Akt* and T = *TCL1A*; expression of individual protein was confirmed by western blotting as shown in Supplementary Figure 2) and transplanted the cells into NSG mice ($n = 6$). The expression of cell surface antigens on the transduced cells *in vitro*, which reflects the developmental stages of B cells, was not affected by gene transduction, and was similar to that of *Myc/Bcl2*-transduced cells previously described[7] (Supplementary Figure 4). All mice became prostrate 20 days following transplantation (Supplementary Figure 5). Upon dissection, all mice exhibited enlarged spleen, bloody ascites and bulky mass in the peritoneal cavity (Figure 1b, left). Remarkably, although only a small fraction of transplanted cells were GFP/hKO/hCD4/hCD8 quadruple positive (leftmost column of Figure 1c and Supplementary Figure 6), the majority of the tumor cells in the spleen of the diseased mice were GFP/hKO/hCD4/hCD8 quadruple positive, with a small fraction of accompanying GFP/hKO/hCD4-triple-positive cells (second leftmost column to the right in Figure 1c). The tumor cells were highly proliferative (Ki67 proliferation index >95%) (Supplementary Figure 7), and oligoclonal without any somatic hypermutations in VDJ regions of recombined immunoglobulin genes (Supplementary Figure 8). These findings, coupled with a very short latency for disease manifestation, may imply that a

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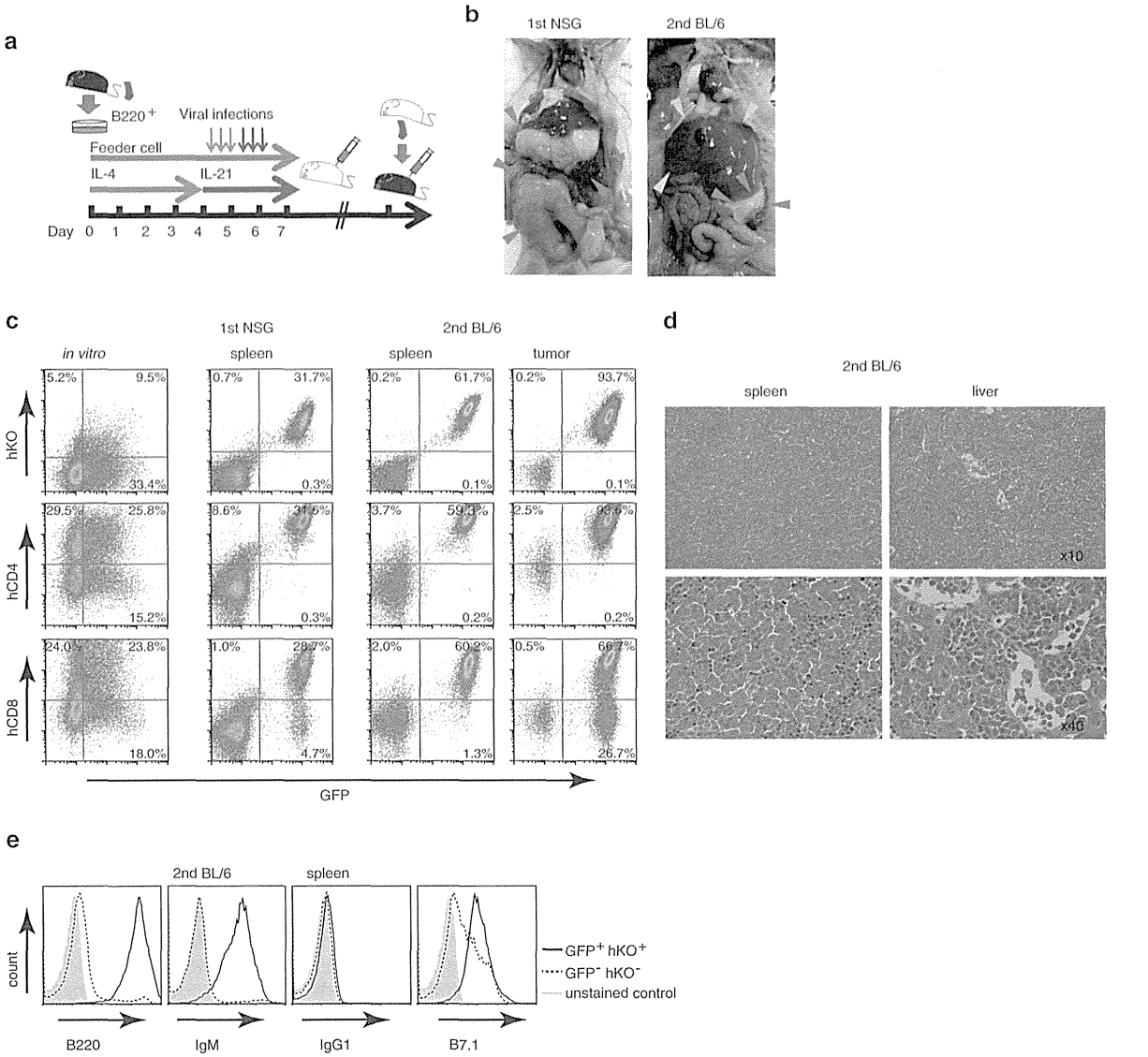

