composed of peripheral blood and lymph nodes showed many subclones, and that the genome profiles of the peripheral blood samples frequently differed from those of the lymph node samples. ATL cells in lymph nodes contain more diverse subclones than those in peripheral blood, although some subclones seen in lymph nodes exist in peripheral blood, which indicates the accumulation of genomic abnormalities and clonal evolution of ATL cells in lymph nodes.[32]

A distinct subgroup has been reported in peripheral T-cell lymphoma-unspecified, which possesses a similar genomic imbalance to lymphoma-type ATL. Tumour cells in this particular subgroup of peripheral T-cell lymphoma-unspecified exhibit similar histopathological characteristics with the frequent expression of CC chemokine receptor 4 (CCR4), which is a characteristic phenotype of ATL cells, and the outlook for these patients is as poor as that for patients with ATL. These results imply common mechanisms for oncogenesis between lymphoma type ATL and this particular subgroup of peripheral T-cell lymphoma-unspecified, and further study is warranted.[33]

Identification of high-risk HTLV-1 carriers for development of ATL

The lifetime risk of development of ATL in HTLV-1 carriers is only 3–5%. Currently, we have no established method to predict the risk of progression to ATL in HTLV-1 carriers, and no information is available about whether a routine clinical check up of HTLV-1 carriers is useful for the early detection of progression and whether it ultimately improves outcomes. To delineate the risk factors for development of ATL in HTLV-1 carriers will be beneficial. HTLV-1 proviral load was significantly higher in patients with acute or chronic type ATL than in patients with HAM-TSP or lymphoma type ATL, which have similar proviral loads. A high proviral load in peripheral blood mononuclear cells has been suggested to be a risk factor for the development of ATL.[34,35] The Joint Study on Predisposing Factors of ATL Development (JSPFAD)[36] has been undertaking a nationwide large prospective study in Japan, in which 14 of 1218 asymptomatic carriers developed ATL (two acute, two lymphoma, ten smoldering); the cumulative probability of progression to ATL was 4·8% (95% CI 1·9–11·8) with

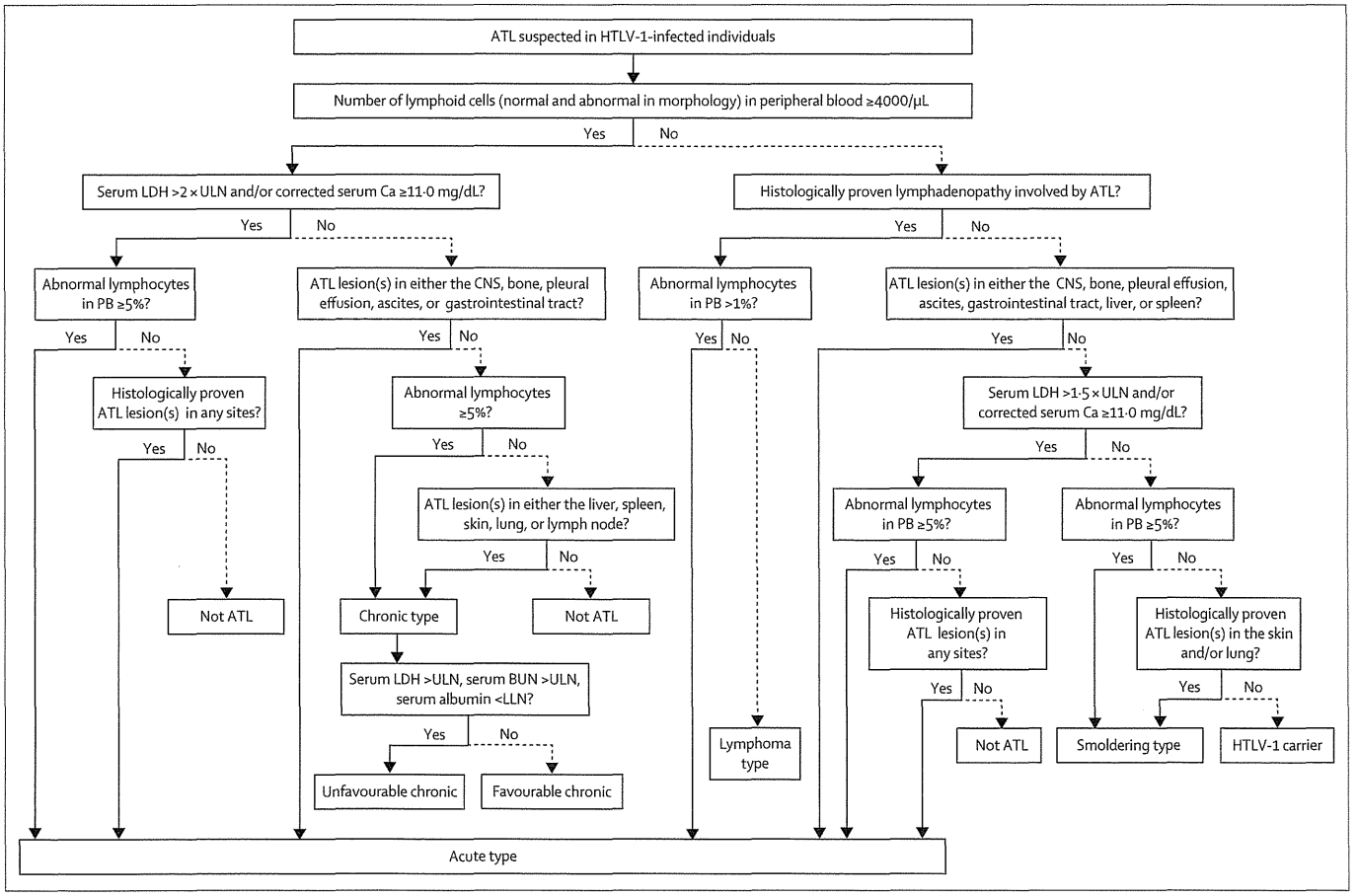

Figure: **Determination of the ATL clinical subtype classification according to Shimoyama criteria[10]**
ATL=Adult T-cell leukemia-lymphoma. ULN=upper limit of normal. LLN=lower limit of normal. (Courtesy of JCOG1111 coordinating office).

Panel: Therapeutic options for ATL outside a clinical trial setting

Aggressive ATL (acute, lymphoma, and unfavourable chronic types)

First-line treatment

- Multiagent chemotherapy* with or without mogamulizumab†
  - VCAP-AMP-VECP
  - CHOP14
  - CHOP21
  - ATL-G-CSF
  - mEPOCH
  - Hyper CVAD
- IFN-AZT with or without chemotherapy‡
- Single agent chemotherapy for palliative purposes
  - Etoposide
  - Sobuzoxane

Consolidation after first-line treatment

- Allogeneic HSCT if feasible§
  - Myeloablative conditioning
  - Reduced intensity conditioning

If relapse or refractory

- Multiagent chemotherapy containing drugs not used in the first-line regimen with or without mogamulizumab¶
- Mogamulizumab
- Allogeneic HSCT if feasible
- Single agent chemotherapy for palliative purposes

Indolent ATL (smoldering and favourable chronic types)

If asymptomatic

- Watchful waiting

If symptomatic

- IFN-AZT
- Watchful waiting

If skin lesions are present

- Skin-directed therapy
  - Topical steroids
  - Ultraviolet light
  - Radiation
- Systemic therapy
  - Steroids
  - Oral retinoids
  - Interferon γ
  - Single agent chemotherapy

