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Chapter 5

Adult T-Cell Leukemia/Lymphoma (ATL): Pathogenesis, Treatment and Prognosis

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Additional information is available at the end of the chapter

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1. Introduction

Adult T-cell leukemia/lymphoma (ATL) was first described in 1977 as a distinct clinicopathological entity with a suspected viral etiology. Subsequently, a RNA retrovirus, human T-cell leukemia /lymphotropic virus type 1 (HTLV-1) was isolated as a carcinogenic pathogens [1].

HTLV-1 infects approximately 15 to 20 million people worldwide, with endemic areas in Japan, the Caribbean, and Africa.

After prolonged latency periods, approximately 3 to 5% of HTLV-1 infected individuals will develop either ATL or other disorders such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).

2. Transmission and spread

The three major routes of HTLV-1 transmission are, 1)mother-to-child infections via breast milk, 2)sexual intercourse, and 3)blood transfusions. HTLV-1 infection early in life, presumably from breast feeding, is crucial in the development of ATL [2].

3. Initial infection

HTLV-1 infects CD4+ and CD8+ T lymphocytes and can also efficiently infect dendritic cells [3].

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The ubiquitous glucose transporter 1 and the neuropilin 1 were identified as members of the HTLV-I receptor complex [4,5].

Moreover, surface heparan sulfate proteoglycans were shown to be required for efficient virus entry [6]. Clonal expansion of HTLV-infected cells mostly relies on the promotion of cycling CD4+ T cells [7].

4. Infected cell types

CD4+ lymphocytes and to a lesser extent CD8+ T cells are considered to be as the main targets of HTLV-1. Plasmacytoid dendritic cells (pDC) were also infected by HTLV-1 in patients. In fact, all types of dendritic cells have been shown to be easily infected by HTLV-1 in vitro and efficiently transmit HTLV-1 to T cells in free viral transmission [8].

The proviral load was higher in isolated pDCs than in T cells. pDCs was found to be stimulated type I interferon α and β which interacted with their cognate receptors on virus infected cells and, through IFN-inducible genes, interfered with viral replication. pDCs from ATL patients were known to be impaired in their production of IFN-α. These observations supported a role for pDC in viral persistence and disease progression [9].

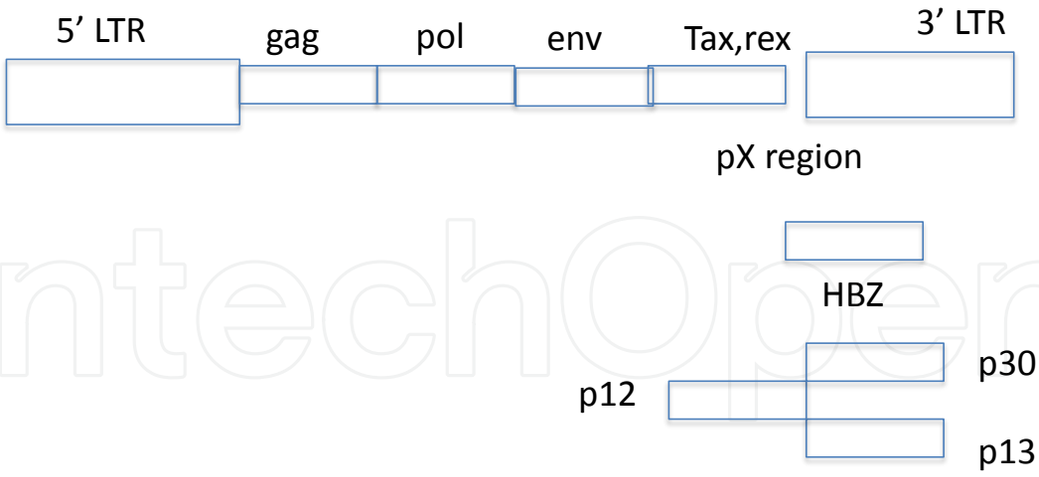
CD4+ T cells can be divided into two major categories: effector T cells and regulatory T cells(Treg). Effector T cells induce the activation of immune responses by secreting proinflammatory cytokines, whereas Treg which express the transcription factor FoxP3, suppress immune responses by both cell-contact dependent and –independent mechanisms. A proportion of HTLV-1 infected CD4+ T cells express FoxP3. It showed that HTLV-1 infection induces the phenotype of FoxP3+CD4+ T cells [7].

