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Clinical Cancer Research

Human T-cell Lymphotropic Virus Type I–Associated Adult T-cell Leukemia–Lymphoma: New Directions in Clinical Research

Kunihiro Tsukasaki and Kensei Tobinai

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Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma

Kenji Ishitsuka, Kazuo Tamura

Adult T-cell leukaemia-lymphoma (ATL) is a malignancy of peripheral T lymphocytes caused by human T-lymphotropic virus type I (HTLV-1), and its prognosis is poor. There are an estimated 5 million to 20 million HTLV-1 infected individuals worldwide; their lifetime risk of developing ATL is 3–5%, and high HTLV-1 proviral loads have been shown to be an independent risk factor. Recent advances in the treatment of ATL are the introduction of treatment targeted against CC chemokine receptor 4 (CCR4), which is abundantly expressed on most ATL cells, and allogeneic haemopoietic stem-cell transplantation for aggressive ATL. Promising outcomes are also reported with early intervention for indolent ATL with interferon α and zidovudine. Clinical trials should incorporate a validated prognostic index to assess the results, because of the difficulties associated with undertaking large-scale trials and significant diversity of clinical features with ATL, even in the same clinical subtypes (acute, lymphoma, chronic, and smoldering).

Introduction

Adult T-cell leukaemia-lymphoma (ATL) is a malignancy of peripheral T lymphocytes caused by human T-lymphotropic virus type I (HTLV-1), and its prognosis is poor compared with other aggressive non-Hodgkin lymphomas. The clinical entity of ATL was first proposed in 1977 as a distinct T-cell neoplasm frequently observed in southwestern Japan, and the RNA retrovirus HTLV-1 was subsequently isolated as the causative virus.^{1,2} HTLV-1 also causes HTLV-1-associated myelopathy-tropical spastic paraparesis (HAM-TSP), a chronic inflammatory disease of the CNS characterised by slowly progressive spastic paraparesis, lower limb sensory disturbance, and bladder or bowel dysfunction.^{3,4} Differences in the immune response to HTLV-1 in infected individuals, which are at least partially dependent on the HLA haplotypes—ie, low immune responders to HTLV-1 infected cells are at risk of ATL but high immune responders to HTLV-1 infected cells are at risk of HAM-TSP—have been proposed as the reasons why the same virus causes two distinctive diseases, one a malignant disease and the other an inflammatory disease.^{5,6} By contrast, a less efficient response by cytotoxic T cells against HTLV-1 is reported to be the cause of risk of HAM-TSP since it causes a higher proviral load and higher antigen expression that activates and expands antigen-specific T-cell responses, followed by induction of large amount of proinflammatory cytokines and chemokines.⁷ In HTLV-1 carriers in Japan, the lifetime risk of ATL is estimated 3–5% (5–7% for men and 2–4% for women) and of HAM-TSP is 0.25%.^{8,9}

The clinical course of ATL is very heterogeneous, and the Japan Clinical Oncology Group (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. Acute, lymphoma, and unfavourable chronic types are considered to be aggressive ATLs, and favourable chronic and smoldering types are indolent ATLs.^{10,11}

In this Review, we discuss the epidemiology of HTLV-1, transmission of HTLV-1 and its prevention, recent advances in the oncogenesis and pathophysiology of ATL, identification of HTLV-1 carriers at high risk of development of ATL, and the clinical features, treatment, and prognostic index of this disease.

Epidemiology of HTLV-1

HTLV-1 is endemic in southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea, and the prevalence of patients with ATL and HAM-TSP has been linked to the distribution of HTLV-1.¹²

The origin of HTLV-1 is considered to be primate T-cell lymphotropic virus (PTLV) in African non-human primates. It migrated within a simian reservoir towards Asia, and evolved into simian T-cell leukaemia virus type-I (STLV-1). This STLV-1 lineage spread to Japan and India, and Indonesia where it may have crossed the simian–human barrier for the first time, which resulted in the HTLV-1c (Australo-Melanesian) subtype. STLV-1 returned to Africa from Asia and evolved into several subtypes of HTLV-1a (the cosmopolitan subtype), 1b (the central African subtype), 1d, 1e, and 1f around 19 000 to 35 500 years ago. HTLV-1a arose in west Africa, and spread to the USA, Japan, the Middle East, and North Africa (known as HTLV-1a late) because of the slave trade and the increased mobility of human beings.¹³