Upon progression to aggressive ATL

- Treat as aggressive ATL

ATL=adult T-cell leukaemia-lymphoma. VCAM-AMP-VECP=sequential combination chemotherapy consisting of VCAP (vincristine [VCR], cyclophosphamide [CPM], doxorubicin [DOX], and prednisolone [PSL]), AMP (DOX, ranimustine [MCNU], and PSL), and VECP (vindesine [VDS], etoposide [VP-16], carboplatin [CBDCA], and PSL). CHOP=combination chemotherapy consisting of CPM, DOX, VCR, and PSL. CHOP14=CHOP every 2 weeks. CHOP21=CHOP every 3 weeks. ATL-GCSF=combination chemotherapy consisting of VCR, VDS, DOX, mitoxantrone (MIT), CPM, VP-16, MCNU and PSL with prophylactic support by granulocyte-colony stimulating factor. mEPOCH=combination chemotherapy consisting of VP-16, PSL, VCR, CPM, and DOX with modification. Hyper CVAD=combination chemotherapy consisting of hyperfractionated CPM, VCR, DOX, and dexamethasone. IFN-AZT=combination of interferon α and zidovudine. HSCT=haemaopoietic stem-cell transplantation. *The efficacy of VCAP-AMP-VECP and CHOP14 was assessed in a phase 3 clinical trial.[43] †Clinical trials of VCAP-AMP-VECP with or without magamulizumab have been completed.[44] However, the optimum regimen(s) to combine with mogamulizumab has not been determined. ‡UK retrospective data showed that low-dose IFN-AZT with chemotherapy is a option for acute and lymphoma type ATL.[45] § Allogeneic HSCT should be considered during the first remission. ¶The benefit of combining mogamulizumab with chemotherapy later than first-line therapy has not been established.

a median follow-up of 5·4 years. Multivariate analysis showed that higher proviral load, advanced age, family history of ATL, and detection of HTLV-1 infection during treatment of other diseases were independent risk factors for progression to ATL. This study is still ongoing, and longer follow-up data are awaited. In a recent prospective UK study, four of 153 patients (92 asymptomatic carriers including at least 15 patients with smoldering ATL, and 61 patients with HTLV-1 associated inflammatory disease including 57 with HAM-TSP) ultimately developed aggressive ATL during a median follow-up of 4·5 years. Investigators reported an association between high HTLV-1 proviral load, but not the percentage of abnormal lymphocytes, and increased risk of progression to aggressive ATL.[37]

Clinical features of ATL

Patients with ATL exhibit diverse clinical features such as generalised lymphadenopathy, skin lesions, hepatosplenomegaly, leucocytosis with increased abnormal lymphocytes showing cerebriform or flower-like nuclei or with increased neutrophils, hypercalcaemia, and frequent complication of opportunistic infections due to *Pneumocystis jirovecci*, candida, cytomegalovirus, and *Strongyloides stercoralis*. ATL cells characteristically express CD3, CD4, CD25, CCR4, and FOXP3 on their surface, and monoclonal integration of HTLV-1 proviral DNA is detectable by Southern blotting.[10,38,39] There is controversy regarding the actual function of the ATL cells; however, the immunosuppressive state of HTLV-1-infected individuals could be partially explained by the increased number of T cells which express regulatory T-cell phenotype.[40] The clinical course of ATL is very heterogeneous, and JCOG has proposed four clinical subtypes (acute, lymphoma, chronic, and smoldering types) based on the prognostic factors, clinical features, and the natural history of the disease according to an analysis of 854 registered patients with newly diagnosed ATL between 1983 and 1987.[10] Chronic type ATL can be further divided into favourable and unfavourable types based on either lactate dehydrogenase or blood urea nitrogen concentrations that are more than the upper limits of normal, or an albumin concentration that is less than the lower limit of normal.[11] This system is known as Shimoyama classification, which is widely used to establish therapeutic strategies. Acute, lymphoma, and unfavourable chronic types showing comparable prognoses with acute and lymphoma types are defined as aggressive ATL, and favourable chronic and smoldering types of ATL are defined as indolent ATL (figure).

Frequent opportunistic infections that are due to impairment of cellular immunity, and intrinsic tumour cell resistance to conventional chemotherapeutics due to the expression of P-glycoprotein, lung resistance-related protein (LRP), and anti-apoptotic proteins, have been suggested as reasons why the prognosis of aggressive ATL is very poor.[41,42]

Treatment of adult T-cell leukaemia-lymphoma

Aggressive ATL: chemotherapy

The treatment strategies for aggressive ATL and indolent ATL were developed on the basis of those for other malignant lymphomas such as diffuse large B-cell lymphoma and chronic lymphocytic leukaemia, respectively (panel).

An international consensus meeting[46] recommended first-line treatment for ATL with chemotherapies such as the VCAP-AMP-VECP regimen, which is a sequential combination chemotherapy consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone (VCAP); doxorubicin, ranimustine, and prednisolone (AMP); and vindesine, etoposide, carboplatin, and prednisolone (VECP), with or without subsequent allogeneic haemopoietic stem-cell transplantation (HSCT) for acute, lymphoma, and unfavourable chronic types of ATL, or interferon α and zidovudine for acute and unfavourable chronic type ATL.[46]

Among six prospective clinical trials for first-line treatment of aggressive ATL undertaken by the JCOG, good progress was observed in JCOG9303, a phase 2 trial of VCAP-AMP-VECP, and JCOG9801, a randomised phase 3 trial that compared VCAP-AMP-VECP with biweekly CHOP (CHOP-14; cyclophosphamide, doxorubicin, vincristine, and prednisolone).[43,47–49] Overall survival at 3 years (24% *vs* 13%) and the proportion of patients who achieved complete remission (40% *vs* 21%) were higher with VCAP-AMP-VECP than CHOP-14; however, VCAP-AMP-VECP had more toxic effects. CNS involvement in patients with ATL was 10–20%; CNS prophylaxis was therefore incorporated into the JCOG9303 and JCOG9801 trials. Additional chemotherapy regimens frequently used in clinical practice in Japan are listed in the panel.[50] No salvage treatment has been established for relapsed or resistant ATL. The therapeutic outcome in Japanese patients treated in clinical trials and in practice is shown in table 1.

Single agent chemotherapy with either low-dose daily etoposide or sobuzoxane is frequently used for patients with comorbidities or for palliative purposes; however, no comparative studies have been done.

Aggressive ATL: interferon α and antiretroviral agents

Interferon α has been used for the treatment of some tumours such as renal cell carcinoma and melanoma and for the eradication of hepatitis B and C virus, and zidovudine has been used for HIV infection for years. The effectiveness of combined interferon-α and zidovudine to treat aggressive ATL has been reported in some uncontrolled studies. Gill and colleagues[53] and Hermine and colleagues[54] were the first to independently report the effectiveness of this treatment. Gill and colleagues reported that 58% (seven of 12) of previously untreated and 57% (four of seven) of previously treated patients achieved complete remission or partial remission, and the median survival time was 3 months for all patients.[53] Hermine and colleagues reported its effectiveness in five patients (data not shown).[54] In a subsequent study, Hermine and colleagues[55] reported that 54% (seven of 13) of untreated patients achieved complete remission and 31% (four of 13) of untreated patients achieved partial remission, and 33% (two of six) of previously treated patients achieved complete remission. Median overall survival for all patients was 11 months.[55] Matutes and colleagues[56] reported response rates (complete remission

	Acute		Lymphoma		Acute and lymphoma	Chronic and smoldering
	JCOG9303[49]	JCOG9801[43]	JCOG9303[49]	JCOG9801[43]		
First-line treatment	Chemotherapy (n=56)	Chemotherapy (n=39)	Chemotherapy (n=27)	Chemotherapy (n=12)	Clinical practice*[51] (n=807)	Watch and waiting[52] (n=90)
Median OS (months)	11	13	20	14	8	49
3-year OS	NA	23%	NA	17%	NA	47%

ATL=adult T-cell leukaemia-lymphoma. OS=overall survival. NA=not applicable. *No patients received combined interferon α and zidovudine (IFN/AZT), and patients who underwent allogeneic transplantation are excluded.

