3 ATLに対するインターフェロンα＋抗レトロウイルス剤の位置づけ

A 序論

成人T細胞白血病・リンパ腫（adult T-cell leukemia-lymphoma：ATL）は，九州・沖縄地方を中心とする西南日本に多発するT細胞性腫瘍として，1977年に高月らによって提唱された疾患概念である[1]．1980年代の初めには原因ウイルスとしてレトロウイルスであるhuman T-lymphotropic virus type I（HTLV-1）が発見され，現在では，HTLV-1プロウイルスがATL細胞のDNAに単クローン性に組み込まれている末梢性T細胞腫瘍をATLと定義する．ATLの臨床病態は白血球増多，リンパ節腫脹，高LDH血症，高Ca血症，日和見感染症，浸潤による臓器障害などが主なものであるが，きわめて多彩であることが知られている．

予後因子としては，年齢，全身状態（PS），総病変数，高Ca血症，高LDH血症が重要である[2]．予後因子解析と臨床病態の特徴から，白血化，臓器浸潤，高LDH血症，高Ca血症の有無により病型分類が提唱され，これが治療法選択の重要な指標とされる．生存期間中央値（MST）は急性型6カ月，リンパ腫型10カ月，慢性型24カ月，くすぶり型は3年以上であった[3]．

ATLは世界的にみても，日本以外では主に中央アフリカおよびカリブ海沿岸での発生に限られ，日本が最大の発生地である．悪性リンパ腫/白血病のなかできわめて希少な疾患であり，まとまった患者が登録される臨床試験を実施するのは日本以外では困難である．現在，日本には100万人程度のHTLV-1キャリアが存在するとされており，そのなかから1年に1,000人に1人の割合でATLを発症するとされている．年齢の分布は20歳代の患者はきわめてまれで，30歳ぐらいから徐々に患者が増加し，60歳代をピークにして徐々に減少する．1人のHTLV-1キャリアが，生涯でATLを発症する割合は約5%程度と考えられている．

ATLの発症年齢は，2001年には平均値61歳であったが，2010年には中央値67歳と報告されており，患者の高齢化が進んでいる．HTLV-1キャリアの高齢化も報告されている．

B 指針

日本では，aggressiveな急性型/リンパ腫型/予後不良因子を有する慢性型ATLには，CHOP-14療法との第3相比較試験の結果からVCAP-AMP-VECP療法が標準治療とされる[4]．しかしその3年生存割合は約25%と不良であることから，GvATL効果により有望な成績が報告されている同種造血幹細胞移植療法（allo-HSCT）も標準治療として推奨されている[5]．一方，indolentなくすぶり型/予後不良因子を有さない慢性型ATLは無治療でも一部は長期生存するが，多くは数年のうちに急性転化し，その後の経過はaggressive ATLと同様である．標準的な治療法がない現在，予後不良因子をもたないindolent ATLは急性転化するまではwatchful waitingが原則とされる[5]．

表1 未治療のATLに対する方針：International Consensus Report on ATL

くすぶり型あるいは予後不良因子を有さない慢性型ATL
・前向き臨床試験への参加を考慮
・症候を有する患者（皮膚病変，日和見感染症ほか）：AZT/IFN療法またはWatch and Waitを考慮
・症候のない患者：Watch and Waitを考慮
予後不良因子を有する慢性型あるいは急性型ATL＊
・前向き臨床試験への参加を考慮
・臨床試験に参加しない場合，予後因子（臨床的因子と可能であれば分子生物学的因子）をチェック：
—予後良好群：化学療法（VCAP-AMP-VECP evaluated by a phase Ⅲ trial against biweekly-CHOP）あるいはAZT/IFN（evaluated by a meta-analysis on retrospective studies）を考慮
—予後不良群：化学療法に引き続いての骨髄破壊的，または非破壊的同種造血幹細胞移植療法（evaluated by retrospective and prospective Japanese analyses, respectively）を考慮．
—初期治療の奏効が不十分：骨髄破壊的，または非破壊的同種造血幹細胞移植療法を考慮
＊：リンパ腫型も同様の戦略をとる．ただし実態調査結果からはこの病型への有用性が低かったAZT/IFN療法は推奨されていない．