An estimated 5 million to 20 million individuals are infected with HTLV-1 worldwide.^{14,15} In a study by Satake and colleagues,¹⁶ the seropositivity of HTLV-1 among first-time blood donors was reported to be 0.32% (3787 of 1196 321) in Japan between 2006 and 2007. Adjusted overall prevalences were estimated to be 0.66% in men and 1.02% in women, and the number of HTLV-1 carriers aged 0–99 years is estimated to be at least 1.08 million in Japan, which is 10% lower than reported in the 1988 database cited in their article.¹⁶ Most carriers are aged 70–80 years; this finding differs from that reported in the 1988 database, in which the most carriers were aged

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Division of Oncology,
Hematology and Infectious
Diseases, Department of
Internal Medicine, Fukuoka
University, Fukuoka, Japan
(K Ishitsuka MD;
Prof K Tamura MD)

Correspondence to:
Dr Kenji Ishitsuka, Division of
Oncology, Hematology and
Infectious Diseases, Department
of Internal Medicine, Fukuoka
University, 7-45-1 Nanakuma
Jonan, Fukuoka 814-0180, Japan
kenjiishitsuka@fukuoka-u.
ac.jp

50–60 years. A marked decrease in the prevalence of HTLV-1 based on the age of the blood donor has been reported. For example, the mean carrier rate for all donors in one prefecture located in southwestern Japan was 1.95%, whereas the rate was 8.7% in men aged 60–64 years, and 14.0% in women aged 60–64 years. Sex differences in HTLV-1 prevalence increase after age 20 years, with more women infected than men.¹⁶ In Brazil, the prevalence of HTLV-1 among first-time blood donors was 0.14% (363 of 281760) between 2007 and 2009, and was significantly correlated with age (adjusted odds ratio [aOR] 5.23 for age >50 vs <20 years), female sex (aOR 1.97), and black (aOR 2.70 vs white) and mixed race (aOR 1.78 vs white), and inversely correlated with education (aOR 0.49, college graduates vs those who did not complete high school).¹⁷ By contrast, a study showed that the prevalence of HTLV-1 in first-time blood donors in European countries was 0–0.0048%, except for Romania, where it was 0.05%.^{18–20} Most HTLV-1 infected donors in these countries were either from an endemic area or had a sexual partner from an endemic area.¹⁸

Transmission and prevention of HTLV-1

Clustering of HTLV-1 carriers was reported in family members of patients with ATL soon after the identification of the virus, suggesting that this virus is transmitted by close contact within the family.^{21,22} Three major HTLV-1 transmission routes are mother-to-child, sexual intercourse, and blood transfusions containing cellular components—ie, HTLV-1 infected lymphocytes.²³

Transmission via transfusion has been almost eliminated through viral screening of donated blood, which has been done since 1986 in Japan, 1988 in the USA, 1991 in France, 1993 in Brazil, and 2002 in the UK. However, some European countries have not introduced screening, and Norway and Finland decided to stop screening because no positive donors were found after 7 and 13 years of testing, respectively.¹⁸

Sexual transmission is mainly male to female via HTLV-1-infected lymphocytes in semen, and can be prevented by use of a latex condom. Although the prevalence of HTLV-1 in the husbands of HTLV-1 carrier wives was not higher than that in the general population, the wives of carrier husbands in elderly populations were almost invariably infected.²¹ The prevalence of HTLV-1 increases in women in an age-dependent manner after they reach their 20s, which supports the male-to-female transmission of HTLV-1; however, individuals infected with HTLV-1 after adolescence are considered to be at very low risk of developing ATL. Therefore, mother-to-child transmission is currently the most important risk factor of HTLV-1 infection associated with the subsequent development of ATL. A Japanese long-term prospective study²⁴ reported HTLV-1 transmission rates from infected mother to child of 20.5% after the child was breastfed at least 6 months, of 8.3% after breastfeeding for less than 6 months, and of 2.4% when exclusively

formula-fed. On the basis of these findings, a nationwide programme to prevent mother-to-child infection was initiated in Japan in April, 2011, by screening all pregnant women for HTLV-1 infection and recommending either exclusive formula feeding, freeze-thawing of expressed breast milk to destroy HTLV-1-infected lymphocytes, or breastfeeding for a maximum of 3 months if the mother is infected, unless they give birth to high-risk infants such as premature babies.