Table 1: Therapeutic outcome of ATL

	Gill et al[53]	Hermine et al[55]	Matutes et al[56]	White et al[57]
Previously untreated	12 acute or lymphoma	11 acute, 2 lymphoma	2 acute, 1 lymphoma	3 acute
CR or PR (%)	58% (CR+PR)	54%CR, 31% PR	100% (CR+PR)	33% CR, 33% PR
Median OS (months)	NA	11	NA	NA
Previously untreated and treated	17 acute, 2 lymphoma	15 acute, 4 lymphoma	11 acute, 2 lymphoma, 2 chronic	11 acute, 5 lymphoma, 2 chronic
CR or PR (%)	26% CR, 32% PR	47% CR, 21% PR	67% (CR+PR)	6% CR, 11% PR
Median OS (months)	3	11	18	6

ATL=adult T-cell leukaemia-lymphoma. IFN=interferon α. AZT=zidovudine. CR=complete remission. PR=partial remission. OS=overall survival. NA=Not available.

Table 2: Representative reports of IFN-AZT for ATL

	Acute type		Lymphoma type		Chronic and smoldering type	
First-line treatment	IFN-AZT (n=45)	Chemotherapy (n=53)	IFN-AZT (n=13)	Chemotherapy (n=47)	IFN-AZT (n=17)	Chemotherapy (n=6)
Median OS (months)	9	6	7	16	NR	60
5-year OS	28%	10%	0%	18%	100%	42%

ATL=adult T-cell leukaemia-lymphoma. IFN=interferon α. AZT=zidovudine. NR=not reached. OS=overall survival.

Table 3: Meta-analysis reported by Bazarbachi and colleagues of IFN/AZT versus chemotherapy for ATL[58]

plus partial remission) of 100% (three of three) for previously untreated patients and 67% (ten of 15) for treated patients, with a median overall survival of 18 months for all patients. White and colleagues[57] showed an inferior response rate of one complete remission and two partial remission in 18 patients; inadequate doses of interferon α and zidovudine were suggested as the reason for this response (table 2).

A meta-analysis showed that first-line treatment with interferon α and zidovudine was significantly more effective than chemotherapy alone for patients with acute type ATL, but chemotherapy was more effective than interferon α and zidovudine for lymphoma type ATL (table 3).[58] The median overall survival of patients with acute type ATL given chemotherapy was worse than that reported in Japanese studies (table 1). However, the baseline characteristics of patients might have differed between the studies. Hodson and colleagues[45] showed that the median overall survival of patients with not only acute but also lymphoma type ATL was significantly longer with combined first-line treatment with interferon α plus zidovudine plus chemotherapy, than chemotherapy alone. Moreover, the use of interferon α and zidovudine at any time prolonged survival, and was the only factor associated with a reduction in the risk of death in patients with aggressive ATL in their study.[45] A small Japanese pilot study showed modest activity of interferon α and zidovudine in patients with heavily treated aggressive ATL.[59] Prospective studies are needed to lend support to these results.

Aggressive ATL: HSCT

High-dose chemotherapy with allogeneic HSCT has frequently been incorporated in the treatment of aggressive ATL in Japan. Autologous HSCT has been shown to have modest benefit, but mainly resulted in early relapse.[60] Allogeneic HSCT was able to induce long-term survival in 25–40% of patients, although treatment-related mortality was high, with up to 40% of patients affected.[61–63] No prospective study has yet been done to identify any advantage of allogeneic HSCT, and it is not possible to compare outcomes between patients who did or did not undergo transplantation because of inevitable biases in different characteristics between patients, such as performance status, disease control, and age. However, as few as 10% of patients achieved long-term survival without allogeneic HSCT relative to 25–40% with allogeneic HSCT.[10,51] The major problem with allogeneic HSCT is the limited applicability of a myeloablative conditioning regimen because more than 80% of patients with ATL are older than 55 years in Japan. A retrospective Japanese study[64] analysed 586 patients who underwent allogeneic HSCT with bone marrow or peripheral blood stem cells between 1992 and 2009. Median overall survival was 9·9 months, and 36% of patients were alive at 3 years after transplantation, which indicated that both a myeloablative conditioning regimen and a reduced intensity conditioning regimen (RIC) are effective in achieving long-term survival. 52% (306 of 586) of the patients received RIC and achieved overall survival similar to that achieved with the myeloablative conditioning regimen (median overall survival: 9·5 months *vs* 10·0 months). RIC was significantly associated with ATL mortality compared with the myeloablative conditioning regimen; however, RIC contributed to a better overall survival in older patients. Furthermore, the feasibility of unrelated cord blood transplantation has been confirmed, and a prospective study is ongoing in Japan (clinical trial registry number UMIN000007927).[62,65]

The development of mild-to-moderate acute graft versus host disease has been reported to contribute to increased overall survival.[61–63] The contribution of donor-derived Tax-specific CD8+ cytotoxic T cells and Tax-specific CD4+ T cells, and HBZ-specific CD4+ T cells has been suggested to induce potent and selective anti-ATL effects with allogeneic HSCT.[66–68]

Aggressive ATL: novel agents

Progress in treatment for aggressive ATL is still slow. Some promising therapeutic advances include the introduction of the CCR4 monoclonal antibody mogamulizumab for the treatment of patients with relapsed or resistant ATL in Japan. CCR4 is a seven-transmembrane G-protein coupled receptor that is selectively expressed on Th2 cells and regulatory T cells, and tumour cells in most patients with ATL also strongly express the antigen.[69] Mogamulizumab is an anti-CCR4 immunoglobulin G_1 monoclonal antibody that markedly enhances antibody-dependent cellular cytotoxicity by increasing binding affinity to the Fcγ receptor on effector cells by the defucosylation of its Fc region.[70] Single agent activity of this drug in a phase 1 trial showed a response rate of 31%, and a subsequent single agent phase 2 trial

	Action	Clinical trial identification number	Phase
Novel agents			
Bortezomib	Proteasome inhibitor	UMIN000004061	2
Lenalidomide	Immunomodulatory drug	NCT01274533 NCT01724177	2
Panobinostat	Histone deacetylase inhibitor	NCT01261247	2
Alisertib	Aurora A kinase inhibitor	NCT01466881	2
Ruxolitinib	JAK1/2 inhibitor	NCT01712659	2
Denileukin diftitox	Anti-CD25	NA	NA
Forodesine	Purine nucleoside phosphorylase inhibitor	NA	NA
Pralatrexate	Folate analogue metabolic inhibitor	NA	NA
Novel agents in combination with conventional therapy			
LMB-2 with fludarabine and cyclophosphamide	Anti-CD25	NCT00924170	2
Bortezomib with EPOCH chemotherapy	Proteasome inhibitor	NCT01000285	2
Brentuximab vedotin and CHP versus CHOP	Anti-CD30	NCT01777152	3
Pralatrexate versus observation following CHOP-based chemotherapy	Folate analogue metabolic inhibitor	NCT01420679 EudraCT2010-022230-81	3
Others			
Allogeneic haemopoietic stem-cell transplantation using myeloablative conditioning regimen (JCOG0907)	Disease status: aggressive ATL	UMIN000004147	2
Cord blood cell transplantation using reduced intensity conditioning regimen (ATL-NST-5)	Disease status: aggressive ATL	UMIN000007927	1
Therapeutic vaccine with autologous dendritic cells pulsed with Tax peptides	Disease status: aggressive ATL	UMIN000011423	1
Combination with arsenic trioxide/interferon α/zidovudine and conventional chemotherapy	Disease status: aggressive ATL	UMIN000012268	2
Interferon α and zidovudine versus watchful waiting (JCOG1111)	Disease status: indolent ATL	UMIN000011805	3

EPOCH=combination chemotherapy consisting of VP-16, PSL, VCR, CPM, and DOX. CHP=combination chemotherapy consisting of CPM, DOX, and PSL. CHOP=combination chemotherapy consisting of CPM, DOX, VCR, and PSL.