5. HTLV-1 virus

5.1. HTLV-1-encoded proteins

The HTLV-1 genome contains typical structural and enzymatic genes (*gag*, *pro*, *pol* and *env*) flanked by two long terminal repeats (LTRs). (Fig. 1). The long terminal repeats (LTR) are subdivided into three regions (i.e., U3, R and U5) that contain the *cis*-acting elements essential for viral gene expression: transcription factor-binding sites, transcription start and termination sites, polyadenylation and splicing sites. A region called pX, which is located between the *env* gene and the 3′-LTR, contains at least four partially overlapping reading frames (ORFs) encoding accessory proteins (p12I, p13II, p30II), the post-transcriptional regulator Rex (ORF III) and the Tax transactivator (ORF IV). In addition, HBZ is encoded from the 3′ LTR in the complementary strand of the genome. Among all these regulatory proteins, Tax and HBZ proteins appear to have particularly important roles in viral persistence and pathogenesis [10].

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LTR : long terminal repeat
Tax : transcriptional transactivator
HBZ : HTLV-1 bZIP

Figure 1. HTLV-1 proviral gene

5.2. Tax (transcriptional transactivator) (p40)

Tax is a major factor that mediated the following: 1)viral persistence and disease development. 2) oncogenic potential, 3)cell-signalling pathways, 4)interferes with checkpoint control and inhibition of DNA repair, and 5) modulation of the miRNAs environment [11].

Among the cellular pathways activated by Tax, CREB/ATF, NF-κB and AP1 are thought to have predominant roles in T-cell proliferation and transformation.

Tax -mediated NF-κB activation stimulates expression of cytokines and their receptors such as interleukin 2 (IL2)/IL2 receptor (IL2R), IL9, IL13 and IL15/IL15R as well as members of the tumour necrosis factor receptor family.

A major activity of Tax in signaling pathways is the stimulation of G1/S transition. Tax increases the levels of type D cyclin levels in G1 and activates cyclin-dependent kinases (i.e., CDK4 and CDK6) through direct binding, leading to Rb hyperphosphorylation, subsequent release of E2F transcription factor and accelerated transition from G1 to S. Tax also directly interacts with and promotes the degradation of Rb. Furthermore, Tax modulates expression of CDK inhibitors such as p18INK4c, p19INK4d, p21WAF1 and p27KIP1 and inactivates p15INK4b and p16INK4a through direct binding, thereby restraining their inhibitory activity toward CDKs.

Tax stimulate viral production and infection, however, the Tax expression is transient and rapidly turned off (Fig 2). Cells that failed to shut off the Tax are rejected by host immune response, such as cytotoxic T lymphocytes (CTL) and only the cells with latent viral expression should survive. Repeating these cycles for long periods, results in the persistence of infected individuals in a virus carrier state, however Tax-incuced mutaions accumulated in infected cells.

Three mechanisms have been described for inactivating Tax expression in ATL cells have been described: 1) genetic changes (nonsense mutation, deletion, and insertion) in the *tax* gene, 2) deletion of the 5' long terminal repeat (LTR) that contains the viral promoter, and 3) DNA methylation of the 5 ' LTR leading to promoter inactivation.

Tax-mediated mutation would be a critical event in ATL that triggers the clonal selection of infected T cells as malignant leukemia cells [12].

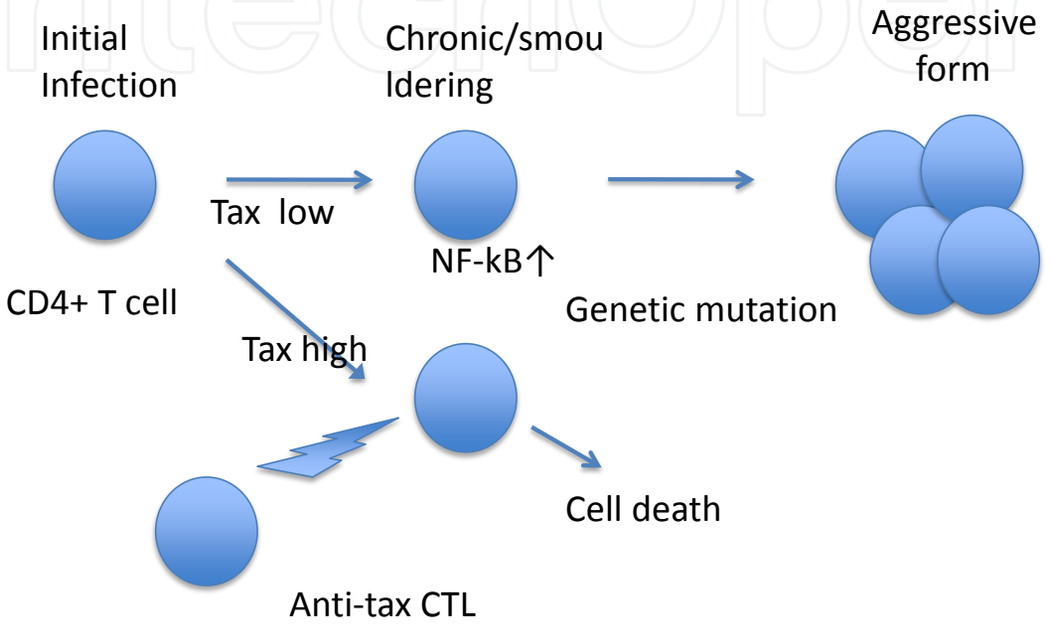


Figure 2. Probable mechanism of pathogenesis in ATL progression

5.3. Other proteins; Rex, p12, p13 and p30

Rex (p27) is an RNA-binding post-transcriptional regulator that binds to its *cis*-acting target sequence, the Rex response element (RRE), located at the 3'-end of sense viral mRNAs.