文献5より改変，引用

ATLに対する標準治療についての臨床試験の報告は限られている．このようななか，2009年にATLに対する治療戦略についての国際的合意が形成され，J Clin Oncol誌に公表された（表1）[5]．ただエビデンスレベルの高い報告は少ないため，これはガイドラインではなく，考慮すべき治療法の推奨について合意したコンセンサスレポートである．表に示すIFN/AZT療法は，下記のエビデンスで示すいくつかの報告によって米国・欧州のみならず，ATLの多発地域である中南米諸国でも標準治療に1つとして広く用いられている[6-12]．

C エビデンス

1 Gill PS, et al（N Engl J Med. 1995; 332: 1744）[6]（Prospective study）

目的▶ インターフェロンα（IFN α）と逆転写酵素阻害剤のジドブジン（AZT）のATLに対する臨床的効果を明らかにする．

方法▶ 急性型またはリンパ腫型のATLに対しAZT 1000 mg内服とIFNα 500ないし1000万単位皮下注を連日行った．

結果▶ Aggressive ATL 19例（うち7例は再発・難治）の58%が寛解（5例のCRと6例のPR）に導入された．

結論▶ ジドブジンとインターフェロンαの併用は，前治療歴があるATLにも効果を発揮するので，本疾患の治療法としてさらに評価されるべきである．

2 Bazarbachi A, et al（J Clin Oncol. 2010; 28: 4177-83）[10]（Retrospective study）

目的▶ インターフェロンα（IFN α）と逆転写酵素阻害剤のジドブジン（AZT）のATLに対する臨床的効果を明らかにする．

方法▶ 米国（59名），英国（13名），Martinique（西インド諸島東部のフランス海外県；111

名），フランス本国（67名）の計250名の後ろ向き観察研究の報告を行った．

結果▶ 解析対象となったATL 231名のうち207名に治療が実施されていた．75名が初回治療としてIFNα/AZT療法を受けており，生存期間中央値17カ月，5年生存割合46%と良好な結果であった．さらに，IFNα/AZT療法を受けたくすぶり型，慢性型17名のみを対象とすると，観察期間中央値5年で10年生存割合が100%であった．

結論▶ 今回の併合解析結果はこれまでの小規模な報告でのAZTとIFNの高い有効性を再現しており，この併用療法は白血化したATLに対する優れた標準治療であると考えられるべきである．