Table 4: **Clinical trials for ATL which are ongoing or under consideration**

reported a response rate of 50%, progression-free survival of 5·3 months, and overall survival of 13·7 months, in patients with relapsed ATL.[71,72] Results of a randomised phase 2 trial comparing VCAP-AMP-VECP with or without mogamulizumab have been reported (clinical trial registry number NCT01173887),[44] and a clinical trial for ATL with mogamulizumab is ongoing in the USA and UK (NCT01626664). Mogamulizumab depletes normal regulatory T cells expressing CCR4, therefore attention should be paid to immune-related adverse events including Stevens-Johnson syndrome and toxic epidermal necrosis that might be induced by the interaction of activated cytotoxic T cells and keratinocytes.[73] The safety and benefits of mogamulizumab before or after allogeneic HSCT should be assessed.

Results are awaited of clinical trials of bortezomib, lenalidomide,[74] forodesine, pralatrexate,[75] and denileukin diftitox, and EPOCH chemotherapy with bortezomib; LMB-2 (an anti-CD25 recombinant immunotoxin containing an antibody Fv fragment fused to truncated *Pseudomonas* exotoxin) with fludarabine and cyclophosphamide; pralatrexate versus observation after CHOP-based chemotherapy; and brentuximab vedotin with CHP versus CHOP for CD30-positive patients. Table 4 lists clinical trials for ATL that are currently ongoing or under consideration.

Indolent ATL

An international consensus meeting[46] recommended treatment with interferon α and zidovudine or watchful waiting if patients are symptomatic, and watchful waiting alone if patients are asymptomatic.

A Japanese retrospective analysis showed that conventional chemotherapy did not improve the prognosis of patients with indolent ATL; however, prospective confirmation has not yet been reported. Some patients with indolent ATL have skin lesions, which could be treated by skin-directed therapy such as topical steroids, ultraviolet light, and radiation, or systemic therapy such as steroids, oral retinoids, interferon γ, or single agent chemotherapy; however, the beneficial effects of these approaches have not yet been confirmed.

Another Japanese retrospective study[52] reported that the prognosis of chronic and smoldering type ATL mainly observed by use of a watchful-waiting approach, was poorer than expected, and mean survival was only 2·9 years (95% CI 1·3–7·1) with no plateau in overall survival.

A retrospective meta-analysis of patients with chronic and smoldering type ATL[58] reported 100% of patients given interferon α and zidovudine surviving for 5 years but only 42% of those who received chemotherapy (table 3). Few patients were included in this analysis, and

possible bias due to its retrospective nature cannot be avoided; hence, a prospective study is needed. The JCOG have also started a phase 3 study comparing interferon α and zidovudine with watchful waiting for indolent ATL (study number JCOG1111; clinical trial registry number UMIN000011805). This study will show whether there are any benefits from early intervention for indolent ATL with interferon α and zidovudine in Japanese patients.

Several suggested mechanisms of the anti-ATL effects induced by interferon α and zidovudine have been reported; however, they should be delineated more clearly.[76] The feasibility and efficacy of combination arsenic trioxide plus interferon α and zidovudine have been reported in a few patients with chronic type ATL in a phase 2 trial.[77]

Supportive care for ATL

Infections are frequently noted in patients with ATL. Among them, *Pneumocystitis* pneumonia has been associated with high mortality. Trimethoprim-sulfamethoxazole should be routinely given as a prophylactic during treatment for ATL. Additionally, treatment for other opportunistic infections such as deep-seated fungal infections, cytomegalovirus, and reactivation of herpes-zoster virus should be initiated promptly. Hypercalcaemia is another frequent complication of ATL, which should be treated as an oncological emergency with hydration, intravenous bisphosphonates, calcitonin, and glucocorticoids.[78]

Prognostic index for ATL

The huge diversity in the clinical course of ATL, even for the acute and lymphoma types, and the absence of a validated prognostic index specific to this cohort of patients, has made it difficult to assess the results of single group studies and to consider risk-adapted treatment strategies. A prognostic index for acute and lymphoma type ATL was developed using a retrospective analysis of medical records from 807 patients in Japan.[51] Multivariable analysis showed that the variables of Ann Arbor stage (I–II *vs* III–IV), Eastern Cooperative Oncology Group performance status (ECOG PS; 0–1 *vs* 2–4), age, serum albumin, and soluble interleukin-2 receptor (sIL-2R) were independently and significantly prognostic.[51] A simplified ATL prognostic index was established as follows: prognostic score=2 (if stage=III or IV); +1 (if ECOG PS >1); +1 (if age >70); +1 (if albumin <35 g/L; +1 (if sIL2R >20 000 U/mL).

Scores from 0 to 2 were categorised as low risk, 3 to 4 as intermediate risk, and 5 to 6 as high risk. In the validation sample, 77 patients (19%) were low risk, 208 patients (52%) were intermediate risk, and 118 patients (29%) were high risk. Low-risk patients had a median overall survival of 16·2 months (95% CI 13·4–23·2), and 37% (95% CI 25–49) were alive at 2 years; intermediate-risk patients had a median overall survival of 7·0 months (95% CI 6·3–8·6), with 17% (95% CI 12–23) alive at 2 years; and high-risk patients had a median overall survival of 4·6 months (95% CI 2·6–5·4) months, with 6% (95% CI 2–12) of patients alive at 2 years. The ATL prognostic index more clearly distinguished the risk of patients than the International Prognostic Index or the prognostic index for peripheral T-cell lymphoma-unspecified.[79,80]

Search strategy and selection criteria

References for this Review were identified by searching PubMed for English-language articles with the terms "ATL or ATLL", "human T-cell lymphotropic virus type I or HTLV-1", and "HAM or TSP" up to February, 2014. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Discussion

The therapeutic outcome of patients with ATL has been improved by the introduction of multiagent chemotherapy, antiviral therapies, allogeneic HSCT, and advances in supportive care. However, the outlook for these patients is still poor. The reasons for the difficulties associated with doing clinical trials of this disease include its rarity and scattered distribution worldwide. The main differences of therapeutic approach between Japan and other countries are frequent incorporation of allogeneic HSCT in Japan for aggressive ATL, and use of interferon α and zidovudine in acute, chronic, and smoldering ATL outside Japan. The problem is that no prospective randomised trials have been undertaken yet to establish the effectiveness of either approach.

For a long time, no clinical trials took place that incorporated novel drugs to treat ATL, and until recently similar cytotoxic agents used for aggressive non-Hodgkin lymphoma were used to treat aggressive ATL. However, this situation is changing, and apart from mogamulizumab, which was developed and approved for use in Japan, some clinical trials of novel agents are ongoing or under consideration for ATL; the successful translation of research to novel treatments is eagerly awaited.

The Japanese intervention programme to prevent mother-to-child infection by screening all pregnant women for HTLV-1 infection will hopefully reduce the number of HTLV-1 carriers, as has already been reported by a few local intervention programmes in Japan, and also the number of patients with ATL in the future. However, this approach might not be applicable in developing countries where economical and medical resources are scarce, and neonatal and childhood mortality rates are high; therefore, alternative strategies should be investigated. International collaboration is needed to reduce the prevalence of HTLV-1 and improve the outcome of ATL.

Contributors

KI and KT searched the scientific literatures, prepared the manuscript, and submitted the Review for publication.

Declaration of interests

We declare no competing interests.