Figure 1. Synergistic effect of Myc, cell cycle regulators and the Akt pathway in lymphomagenesis. (**a**) Simplified scheme of the experiment. (**b**) Gross anatomy of primary transplanted NSG mice (left) and secondary transplanted BL6 mice (right). (**c**) Flow cytometric analyses of transplanted graft (leftmost), and cells from primary (second leftmost) and secondary transplanted mice (spleen, third leftmost; abdominal tumor, rightmost). GFP, hKO, hCD4 and hCD8 were surrogate markers for $CCND3^{T283A}$/Myc, TCL1A, myr-Akt and $E47^{V557E}$, respectively. Flow cytometry was performed using a FACSCalibur instrument (BD Biosciences, Franklin Lakes, NJ, USA) and FlowJo software version 6.7.5 (Tree Star, Ashland, OR, USA). (**d**) Hematoxylin and eosin staining of tissues from secondary transplanted mice (upper panels, x10; lower panels, x40). (**e**) Phenotypical analyses of spleen cells from secondary transplanted mice (solid line, GFP^+hKO^+; dotted line, GFP^-hKO^-; gray filled, unstained control).

combination of the five genes (MCEAT) is sufficient for the development of lymphoma. However, the potential contribution of retroviral insertional mutagenesis to lymphomagenesis awaits further study. All secondary B6 mice ($n=14$) that received a transplant with spleen cells from primary mice rapidly (<21 days) became diseased with hepatosplenomegaly (Figure 1b, right), infiltrated by $B220^+IgM^+IgG1^-B7.1^+$ lymphoma cells (Figure 1e) that were GFP/hKO/hCD4/hCD8 quadruple positive (third column to the right in Figure 1c), confirming the tumor-propagating activity of the cells.

To corroborate the synergy of the five genes (MCEAT) in the development of lymphoma, mice that received cells transduced with fewer than five genes became moribund or succumbed only after significantly prolonged latency (Supplementary Figure 5).

Although alterations of the five MCEAT genes are specifically involved in human BL and MCEAT-driven lymphoma that had developed in our model displayed some features of BL (highly proliferative with Ki67 > 95% and negative for Bcl2 expression; Supplementary Figure 9), histological findings of the MCEAT lymphoma in mice was nevertheless compatible with aggressive DLBCL rather than BL (Figure 1d). Reasons for the apparent discrepancy are unknown, but may reflect lack of antigen stimulation and germinal center reaction, and the lack of fine-tuned balance between proliferation and apoptosis.

Although Myc upregulates miR17 ~ 92 expression,[15] which increases PI3K signaling by targeting PTEN, Myc alone is insufficient to induce lymphoma and requires introduction of a constitutively active form of PI3K in animal models.[5] Interestingly, mutations in *Ccnd3* are frequently found in lymphomas arising in *Myc/PI3K* transgenic animals, suggesting a possible contribution of mutated *Ccnd3* to *Myc/PI3K* lymphoma in the transgenic models.