3 Ishitsuka K, et al（Int J Hematol. 2010; 92: 762–4）[11]（Prospective and pilot study）

目的▶ 海外からATLに対して有望と報告されているインターフェロンα（IFNα）とジドブジン（AZT）併用療法を日本人で検討する．

方法・結果▶ 3名の患者を対象とした小規模な研究結果から結論を導くことは困難であるが，IFN/AZT療法は明らかな抗ATL効果を示した．

結論▶ 本報告は，日本での今後のATL治療の開発に貢献することが期待される．

D 根拠となった臨床試験の問題点と限界

IFN/AZT療法についての上記の報告の多くは有望であるが，小規模な第2相またはパイロット試験結果と多施設の診療録調査による併合解析結果であり，ともに質の高いエビデンスに基づいているわけではない．当初のNEJM誌への報告結果も初発例に限るとその奏効割合とMSTは当時のJCOG-LSGで検討された化学療法より下回っていたことから，日本でこの治療法は本格的に検討されなかった[13]．ただIFNα/AZT療法の毒性は全身化学療法と比較すると軽微なこともあり，最近の併合解析結果をもとに，表の国際合意とNCCNガイドラインでは，エビデンスレベルは低いがリンパ腫型以外のATLに対してIFN/AZT療法を推奨している．しかし2の報告では，IFN/AZT療法群での治療成績は白血化している3病型で化学療法群よりも上回っていたが，急性型ATLに対する彼らの化学療法の治療成績は，日本での化学療法の成績と比べて下回っていた（図1）．一方，慢性型とくすぶり型では，症例数は少ないものの観察期間中央値5年で全例が生存しており，皮膚病変の改善にも有用であったと報告されている．この結果は，同病型に対する日本でのWatchful waitingの5年，10年，15年生存割合は47.2%，25.4%，14.1%であり，生存曲線にプラトーはなかったことに比べて有望である[14]．

IFN/AZT療法は，長期にわたる治療が必要であり，毒性としては倦怠感などの全身症状，造血障害など多様であるが，化学療法やallo-HSCTに比べて毒性は低いと報告されている．

E 本邦の患者に適応する際の注意点

IFN/AZT療法は，確かにATLに対して有望な治療法であるが，これまでの海外での小規模な臨床的検討と後方視的解析によるevidence levelが十分でないことから，現時点では一般診療では推奨されない．なお，IFN，AZTともに現在わが国におけるATLに対する保険適用はな