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bjh research paper

Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A)

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Summary

This study evaluated the clinical features of 276 patients with aggressive adult T-cell leukaemia-lymphoma (ATL) in 3 Japan Clinical Oncology Group (JCOG) trials. We assessed the long-term survivors who survived >5 years and constructed a prognostic index (PI), named the JCOG-PI, based on covariates obtained by Cox regression analysis. The median survival time (MST) of the entire cohort was 11 months. In 37 patients who survived >5 years, no disease-related deaths in 10 patients with lymphoma-type were observed in contrast to the 10 ATL-related deaths in other types. In multivariate analysis of 193 patients, the JCOG-PI based on corrected calcium levels and performance status identified moderate and high risk groups with an MST of 14 and 8 months respectively (hazard ratio, 1·926). The JCOG-PI was reproducible in an external validation. Patients with lymphoma-type who survived >5 years might have been cured. The JCOG-PI is valuable for identifying patients with extremely poor prognosis and will be useful for the design of future trials combining new drugs or investigational treatment strategies.

Keywords: adult T-cell leukaemia-lymphoma, Japan Clinical Oncology Group trials, long-term survivors, prognostic index.

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Adult T-cell leukaemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I (HTLV-1) (Uchiyama *et al*, 1977; Poiesz *et al*, 1980; Hinuma *et al*, 1981; Miyoshi *et al*, 1981; Yoshida *et al*, 1982). Classification of clinical subtypes into acute, lymphoma, chronic and smouldering was proposed based on prognostic factors, clinical features and the natural history of the disease (Shimoyama, 1991). Patients with aggressive ATL (i.e., acute, lymphoma and unfavourable chronic types) have frequently been treated as a subtype of aggressive non-Hodgkin lymphoma (NHL), whereas those with indolent ATL (i.e., favourable chronic and smouldering types) have been managed as a subtype of chronic lymphoid leukaemia (Shimoyama, 1994; Tobinai & Watanabe, 2004). Aggressive ATL typically has a very poor prognosis compared with aggressive B-cell lymphomas, such as diffuse large B-cell lymphoma and peripheral T-cell lymphoma excluding ATL (The International Non-Hodgkin's Lymphoma Prognostic Factor Project's, 1993; Shimoyama, 1994; Gallamini *et al*, 2004; Watanabe *et al*, 2010). In the 1980's, patients with aggressive ATL were reported to have a median survival time (MST) of approximately 8 months, with a 2-year survival rate of <5% because of the multidrug-resistant phenotype of their malignant tumour cells, rapid proliferation of the tumour cells, a large tumour burden with multi-organ failure, hypercalcaemia, and/or frequent opportunistic infections (Lymphoma Study Group, 1991; Shimoyama, 1991, 1994; Tobinai & Watanabe, 2004).

The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) has conducted consecutive clinical trials to improve the survival of patients with ATL. Earlier trials (JCOG7801, JCOG8101, and JCOG8701) revealed poor prognosis of ATL compared with other aggressive NHLs (Shimoyama *et al*, 1988; Tobinai *et al*, 1994). Furthermore, the disappointing results with conventional chemotherapies in the 1980s and the proposal for a subtype classification of ATL led us to conduct clinical trials with new agents that exclusively targeted aggressive ATL. The first phase II trial, JCOG9109 (1991–1993), evaluated combination chemotherapy with deoxycoformycin, an inhibitor of adenosine deaminase, which had been effective as a single agent against relapsed or refractory ATL (Tobinai *et al*, 1992). However, the results were disappointing with an MST of 7 months, similar to the findings of previous JCOG-LSG trials (Tsukasaki *et al*, 2003). The next phase II trial, JCOG9303 (1994–1996), evaluated the chemotherapy regimen VCAP-AMP-VECP (LSG15) against aggressive ATL. This dose-intensified multi-agent chemotherapy consisted of vincristine, cyclophosphamide, doxorubicin (DXR) and prednisone (PSL) for VCAP, DXR, ranimustine and PSL for AMP, and vindesine, etopside, carboplatin and PSL for VECP, supported by granulocyte colony-stimulating factor and intrathecal (IT) prophylaxis with methotrexate (MTX) and PSL. This phase II trial showed promising results, with complete remission (CR) and overall response rates of 36% and 81%, respectively, and an MST of 13 months at the expense of haematological and other toxicities (Yamada *et al*, 2001). Based on these results, we proceeded to the phase III trial JCOG9801 (1998–2003), which compared a modified VCAP-AMP-VECP regimen (shortened from 7 to 6 courses), to which cytarabine was added to the IT prophylaxis, *versus* CHOP (cyclophosphamide, DXR, vincristine and PSL)-14 supported by granulocyte

colony-stimulating factor and IT prophylaxis identical to the former regimen. The CR and 3-year overall survival (OS) were higher in the modified VCAP-AMP-VECP arm than in the CHOP-14 arm (40% vs. 25% and 24% vs. 13% respectively), suggesting that the former is a more effective regimen at the expense of greater toxicity for patients with newly diagnosed aggressive ATL (Tsukasaki *et al*, 2007).

Through these 3 JCOG trials for patients with aggressive ATL, the 5-year OS was improved, from 5% in the 1980's to 15% in the 1990s. To characterize the long-term survivors of aggressive ATL and to develop a new prognostic index (PI) for the disease, we performed a combined analysis (JCOG0902A) of all the patients enrolled in the 3 JCOG trials.

Methods

Study population

A total of 276 patients who were registered in the 3 JCOG trials described above were enrolled in this study (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Some patients did not receive anti-viral therapy using interferon-alpha and zidovudine because these drugs for ATL was not covered by the National Health Insurance in Japan. The eligibility criteria for the 3 JCOG trials were detailed in previous reports (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Briefly, patients were eligible to participate if they had aggressive ATL (i.e., acute, lymphoma, or unfavourable chronic type) with no prior chemotherapy, were aged 15–69 years and had preserved organ functions, no proven central nervous system (CNS) involvement and a performance status (PS) of 0–3 or 4 due to hypercalcaemia caused by ATL. The diagnosis of ATL was made based on seropositivity for HTLV-1 antibody and histologically and/or cytologically proven peripheral T-cell malignancy. Monoclonal integration of HTLV-1 provirus was analysed in 104 of 276 patients studied. Among these 104 patients, integration was detected in 100 patients and not detected in four patients.

The PI for the JCOG trials, which we refer to as the JCOG-PI, was constructed from the data of patients who participated in these trials (training set) and was then applied to an external validation set. The external validation set consisted of 136 patients who had not participated in prior JCOG studies but had received anthracycline-containing regimens as initial chemotherapy at three sites (Nagasaki University Hospital, Nagasaki Medical Centre, and Sasebo City General Hospital) under the remit of the JCOG-LSG. These patients were a subset of those from a previous retrospective study (Katsuya *et al*, 2012) and their OS and corrected calcium levels were reviewed.

Data and analysis sets

The endpoint of this study was OS, defined as the duration between registration to each JCOG trial and death from any cause or censored at the last follow up in living patients. For the validation data set, we substituted the date of treatment initiation for the date of registration.

Candidate covariates were sex, age, Eastern Cooperative Oncology Group (ECOG) PS, B symptoms, clinical stage, liver involvement, lactate dehydrogenase, blood urea nitrogen (BUN), corrected calcium levels, serum total protein, serum albumin, white blood cell count, total (normal and abnormal) lymphocyte count, neutrophil count and platelet count. We excluded the treatment regimen from the covariates because our aim was to create an index that could stratify the patients' prognosis and be applicable to future clinical trials evaluating various promising regimens. Cut-off values were determined clinically by dividing the continuous biological and laboratory test variables into no more than three categories. The data of 193 patients with a complete set of candidate covariates were used for the training set (Fig 1).

The protocol of this study was reviewed and approved by the JCOG Protocol Review Committee.