Oncogenesis and pathophysiology of ATL

HTLV-1-infected cells express the virus protein Tax, which has various cellular functions including activation of NF- κ B, Akt signalling, and cyclin-dependent kinases, and silencing of P53 function. Tax has been considered to play a key part in the oncogenesis of ATL in the early stages, because Tax could immortalise T lymphocytes in vitro,²⁵ and transgenic mice which expressed Tax showed oncogenic capabilities.²⁶ However, because Tax is a target for the host cytotoxic T cells, there is some survival advantage for Tax expression to be impaired to enable HTLV-1-infected cells to escape immune surveillance and survive in the host.²⁷ Studies have shown that Tax transcript could not be detected in fresh ATL cells derived from more than half of patients with this disease because of the accumulation of non-sense mutations, insertions and deletion in Tax, silencing of viral transcription by DNA methylation of the provirus, or deletion of the proviral 5' LTR.²⁷ It suggests the possibility that Tax is not necessarily important to develop ATL in the late stage of oncogenesis.

The universal expression of HTLV-1 basic leucine zipper (HBZ), an antisense mRNA transcribed from the 3' LTR, has been reported in fresh ATL cells and HTLV-1-infected cells.²⁷ The suppression of HBZ gene transcription inhibits the proliferation of ATL cells, while expression of HBZ gene promoted the proliferation of a human T cell line in vitro.²⁸ HBZ selectively inhibits classic NF- κ B pathways without inhibiting alternative NF- κ B pathways. Moreover, HBZ induced the expression of FOXP3 in naive T cells, which is consistent with one of the established characteristic phenotypes of ATL cells.^{29,30} These findings strongly suggest that HBZ and Tax play an important part in the oncogenesis of ATL by HTLV-1.

The suppression of ATL cell growth and promotion of apoptosis by inhibition of NF- κ B with miR-31 have been reported in vitro.³¹ Repression of miR-31, which negatively regulates NF- κ B signalling by inhibiting NF- κ B-inducing kinase (NIK), was confirmed by profiling cellular microRNA on primary ATL cells. Therefore, the activation of NIK by genetic and epigenetic loss of miR-31 has been suggested as a possible mechanism for the constitutive activation of NF- κ B in ATL cells that are not expressing Tax.³¹

An analysis using oligoarray comparative genomic hybridisation against paired samples with acute-type ATL