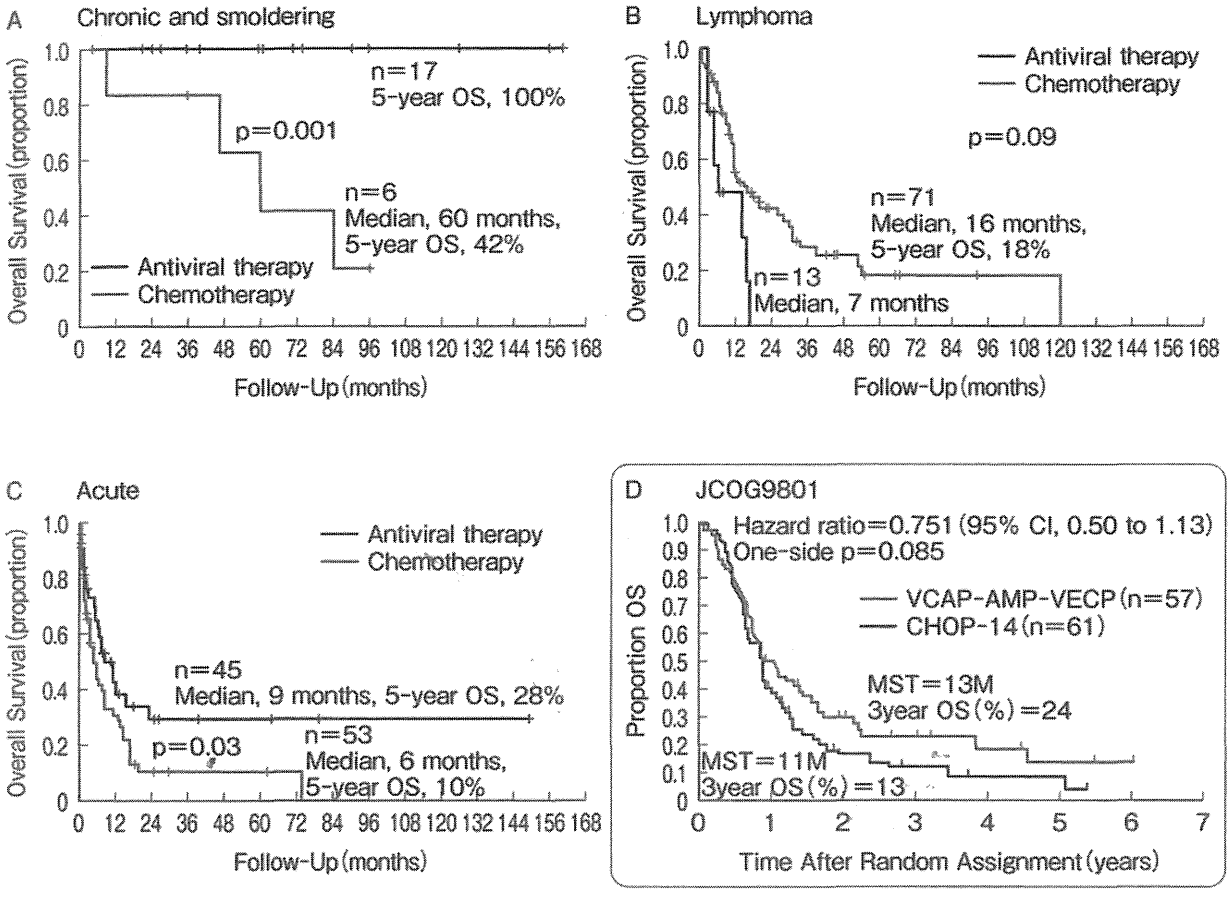

図1 米国，欧州，中米におけるATLに対するIFN/AZT療法と化学療法による全生存割合の病型別比較

（文献4と10より改変，引用）

A）慢性型およびくすぶり型

B）リンパ腫型

C）急性型

参考図：

D）日本におけるアグレッシブATLに対するVCAP-AMP-VECP療法とCHOP-14療法の比較視線での全生存割合

い．現在わが国では，indolent ATLに対するIFN/AZT療法と無治療経過観察療法（WW）との比較試験が計画されている．

F コメント

エビデンスではATLに対するIFN/AZT療法についての結果を解説したが，特にindolent ATLに対して有望であることから，WWとの優劣についての早期の検証が望まれる．一方高悪性度ATLに対しては表と別稿にあるように，強力な化学療法，allo-HSCTが標準治療とされ，再発難治の場合は，抗CCR4抗体などの新薬が適用される．IFN/AZT療法は急性型において奏効割合はさほど高くないが，寛解に導入されればその長期予後は良好と報告されている．一方リンパ腫型に本療法が奏効しにくい機序としてp53異常の関連が指摘されている．

最近，同療法に亜ヒ酸を追加したIFNα/AZT/亜ヒ酸併用療法の，慢性型ATLを対象とした第II相試験（10名）の結果が報告され，7名にCR，3名にPRが得られているものの，観察期

間が短く長期予後は明らかではない．さらに毒性はIFNα/AZT併用療法に比べて強かったことから，亜ヒ酸の上乗せの意義は小さいと考えられる[15]．

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Biology and treatment of HTLV-1 associated T-cell lymphomas

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Adult T-cell leukemia-lymphoma (ATL) is a distinct peripheral T-lymphocytic malignancy associated with human T-cell lymphotropic virus type I (HTLV-1) endemics in several regions of the world including the south-west Japan. The three major routes of HTLV-1 transmission are mother-to-child infections via breast milk, sexual intercourse, and blood transfusions. A HTLV-1 infection early in life, presumably from breast feeding, is crucial to the development of ATL. The estimated cumulative risk of developing ATL among HTLV-1-positive individuals is about 3% after transmission from the mother. The diversity in clinical features and prognosis of patients with this disease has led to its subtype-classification into acute, lymphoma, chronic, and smoldering types defined by organ involvement, lactate dehydrogenase (LDH) and calcium values. For the acute, lymphoma and unfavorable chronic subtypes (aggressive ATL), and the favorable chronic and smoldering subtypes (indolent ATL), intensive chemotherapy followed by allogeneic stem cell transplantation and watchful waiting until disease progression has been recommended, respectively, in Japan. A retrospective analysis suggested that the combination of interferon alpha and zidovudine was promising for the treatment of ATL, especially for leukemic subtypes. There are several new trials for ATL, including a defucosylated humanized anti-CC chemokine receptor 4 monoclonal antibody, histone deacetylase inhibitors, a purine nucleoside phosphorylase inhibitor, a proteasome inhibitor and lenalidomide.