Statistical analysis

Patients who survived >5 years were categorized according to ATL subtype (acute, lymphoma or unfavourable chronic types). In addition, to evaluate the ATL-related death events for each subtype, a disease-specific mortality curve was estimated, for only those patients who survived >2 years, by means of a competing risks framework (Kalbfleisch & Prentice, 2002). The proportion of patients who survived >5 and >10 years was calculated to evaluate the association between long-term survival and CR (including CR unconfirmed) for initial treatment. The proportion of cases with

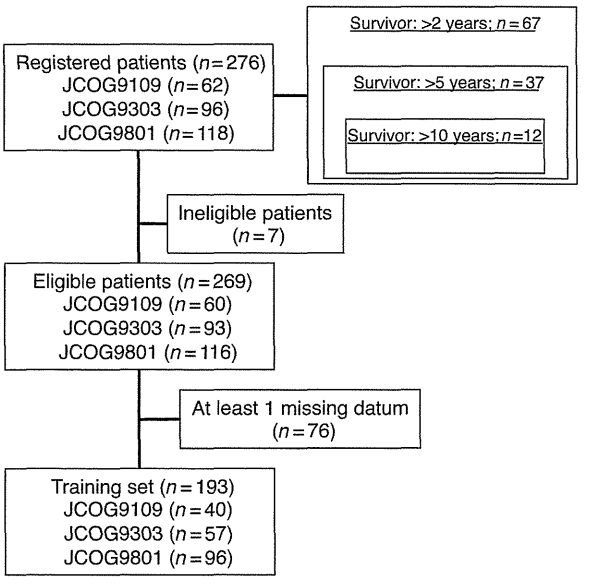

Fig 1. Patient disposition of the training set.

CNS involvement was compared among the JCOG trial regimens in an exploratory evaluation of the efficacy of prophylactic IT treatment. The prophylactic IT treatments against CNS involvement were: none in JCOG9109, MTX and PSL in JCOG9303, and MTX, cytarabine and PSL in both regimens in JCOG9801. Confidence intervals (CIs) for all the above proportions were computed using the Clopper–Pearson method (Clopper & Pearson, 1934).

Analyses for the development and validation of the JCOG-PI were performed according to a pre-specified analysis plan. The JCOG-PI consisted of risk groups that were developed using Cox's proportional hazards model. Before constructing the JCOG-PI, covariates with several definitions were selected for those with the smallest Akaike's Information Criteria (Akaike, 1973) on univariate analysis. Next, we verified the correlations between covariates to avoid multi-colinearity. Stepwise Cox regression analysis was then performed to identify unfavourable prognostic factors for constructing the JCOG-PI. The entry criterion was $P < 0{\cdot}20$ and the removal criterion was $P > 0{\cdot}15$.

The maximum number of risk group strata was set at three, based on the opinions of JCOG-LSG members who commented that too many strata were impractical for evaluating risk. The risk group was divided with patients equally distributed. The log-rank test was used to assess the discrepancy between the risk groups and the Kaplan–Meier method was applied to estimate OS.

All statistical analysis was performed using SAS Release 9·1 (SAS Institute, Inc, Cary, NC, USA). All reported P values are two-sided and $P < 0{\cdot}05$ was considered statistically significant.

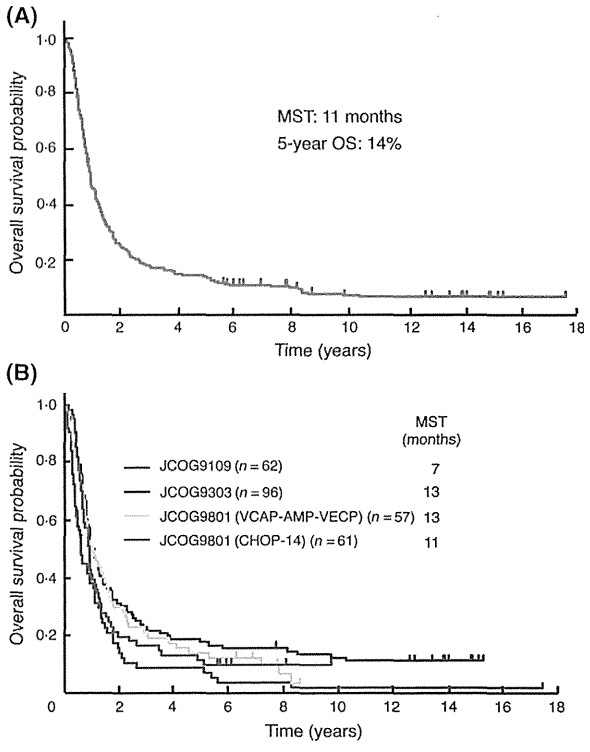

Fig 2. Overall survival (OS) of all registered patients in 3 Japan Clinical Oncology Group (JCOG) trials and according to treatment regimens. (A) OS of all 276 registered patients. Median survival time (MST) and the 5-year OS were 11 months and 14%, respectively.(B) OS according to different treatment regimens. MST was 7 months in JCOG9109, 13 months in JCOG9303, 13 months in VCAP-AMP-VECP of JCOG9801 and 11 months in CHOP-14 of JCOG9801.

Results

Patient characteristics

A total of 276 patients were registered in the 3 trials (JCOG9109, $n = 62$; JCOG9303, $n = 96$; and JCOG9801, $n = 118$) from 58 institutions in Japan. The MST and the 5-year OS of all patients were 11 months and 14% respectively (Fig 2A). The OS of each treatment regimen during the long follow up reconfirmed the findings of each original report (Fig 2B) (Yamada *et al*, 2001; Tsukasaki *et al*, 2003, 2007). Clinical characteristics are shown in Table I.

Long-term survivors according to subtype and initial response

The disease-specific mortality curve of patients who survived >2 years according to subtype is presented in Fig 3. Among the 37 patients (acute, $n = 22$; lymphoma, $n = 8$; unfavourable chronic, $n = 7$) who survived >5 years, there were no ATL-related deaths in lymphoma type, which was in contrast to the 10 ATL-related deaths in the acute and unfavourable chronic types after 5 years.

Of the 276 patients, 88 (32%) achieved CR with initial treatment. Of these 88 patients, 24 (27%) patients had survived >5 years and 11 (13%) patients had survived >10 years. Of the remaining 188 patients who did not achieve CR, 13 (17%) patients who survived >5 years and only 1 (0·5%) patient survived >10 years.

CNS involvement by treatment regimen

CNS involvement was 1·6% (95% CI, 0·04–8·7) in JCOG9109, 6·3% (95% CI, 2·3–13·1) in JCOG9303, and 3·5% (95% CI, 0·4–12·1) in the VCAP-AMP-VECP arm and 8·2% (95% CI, 2·7–18·1) in the CHOP-14 arm of JCOG9801. No significant differences in the proportion of CNS involvement were observed among the regimens.

Development of the PI

In univariate analyses, three covariates showed significant associations with OS, namely PS, corrected calcium level and serum total protein (all $P < 0{\cdot}05$; Table II). Stepwise Cox regression analysis returned three unfavourable prognostic

Table I. Clinical characteristics of 15 covariates in all 276 registered patients.