The lymphoma that developed nevertheless still harbored extensive additional somatic mutations (~100 missense/nonsense mutations per tumor), but their role in lymphomagenesis has not been investigated. Genes encoding *E47* (*TCF3*) or its antagonist *ID3* are mutated in 70% of sporadic BL,[2] and are thus regarded as central for Burkitt lymphomagenesis. Mutations in *E47* and *ID3* lead to elevated expression of E47-driven genes, which is thought to have an important role in the development of BL. However, our study presented here showed insufficiency of mutated *E47* in combination with *Myc*, and the additional requirement of *CCND3*^{T283A}, *Akt* and *TCL1A* for the development of lymphoma. Although our model may not faithfully recapitulate BL with respect to histology, it does provide cues for examination of the possible synergy of the five genes (MCEAT) in transgenic/knockin mice models.

From a clinical point of view, although the combination of targeted therapies is still being investigated, the use of a combination of targeted agents will be increasingly needed in the forthcoming era of genetically personalized medicine. Our findings may provide a basis for a rational combination therapeutic strategy targeting MYC, cell cycle regulators and the AKT pathway.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

KA and ST conceived the study, performed the experiments, analyzed the data and wrote the paper; KO performed the histological analysis; TS contributed to critical discussion and analyzed the data; MS organized the study, analyzed the data and wrote the paper.

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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,

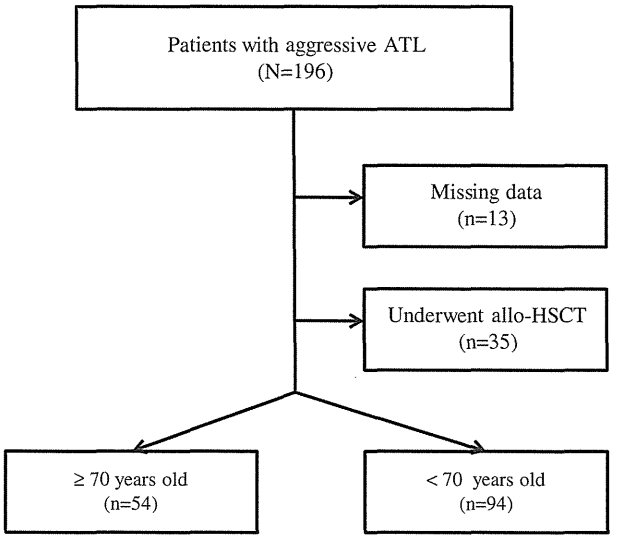

Fig. 1 Flowchart of patients. Allo-HSCT, allogeneic hematopoietic stem cell transplantation