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Introduction

Adult T-cell leukemia (ATL) was first described in 1977 by Uchiyama and Takatsuki as a distinct progressive T-cell leukemia of peculiar morphology, so called "flower cells" with a suspected viral etiology because of the clustering of the disease in the southwestern region of Japan [1]. Subsequently, a novel RNA retrovirus, human T-cell leukemia/lymphotropic virus type I (HTLV-1), was isolated from a cell line established from leukemic cells of an ATL patient, and the finding of a clear association with ATL led to its inclusion among human carcinogenic pathogens [2–5]. In the mid-1980s and 1990s, several inflammatory diseases were reported to be associated with HTLV-1 including tropical spastic paraparesis (TSP)/HTLV-1-associated myelopathy (HAM), HTLV-1 uveitis and infective dermatitis [6–9]. At the same time, endemic areas for the virus and diseases have been found such as the Caribbean islands, tropical Africa, South America, Mid East and northern Oceania [10]. Subsequently, diversity in the clinical features of ATL has been recognized including ATL without leukemic manifestation and nomenclature of adult T-cell leukemia/lymphoma (ATLL) and/or adult T cell leukemia-lymphoma (ATL), and a classification of clinical subtypes of the disease was proposed [11]. This chapter will review the current recognition of ATL focusing on the biology and treatment of the disease.

Recent epidemiological findings of HTLV-1 and ATL in Japan

It has been estimated that there are several tens of million HTLV-1-infected individuals reside in the world, with 1.1 million in Japan, and the annual incidence of ATL is approximately 1,000 in Japan. The annual rate of ATL development among HTLV-1 carriers older than 40 years is estimated at 1.5 per 1000 in males and 0.5 per 1000 in females, and the cumulative risk of ATL development among HTLV-1 carriers is estimated to be 2.5%–5% over the course of a 70-year life span [12].

Recently, the prevalence of HTLV-1 in Japan as determined by screening of blood donors was surveyed [13]. The seroprevalence of HTLV-1 among 1,196,321 Japanese first-time blood donors from 2006 to 2007 was investigated. A total of 3787 such donors were confirmed to be positive for the anti-HTLV-1 antibody. This resulted in an estimation of at least 1.08 million current HTLV-1 carriers in Japan, which is 10% lower than that reported in 1988. The adjusted overall prevalence rates were estimated to be 0.66% and 1.02% in men and women, respectively. The peak in carrier numbers was found among individuals in their 70s, which is a shift from the previous peak observed in the 1988 database among individuals in their 50s. As compared to the survey in the 1980s, carriers were distributed throughout the country, particularly in the greater Tokyo metropolitan area.

Factors reportedly associated with the onset of ATL include the following: HTLV-1 infection early in life, increase in age, male sex, family history of ATL, past history of infective dermatitis, smoking of tobacco, serum titers of antibody against HTLV-1, HTLV-1 proviral load and several HLA subtypes [10,14]. However, definitive risk factors for the development of ATL among asymptomatic HTLV-1 carriers have not been elucidated. Recently, Iwanaga and colleagues evaluated 1218 asymptomatic HTLV-1 carriers (426 males and 792 females) who were enrolled during 2002–2008 for a prospective study on the development of ATL [15]. The HTLV-1 proviral load at enrollment was significantly higher in males than females (median, 2.10 vs. 1.39 copies/100 peripheral blood mononuclear cells (PBMC)) ($P < .0001$), in those aged 40 or more years, and in those with a family history of ATL. During the follow-up period, 14 participants developed ATL. Their baseline proviral loads were high (range, 4.17–28.58 copies/100 PBMC). Multivariate Cox regression analyses indicated that not only a higher proviral load but also advanced age, a family history of ATL, and the first opportunity for HTLV-1 testing during treatment for other diseases were independent risk factors for the progression of ATL from a carrier status.