		JCOG9109 (n = 62)	JCOG9303 (n = 96)	JCOG9801 (n = 118)	Total (n = 276)
Initial date of registration		November 1991	January 1994	July 1998	
Final date of registration		July 1993	December 1996	October 2003	
Number of sites		30	20	27	49
Sex	Male/female	38/24	54/42	61/57	153/123
Age, years	≥20, <30	0	1	0	1
	≥30, <40	2	7	6	15
	≥40, <50	14	29	20	63
	≥50,<60	27	24	44	95
	≥60, <70	19	35	48	102
PS	0/1	23/22	19/25	49/46	91/93
	2/3/4/NE	7/9/1/0	17/9/8/18	18/4/1/0	42/22/10/18
B symptoms	+/−/NE	22/36/4	39/57/0	45/73/0	106/166/4
Stage	I/II/III/IV	1/4/8/49	2/6/14/74	0/4/8/106	3/14/30/229
Liver invasion	+/−	10/52	20/76	25/93	55/221
LDH, iu/l	<−1 × ULN/>	9/53	10/86	20/98	39/237
BUN, mmol/l	<−1 × ULN/>/NE	47/14/1	80/15/1	107/11/0	234/40/2
Corrected Ca, mmol/l	<2·75/≥/NE	49/9/4	75/16/5	93/25/0	217/50/9
Serum protein, g/l	<60/≥/NE	18/44/0	27/69/0	30/87/1	75/200/1
Albumin g/l	<35/35–40/≥40/NE	18/26/15/3	35/39/18/4	28/64/26/0	81/129/59/1
WBC ($\times 10^9$/l)	<3/≥	48/14	77/19	104/14	229/47
Lymphocytes ($\times 10^9$/l)*	<4/4–15/≥15/NE	28/16/14/4	54/19/23/0	64/33/20/1	146/68/57/5
Neutrophils ($\times 10^9$/l)	<8/≥/NE	49/12/1	75/21/0	94/24/0	218/57/1
Platelets ($\times 10^9$/l)	<150/≥	16/46	19/77	19/99	54/222

B symptoms: fever, night sweats, and weight loss.
JCOG, Japan Clinical Oncology Group; ECOG PS, Eastern Cooperative Oncology Group performance status; Ca, calcium level; WBC, white blood cell count; ULN, upper limit of normal; NE, not evaluated.
*total (normal + abnormal) lymphocyte count.

factors associated with OS, namely a high, corrected calcium level, high PS (2–4), and the existence of B symptoms, although the third factor was not statistically significant (Table II). Table II also presents the results of the model when the two significant factors of corrected calcium and ECOG PS were included. The hazard ratios (HRs) estimated by this model were 1·574 (95% CI, 1·088–2·277; P = 0·016) for corrected calcium and 1·554 (95% CI, 1·120–2·157; P = 0·008) for ECOG PS.

The four categories consisting of the two prognostic factors (corrected calcium level and PS) were combined into a dichotomous PI, named the JCOG-PI, by considering its potential for clinical use. Similarly, we constructed a dichotomous PI including B symptoms with two prognostic factors. We excluded B symptoms from further assessment because the Akaike Information Criteria of JCOG-PI (1537·8) was smaller than that of PI (1545·6).

According to the JCOG-PI, the MST and 5-year OS were 14 months and 18% in patients with both corrected calcium <2·75 mmol/l and a PS of 0 or 1 (moderate-risk group) and were 8 months and 4% in patients with corrected calcium ≥2·75 mmol/l and/or a PS of 2–4 (high-risk group) respectively (Fig 4A). The HR and 95% CI were 1·926 and 1·423–2·606 respectively (P < 0·0001).

External validation

Nine patients in the validation set of 136 patients had missing corrected calcium or PS data, resulting in 127 evaluable patients (Fig 5). The median and longest follow-up periods were 9 months and 97 months, respectively. The HR was 2·138 (95% CI, 1·414–3·233, P = 0·0003) with an MST of 18 months and 6 months in the moderate- and high-risk groups respectively and JCOG-PI showed good reproducibility (Fig 4B).

Discussion

In this first prospective analysis of a large cohort of aggressive ATL patients from prospective clinical trials conducted after the clinical subtype classification of ATL was introduced, we constructed the JCOG-PI based on corrected calcium level and PS and validated it with external data. The ascertained discrepancy was stronger among the external validation set. In addition, OS of high-risk patients was worse in the external validation set than in the training set, probably reflecting poor organ functions and other unfavourable prognostic factors in patients not participating in clinical trials. The OS of the moderate-risk patients was better in the

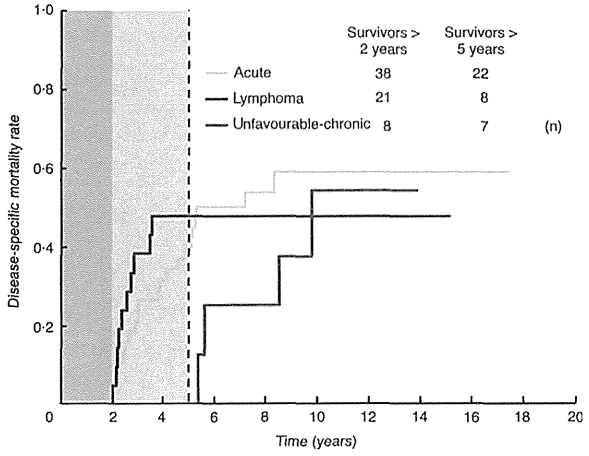

Fig 3. ATL-related deaths of patients who survived >2 years according to subtype. Among the 37 patients who survived >5 years, there were no ATL-related deaths in lymphoma type in contrast to the 10 ATL-related deaths in other types after 5 years.

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.

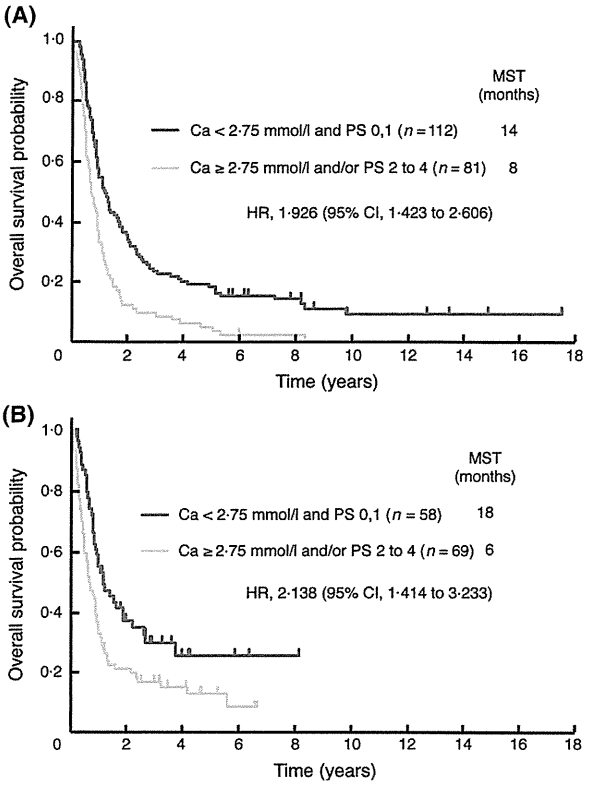

Fig 4. Overall survival of the patients in the training set and in the external validation set according to the JCOG-PI. (A) OS in the training set. The median survival time (MST) and 5-year OS were 14 months and 18% in moderate-risk group (blue line) and were 8 months and 4% in high-risk group (yellow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

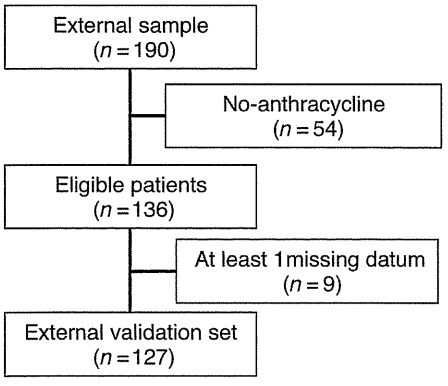

Fig 5. Patient disposition of the external validation set.