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	

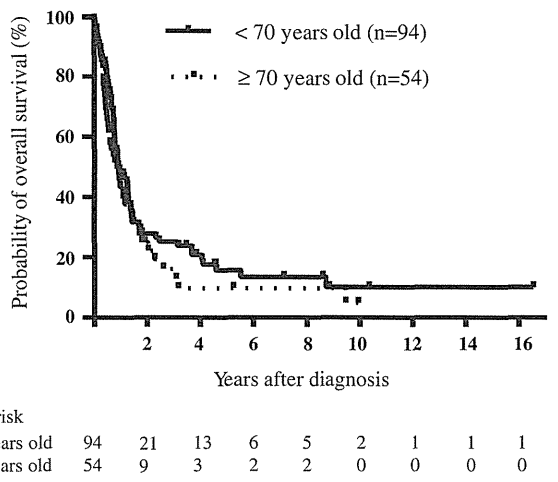

Fig. 2 Survival of patients by age

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

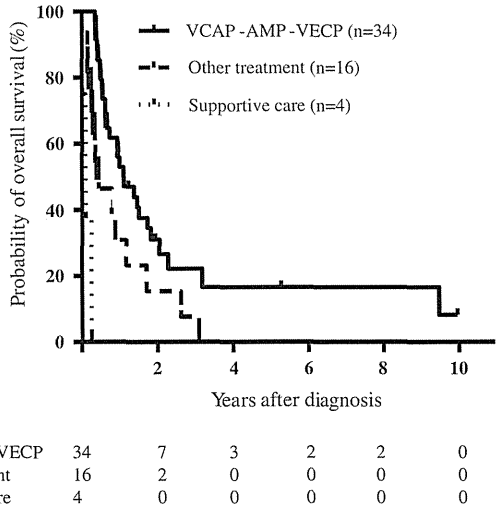

Fig. 3 Survival of the elderly patients according to the initial therapy

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

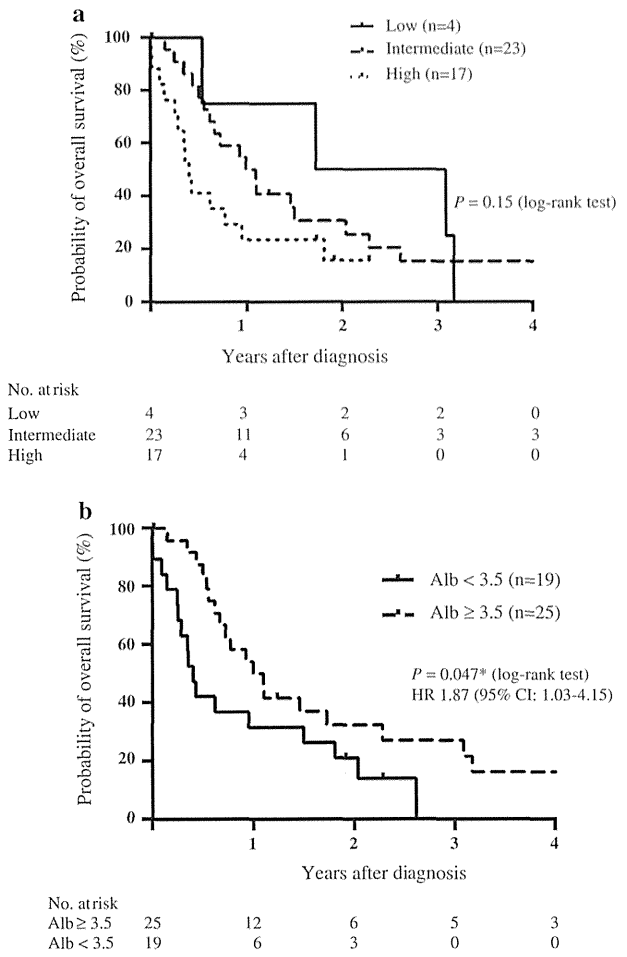

Fig. 4 Survival of elderly patients. **a** Survival according to the simplified ATL-prognostic index (PI). **b** Survival according to Albumin (Alb)

significantly lower in patients with a lower Alb level [≥3.5 (n = 25) vs <3.5 g/dL (n = 19); P = 0.047; log-rank test] (Fig. 4b). However, other factors, such as stage [I, II (n = 5) vs. III, IV (n = 39); P = 0.45], PS [0, 1 (n = 21) vs. 2–4 (n = 23); P = 0.29], and sIL-2R [≤20,000 (n = 29) vs. >20,000 U/mL (n = 15); P = 0.058] did not significantly affect OS.

Discussion

In this retrospective study, we showed the treatment outcome of elderly patients with aggressive ATL. In our hospital, the median ages of patients with aggressive ATL at diagnosis were 61 years between 1994 and 2000 (range 33–84 years) and 65 years between 2001 and 2010 (range 35–85 years). The rate of patients 70 years or older was 16 % (9 out of 57) in the former period and 36 % (45 out of 126) in the latter period (Fig. 5). The age of ATL patients has increased over time in our hospital, similar to the tendency observed in a nationwide survey [14]. Therefore, the best way to treat elderly ATL patients has become a very important issue.

The VCAP-AMP-VECP regimen has been reported to be more likely to benefit younger patients, because no difference was detected in the outcome between patients ≥56 years old treated with VCAP-AMP-VECP and those treated with CHOP-14 [9]. In our study, for patients treated with VCAP-AMP-VECP, MST and OS at 2 years were almost identical to these results in patients ≥56 years old but under 70 years old in a clinical trial [9]. On the other hand, those who received another treatment as the first choice had a poorer prognosis. Selection bias was included