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

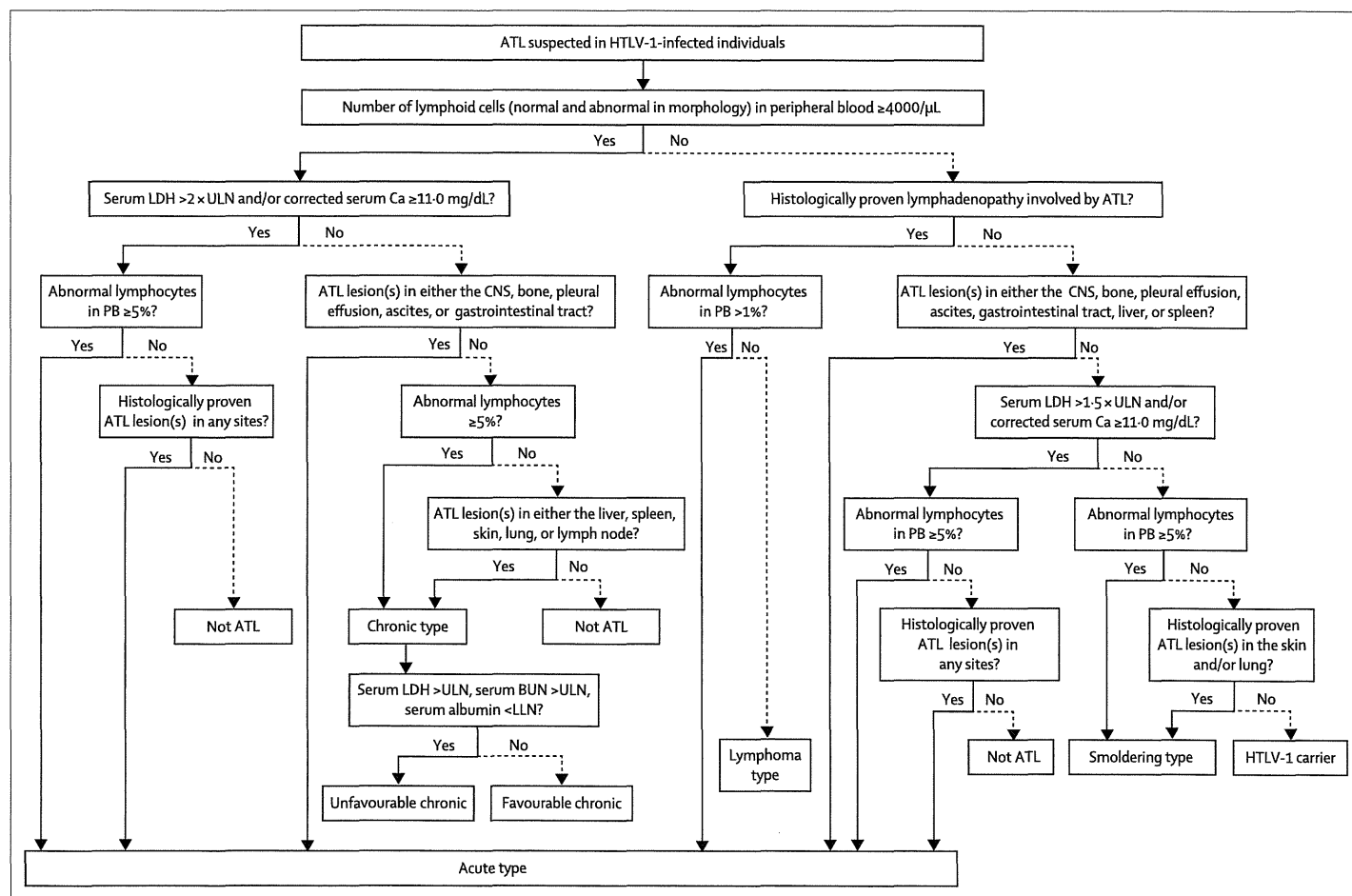


Figure: Determination of the ATL clinical subtype classification according to Shimoyama criteria³⁰
 ATL=Adult T-cell leukemia-lymphoma. ULN=upper limit of normal. LLN=lower limit of normal. (Courtesy of JCOG1111 coordinating office).

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. VCAP-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-G-CSF=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=haemopoietic stem-cell transplantation. *The efficacy of VCAP-AMP-VECP and CHOP14 was assessed in a phase 3 clinical trial.⁹ †Clinical trials of VCAP-AMP-VECP with or without mogamulizumab have been completed.⁴ ‡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.⁴⁰ §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 jirovecii*, 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 meeting⁴⁶ 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 colleagues⁵³ and Hermine and colleagues⁵⁴ 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 colleagues⁵⁵ 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 colleagues⁵⁶ reported response rates (complete remission

	Acute		Lymphoma		Acute and lymphoma	Chronic and smoldering
	JCOG9303 ⁴⁹	JCOG9801 ⁴³	JCOG9303 ⁴⁹	JCOG9801 ⁴³	Clinical practice* ⁵¹	Watch and waiting ⁵²
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=azidothymidine. NR=not reached. OS=overall survival.

Table 3: Meta-analysis reported by Bazarbachi and colleagues of IFN/AZT versus chemotherapy for ATL⁵⁸

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 colleagues⁵⁷ 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 colleagues⁴⁵ 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.^{60,61} 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 study⁶⁴ 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, monoclonal antibody that markedly enhances antibody-dependent cellular cytotoxicity by increasing binding affinity to the Fc γ 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 meeting⁴⁶ 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 study⁵² 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 ATL⁵⁸ 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, *Pneumocystis* 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 >20000 U/mL).

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.

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}

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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