Molecular features of HTLV-1 and ATL

The HTLV-I gene encodes three structural proteins, Gag, Pol and Env, and complex regulatory proteins such as Tax, which not only activates viral replication but also induces the expression of several cellular genes. The expression of the proteins encoded by these cellular genes may enhance the multistep carcinogenesis of ATL. However, the expression including Tax is suppressed in vivo probably

escaping from immune surveillance, and appears just after in vitro culture [10]. A new viral factor, HTLV-1 basic Zip factor (HBZ), encoded by minus strand mRNA was recently discovered and is thought to be involved in viral replication and T-cell proliferation [16]. Several isoforms of HBZ transcripts were reported to be steadily expressed in HTLV-1–infected cells and primary ATL cells in contrast to Tax. The functions of these transcripts and putative proteins in the context of cellular transformation are now under investigation.

Prototypical ATL cells have a mature helper T-cell phenotype (CD3+, CD4+, CD8−). Recent studies have suggested that the cells of some ATL patients may be the equivalent of regulatory T cells because of the high frequency of expression of CD25/CCR4 and about half of that of FoxP3 [17]. By Southern blotting for both HTLV-1 integration and T-cell receptor (TCR) gene rearrangement, about 10–20% of ATL cases showed clonal changes during the transformation from indolent to aggressive disease [18]. Oligoclonal expansion of HTLV-1 infected pre-malignant cells was detected in asymptomatic HTLV-1 carriers by HTLV-1 integrated site-specific PCR [19]. Polycomb-mediated epigenetic silencing of miR-31 is implicated in the aberrant activation of NF-kB signaling in ATL cells [20]. A high rate of chromosomal abnormalities has been detected in HTLV-1-infected T-cell clones derived from HTLV-1 carriers [21]. Abnormalities in tumor suppressors such as p53 and p14/p16 are frequent and rare in acute- and chronic-type ATL, respectively, and both are associated with poor prognosis [22]. Chromosomal abnormalities detected by cytogenetics or comparative genomic hybridization are often more complex and more frequent in acute ATL than in chronic ATL, with aneuploidy and several hot spots such as 14q and 3p [23]. Microarray analyses of the transcriptomes of ATL cells at the chronic and acute stages elucidate the mechanism of stage progression in this disease revealed that several hundred genes were modulated in expression including those for MET, a receptor tyrosine kinase for hepatocyte growth factor and cell adhesion molecule, TSLC1 [24,25].

In summary, ATL is etiologically associated with HTLV-1. However, HTLV-1 does not carry a viral oncogenes, expression of the virus including Tax appears just after in vitro culture. Integration of the provirus into the host genome is random, and chromosomal/genetic abnormalities are complex: therefore, ATL is regarded as a single HTLV-1 disease entity with diverse molecular features resembling the acute-crisis-phase of chronic myeloid leukemia.

Clinical features and prognostic factors of ATL

ATL patients show a variety of clinical manifestations because of various complications of organ involvement by ATL cells, opportunistic infections and/or hypercalcemia [10,11,26]. These three often contribute to the extremely high mortality of the disease. Lymph node, liver, spleen and skin lesions are frequently observed. Although less frequently, digestive tract, lungs, central nervous system, bone and/or other organs may be involved [26]. Large nodules, plaques, ulcers, and erythrodermas are common skin lesions [27–29]. Immune suppression is common. Approximately 26% of 854 patients with ATL had active infections at diagnosis in a prior nationwide study in Japan [14]. The infections were bacterial in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients. Individuals with indolent ATL might have no manifestation of the disease and are identified only by health check-ups and laboratory examinations.