Fig. 5 Age distribution of the patients with aggressive ATL at diagnosis

in the choice of treatment in this retrospective study. Patients treated with chemotherapy other than VCAP-AMP-VECP were older ($P = 0.02$; Mann–Whitney U test) and may have been in worse condition. In addition, patients who did not complete first cycle of VCAP-AMP-VECP were excluded from VCAP-AMP-VECP group in this retrospective analysis, and patients who became treatment-resistant extremely early after the start of chemotherapy may not have been included in the VCAP-AMP-VECP group. Thus, we cannot conclude the superiority of VCAP-AMP-VECP compared to other regimens. However, our result suggests that a nearly identical outcome to the younger patients may be expected in elderly patients receiving a VCAP-AMP-VECP-like regimen if they are in relatively good condition. Dose adjustment may be required for the VCAP-AMP-VECP-like regimen when treating elderly patients to reduce the adverse events, because hematologic toxicity and infections were reported more frequently with the VCAP-AMP-VECP regimen than with CHOP-14. Indeed, only 8.8 % (3/34) of elderly patients were treated with a full dose of VCAP-AMP-VECP as the initial treatment in our study. The degree of dose reduction varied, and the doses were reduced to about half to 80 % in most cases according to the patients' condition.

We should keep in mind that two-fifths of elderly patients were not candidates for an intensive treatment such as VCAP-AMP-VECP, even in our university hospital. The ratio of elderly patients with a worse general condition who were not candidates for this intensive regimen may be higher at the local public hospital. Thus, further improvement in the treatment strategy for elderly ATL patients is required.

The total number of cycles of VCAP-AMP-VECP that constituted a complete treatment was defined as six or seven in the clinical study [8, 9]. In our study, only six out of 32 patients (19 %) completed six cycles of VCAP-AMP-VECP, although some patients were treated with maintenance therapy as described below. Three of the patients who completed six cycles of the VCAP-AMP-VECP regimen survived over 2 years. Thus, continuation of intensive chemotherapy may contribute to prolonged survival. However, the rate of completion of six cycles of VCAP-AMP-VECP was only 32 % even in the clinical study, mainly because of progressive cytopenia and PD during the treatment [9]. Thus, for some elderly patients who responded to VCAP-AMP-VECP, we stopped the intensive chemotherapy after two or three cycles and orally treated them with etoposide and/or sobuzoxane and/or prednisone as maintenance therapy. We cannot conclude the efficacy of maintenance therapy in this study, because the number of patients was not sufficient, and the background may be heterogeneous for patients treated with such a strategy. However, our results appeared to be acceptable, and such a treatment strategy may become an option with an emphasis on quality of life of elderly patients. Further examination is expected to confirm the efficacy of maintenance therapy.

Most elderly patients included in this study were at intermediate or high risk in the ATL-PI, which suggests that our study did not inadvertently select patients with a better disease status. We could not show a significant difference in prognosis with the ATL-PI in our patients. The number of patients may have been too small to analyze the efficacy of the prognostic index. Furthermore, low-risk patients were rare among the elderly patients in our study. The fact that older age itself is included as a risk factor in the ATL-PI may be the main reason for the deviation in the risk group.

The efficacy of mogamulizumab, a humanized anti-CC chemokine receptor 4 antibody, as a single agent has been reported for relapsed ATL [17]. Mogamulizumab is now available in clinical practice for relapsed refractory ATL patients in Japan. Thus, for example, administration of mogamulizumab for maintenance therapy may prevent relapse or regrowth of the disease. On the other hand, a clinical trial for mogamulizumab combined with VCAP-AMP-VECP as the initial treatment for aggressive ATL has been performed, although the result has not been published yet. Thus, mogamulizumab with dose-reduced VCAP-AMP-VECP or a less-toxic regimen as the initial treatment may become a treatment option for elderly patients with aggressive ATL in the near future. An appropriate clinical trial is warranted to reveal the efficacy of such an approach. However, a prospective clinical trial may be difficult in elderly patients with aggressive ATL. In this report, no patient was treated with mogamulizumab, and our results provide a basis for the treatment result in elderly patients before the introduction of antibody therapy for the treatment of ATL.

In conclusion, our results suggest that dose-modified VCAP-AMP-VECP may become an optional regimen for the treatment of elderly patients with aggressive ATL if their general condition is good enough for intensive chemotherapy. In addition, two or three cycles of VCAP-AMP-VECP followed by maintenance therapy may also become a treatment option for elderly patients. However, the outcome is not good enough, and thus, further improvement in the treatment strategy is warranted.

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Conflict of interest The authors declare that they have no conflict of interest.

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