(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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A Retrospective Analysis of Treatment Outcomes in Adult T Cell Leukemia/Lymphoma Patients with Aggressive Disease Treated with or without Allogeneic Stem Cell Transplantation: A Single-Center Experience

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Adult T cell leukemia/lymphoma (ATL) is an aggressive peripheral T cell neoplasm with very poor prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been reported as a curative treatment modality for ATL. However, there are no reports comparing chemotherapy alone with allo-HSCT in ATL. In this report, we retrospectively analyzed data for patients treated with (n = 29, median age 55 years) or without allo-HSCT (n = 37, median age 58 years) for ATL in Kagoshima University Hospital, located in one of the most endemic areas of human T cell lymphotropic leukemia virus type 1 infection. Forty patients (61%) started coordination for allo-HSCT. Ten patients (34.4%) received allo-HSCT while in complete remission (CR), whereas the others were not in CR. Twenty-five patients (86.2%) received reduced-intensity conditioning, and the others received myeloablative conditioning. With a median follow-up period for survivors of 41 months (range, 5 to 125 months), the 3-year overall survival (OS) rate from first chemotherapy for all patients (with or without allo-HSCT) was 35.2%. The 3-year OS from first chemotherapy for patients who received allo-HSCT or only chemotherapy was 44.9% and 27.7%, respectively. Univariate analyses revealed that high serum soluble IL-2 receptor (sIL-2R) levels (≥2000 U/mL) just before the conditioning regimen and progressive disease (PD) status at HSCT (according to Japan Clinical Oncology Group Study 0907 criteria) were significant risk factors for OS in the allo-HSCT group. Multivariate analyses revealed that PD status was a significant risk factor for OS in the allo-HSCT group. In the chemotherapy-only group, the 3-year OS rate was 61.5% (95% CI, 30.8% to 81.8%) in patients with serum sIL-2R levels < 2000 U/mL for >3 months. In contrast, the 3-year OS rate was 5.7% (95% CI, .4% to 22.4%) in patients who did not achieve serum sIL-2R levels < 2000 U/mL for >3 months. Our single-center cohort experience indicates that chemosensitivity is the most important prognostic factor for OS in ATL patients and the use of allo-HSCT is limited in chemorefractory patients with aggressive ATL disease. In the chemosensitive patients, allo-HSCT demonstrated a tendency toward better OS. Further clinical studies are warranted to determine optimal treatments for patients who are less sensitive to conventional chemotherapy.

INTRODUCTION

Adult T cell leukemia/lymphoma (ATL) is a highly aggressive peripheral T cell neoplasm caused by human T cell lymphotropic leukemia virus type 1 (HTLV-1). The prognosis is very poor, with only a 24% 3-year overall survival (OS) rate using standard combination chemotherapy [1]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been considered a curative treatment modality for those with aggressive ATL. However, a nationwide retrospective study demonstrated only a 33% 3-year OS rate [2] in a study in which some patients did not receive allo-HSCT because of refractoriness to induction chemotherapy or the patient's choice. There is no evidence regarding allo-HSCT in a sample

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Table 1
Patient and Transplantation Characteristics in Patients with ATL, Compared Between Treatments

Characteristic	Subcharacteristic	Allo-HSCT Patients (n = 29)	Chemotherapy Only Patients (n = 37)
Age, yr (range)		55 (32-62)	58 (27-69)
Sex	Male	15 (51.7%)	21 (56.8%)
	Female	14 (48.3%)	16 (43.2%)
Disease subtype	Acute	24 (82.8%)	28 (75.7%)
	Lymphoma	5 (17.2%)	9 (24.3%)
Disease status at HSCT (HSCT group)	CR	10 (34.8%)	12 (32.4%)
or initial chemotherapy (chemotherapy-only group)	PR	5 (17.2%)	7 (18.9%)
	SD	1 (3.7%)	
	PD	13 (44.8%)	18 (48.6%)
ATL-PI, mean ± standard deviation		3.0 ± 1.4	3.4 ± 1.1
Days from first chemotherapy to HSCT	Median (range)	204 (90-710)	
	≤90	1 (3.7%)	
	91-180	10 (34.5%)	
	≥181	18 (62.1%)	
sIL-2R level at HSCT, U/mL		2229 (238-35,125)	
Donor	MRD	5 (17.2%)	
	MUD	9 (31.0%)	
	MMD	15 (51.7%)	
Stem cell source	BM	14 (48.3%)	
	PBSC	14 (48.3%)	
	CB	1 (3.4%)	
Conditioning regimen	MAC	2 (6.9%)	
	RIC	27 (93.1%)	
TBI	Yes	13 (44.8%)	
ATG	Yes	10 (34.5%)	
Flu	Yes	24 (82.8%)	
Bu	Yes	19 (65.5%)	
GVHD prophylaxis	CSP + MTX ± MMF	10 (35.7%)	
	TK + MTX ± MMF	18 (64.2%)	
MMF	Yes	7 (25.0%)	

CR indicates complete remission; PR, partial remission; SD, stable disease; PI, prognostic index [16]; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; MMD, HLA-mismatched donor; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation; ATG, antithymocyte globulin; Flu, fludarabine; Bu, busulfan; CSP, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; TK, tacrolimus.

consisting of only ATL patients with aggressive disease. We retrospectively analyzed the treatment outcomes of chemotherapy-only compared with those of chemotherapy followed by allo-HSCT in ATL patients with aggressive disease in a single institution.

METHODS

Clinical data for 66 patients with aggressive ATL who received chemotherapy alone (n = 37) or allo-HSCT (n = 29) for the first time between October 2002 and April 2014 in Kagoshima University Hospital were retrospectively collected and reviewed. The study protocol was approved by the institutional review board of Kagoshima University Hospital.

Clinical subtypes of ATL were categorized according to the Shimoyama criteria [3]. OS was calculated from the day of first chemotherapy or HSCT until death or last observation, as indicated. Patients who remained alive at the time of the last follow-up were censored. The definition of a therapeutic response to HSCT was as previously described, with the following minor modification [4]: The requirement of a 4-week observation period to assess the therapeutic response before HSCT was not used, and unconfirmed complete remission was not applied because 31% of the allo-HSCT patients received a preconditioning regimen for allo-HSCT within the 4-week observation period. Response to treatment was thus divided into 4 categories [4]: complete remission, partial remission, stable disease, and progressive disease (PD). Non-PD was defined as complete remission + partial remission + stable disease.

Statistical Analysis

Comparisons between the groups were performed using chi-square or Fisher exact tests for categorical variables, as appropriate, and Mann-Whitney U tests for continuous variables. The Kaplan-Meier method was used to estimate OS. The 95% confidence interval (CI) of the 3-year OS was calculated. The effects of acute graft-versus-host disease (GVHD) (within 60 days after allo-HSCT) on OS were analyzed in patients who achieved engraftment and survived at least 100 days after transplantation. This landmark method was used to exclude bias that may have arisen from including patients who died or had a relapse too early to develop GVHD in the group without GVHD.

The effects of various patient and disease categorical variables on survival probabilities were examined using the log-rank test, and the following variables were included in the subgroup analyses: age, sex, serum soluble IL-2 receptor (sIL-2R) levels at allo-HSCT, donor, stem cell source, and intensity of the conditioning regimen. Multivariate analysis for OS was performed using the Cox proportional hazards regression model. All P values were 2-sided, and statistical significance was set at $P < .05$. All statistical analyses were performed with EZR [5].

RESULTS

Patient and Allo-HSCT Characteristics

Twenty-nine ATL patients received allo-HSCT after chemotherapy (median age, 55 years; range, 32 to 62 years), and 37 ATL patients received only chemotherapy (median age, 58 years; range, 27 to 69 years) (Table 1, Figure 1). Three donors (10.3%) were seropositive for HTLV-1. The peripheral blood mononuclear cells of these donors were subjected to Southern blot analysis to examine the monoclonal or

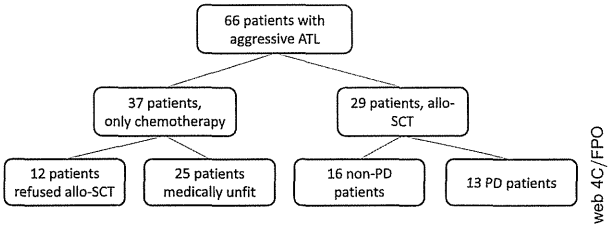

Figure 1. Flowchart of study inclusion of ATL patients who received only chemotherapy or allo-HSCT.