ATL cells, so called "flower cells", are usually detected easily in the blood of affected individuals except in smoldering type, which mainly has skin manifestations and lymphoma type [11]. The histological analysis of aberrant cutaneous lesions or lymph nodes is essential for the diagnosis of the smoldering type with mainly skin manifestations and lymphoma type of ATL, respectively. Because ATL cells in the skin and lymph node can vary in size from small to large and in form from pleomorphic to anaplastic and Hodgkin-like cell with no specific histological pattern of involvement, distinguishing the disease from Sezary syndrome, other peripheral T-cell lymphomas and Hodgkin lymphoma can at times be difficult without examinations for HTLV-1 serotype/genotype [26].

Hypercalcemia is the most distinctive laboratory abnormality in ATL as compared to other lymphoid malignancies, and is observed in 31% of patients (50% in acute type, 17% in lymphoma type and 0% in the other two types) at onset [11]. Individuals with hypercalcemia do not usually have osteolytic bone lesions. Parathyroid hormone-related protein or receptor activator of nuclear factor kappa B ligand (RANKL) produced by ATL cells is considered the main factor causing hypercalcemia [30,31].

The diagnosis of typical ATL is not difficult and is based on clinical features, ATL cell morphology, mature helper-T-cell phenotype and anti-HTLV-1 antibody in most cases [11]. Those rare cases which might be difficult to diagnose can be shown to have the monoclonal integration of HTLV-1 proviral DNA in the malignant cells as determined by Southern blotting. However, its sensitivity is around 5% of ATL cells among normal cells. Furthermore, the monoclonal integration of HTLV-1 is also detected in some HAM/TSP patients and HTLV-1 carriers [32]. After the diagnosis of ATL, subtype-classification of the disease, reflecting prognostic factors, clinical features and natural history of the disease are based on the presence of organ involvement, leukemic manifestation and values for LDH and calcium, is necessary for the selection of appropriate treatment (Table 1) [11,33].

Major prognostic indicators for ATL, elucidated among 854 patients with ATL in Japan by multivariate analysis were advanced performance status, high LDH level, age of 40 years or more, more than three involved lesions, and hypercalcemia [34]. Additional factors associated with a poor prognosis include thrombocytopenia, eosinophilia, bone marrow involvement, a high interleukin (IL)-5 serum-level, CC chemokine receptor 4 (CCR4) expression, lung resistance-related protein (LRP), p53 mutation and p16 deletion by multivariate analysis [33]. Specific for the chronic type of ATL, high LDH, high blood urea nitrogen (BUN), and low albumin levels were identified as factors for a poor prognosis by multi-variate analysis [10]. Primary cutaneous tumoral type generally included among smoldering ATL had a poor prognosis in a uni-variate analysis [27].

Recently, a retrospective review of 807 patients in Japan led to a prognostic index for acute- and lymphoma-type ATL based on five prognostic factors; stage, performance status (PS), age, serum albumin and sIL2R. In the validation sample, the index was reproducible with median survival times (MSTs) of 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively [35]. The Japan Clinical Oncology Group (JCOG)-Lymphoma Study Group (LSG) conducted a meta-analysis of three consecutive trials exclusively for aggressive ATL (see below) [36]. OS analysis of a total 276 patients with acute-, lymphoma- or unfavorable chronic-ATL identified two significant prognostic factors, PS and hypercalcemia. In the validation sample, a proposed prognostic index using the two factors into two strata revealed MSTs of 6.3, and 17.8 months for patients at high and low risk, respectively. In both

Table 1
Diagnostic criteria for clinical subtypes of adult T-Cell leukemia-lymphoma.

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte ($\times 10^3/\mu$UL)	<4	≥4	<4	[a]
Abnormal T lymphocytes	≥5%[d]	+[c]	≤1%	+[c]
Flower cells with T-cell marker	[b]	[b]	No	+
LDH	≤1.5 N	≤2 N	[a]	[a]
Corrected Ca^{2+} (mEq/L)	<5.5	<5.5	[a]	[a]
Histology-proven lymphadenopathy	No	[a]	+	[a]
Tumor lesion				
Skin and/or lung	[a]	[a]	[a]	[a]
Lymph node	No	[a]	Yes	[a]
Liver	No	[a]	[a]	[a]
Spleen	No	[a]	[a]	[a]
Central nervous system	No	[a]	[a]	[a]
Bone	No	No	[a]	[a]
Ascites	No	No	[a]	[a]
Pleural effusion	No	No	[a]	[a]
Gastrointestinal tract	No	No	[a]	[a]

HTLV-1, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.
With permission from Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991; 79:428.

[a] No essential qualification except terms required for other subtype(s).

[b] Typical "flower cells" may be seen occasionally.

[c] If the proportion of abnormal T lymphocytes is less than 5% in peripheral blood, a histologically proven tumor lesion is required.

[d] Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.

studies, however, the 5-year OS rate was less than 15% even in the low risk group, indicating that they are not sufficient to properly identify non-candidates for allo-HSCT which can achieve a cure of ATL despite considerable treatment-related mortality.

Treatment of ATL

Current treatment options for ATL include watchful waiting until the disease progresses, interferon alpha (IFN) and zidovudine (AZT) therapy, multi-agent chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT) and new agents.

Recently, a treatment strategy based on the clinical subtype classification and prognostic factors was suggested as shown in Table 2 [33].

Watchful waiting

At present, no standard management for indolent ATL exists. Therefore, patients with the smoldering or favorable chronic type, may survive one or more years without chemotherapy, excluding topical therapy for cutaneous lesions, are observed and therapy is delayed until disease progression [33]. However, it was recently found that the long-term prognosis of such patients was poorer than expected. In a long-term follow-up study for 78 patients with indolent ATL (favorable chronic- or smoldering-type) with a policy of watchful waiting until disease progression at a single institution in Japan, the MST was 5.3 years with no plateau in the survival curve. Twelve patients remained alive for >10 years, 32 progressed to acute ATL, and 51 died [37].

Chemotherapy

Since 1978, a number of consecutive chemotherapy trials have been conducted for patients newly diagnosed with ATL by the JCOG-Lymphoma Study Group (LSG) (Table 3) [10]. Between 1981 and 1983, JCOG conducted a phase III trial (JCOG8101) to evaluate LSG1-VEPA (vincristine, cyclophosphamide, prednisone, and doxorubicin) vs LSG2-VEPA-M (VEPA plus methotrexate (MTX)) for advanced non-Hodgkin lymphoma (NHL), including ATL [10]. The complete response (CR) rate of LSG2-VEPA-M for ATL (37%) was marginally higher than that of LSG1-VEPA (17%; $P = .09$). However,

Table 2
Strategy for the treatment of adult T-Cell leukemia-lymphoma.

Smoldering-or favorable chronic-type ATL
- Consider inclusion in prospective clinical trials
- Symptomatic patients (skin lesions, opportunistic infections, etc): consider AZT/IFN or watch and wait
- Asymptomatic patients: consider watch and wait

Unfavorable chronic- or acute-type ATL
- If outside clinical trials, check prognostic factors (including clinical and molecular factors if possible):
  - Good prognostic factors: consider chemotherapy (VCAP-AMP-VECP evaluated by a phase III trial against biweekly-CHOP) or AZT/IFN (evaluated by a meta-analysis on retrospective studies)
  - Poor prognostic factors: consider chemotherapy followed by conventional or reduced intensify allo-HSCT (evaluated by retrospective and prospective Japanese analyses, respectively).
  - Poor response to initial therapy: consider conventional or reduced intensity allo-HSCT

Lymphoma-type ATL
- If outside clinical trials, consider chemotherapy (VCAP-AMP-VECP)
- Check prognostic factors (including clinical and molecular factors if possible) and response to chemotherapy:
  - Good prognostic factors and good response to initial therapy: consider chemotherapy followed by observation
  - Poor prognostic factors or poor response to initial therapy: consider chemotherapy followed by conventional or reduced intensity allo-HSCT.