HTLV-1 contains both regulatory and accessory genes in four pX open reading frames. pX. ORF-II encodes two proteins, p13 and p30.

Proviral clones of HTLV-1 with pX ORF-II mutations diminish the ability of the virus to maintain viral loads in vivo. p30 is acting as a repressor of many genes including Tax, in part by blocking tax/rex RNA nuclear export.

p30 expression results in activation of the G2-M cell cycle checkpoint, events that would promote early viral spread and T-cell survival. [13,14].

The role of four open reading frames (ORFs), located between env and the 3' long terminal repeat of HTLV-1. By differential splicing, ORF II encodes two proteins, p13(II) and p30(II). p13(II) localizes to mitochondria and may alter the configuration of the tubular network of this cellular organelle.

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Mutations in pX ORF II diminish the ability of HTLV-1 to maintain high viral loads in vivo and suggest an important function for p13(II) and p30(II) in viral pathogenesis. [15].

The repression in Tax expression is essential to protect infected cells from immune response and to maintain the virus. However, recent studies suggested that a loss of Tax expression also prevents Tax-induced mitotic aberrations that are detrimental to cell proliferation and therefore, to stabilize the karyotype of infected T cells [16].

5.4. HBZ

A recently identified HBZ factor. HTLV-1 bZIP, acts as a negative regulator of Tax-mediated viral transactivation by heterodimerising with CREB, CREB2, and p300/CBP. HBZ RNA expression leads to the upregulation of E2F1 target genes and stimulation of T lymphocyte proliferation [17].

The HBZ protein was first reported to function as a transcription factor that repressed viral expression by competing with Tax-mediated LTR activation.

As previously, Tax is highly immunogenic and its expression induces an immune response that generates CTL primarily directed against this oncoprotein. To escape this CTL-mediated lysis and to maintain viral persistence, HTLV-I infected cells frequently reduce Tax expression by several mechanisms.

HBZ was expected to be responsible for inducing and maintaining the tumor state even after Tax was shut off, which was supported by evidence that *HBZ* transcription was correlated with the proviral load [18-20].

Similar to Tax, HBZ interacts with proteasome subunits and may promote the delivery of cellular factors (such as c-Jun) to the proteasome even in the absence of ubiquitination.

6. Tumor marker

Similar to serum LDH reflecting disease bulk/activity, the soluble form of interleukin-2 receptor α-chain is elevated. [21].

The mean sIL-2R levels of the smoldering, chronic, acute, and lymphoma subtypes of ATL were 1680 U/ml, 6680 U/ml, 45,940 U/ml, and 34,620 U/ml, respectively ($P < 0.01$). The sIL-2R levels of each subtype at the time of diagnosis were more correlated with tumor burden, malignant behavior, and prognosis than LDH levels. In the low, moderate, and high sIL-2R subgroups, the median survival time and percent survival probability at 2 years was 30.2 months (46.0%), 16.5 months (25.0%), and 7.7 months (15.3%), respectively.

These serum markers are useful to detect acute transformation of indolent ATL as well as to detect early relapse of ATL after therapy.

7. Immunophenotype

In most patients, ATL cells exhibit the phenotype of mature CD4+ T cells and express CD2, CD5, CD25, CD45RO, CD29, T-cell receptor $\alpha\beta$, and HLA-DR. Most ATL cells are CD52, CCR4 positive, but occasionally, patients are negative. Immunophenotypic analysis of CD3, CD4, CD7, CD8, and CD25 is the minimum requirement for an ATL diagnosis.

8. Cytogenetics

Karyotypic abnormalities revealed by conventional cytogenetics or comparative genomic hybridization are more common and complex in the acute and lymphoma types compared with the chronic type, with aneuploidy and several hot spots such as 14q and 3p. More sensitive array-comparative genomic hybridization revealed that the lymphoma type had significantly more frequent gains at 1q, 2p, 4q, 7p, and 7q and more losses of 10p, 13q, 16q, and 18p, whereas the acute type showed a gain of 3/3p [22.23].

9. Molecular biology of host genome

Mutation or deletion of tumor suppressor genes, such as *p53* or *p15INK4B/p16INK4A*, is observed in approximately half of ATL patients and is associated with clinical subtypes and prognosis.These new molecular markers may help guide therapeutic decisions. [24].

To predict to respond to antiviral therapy with AZT and IFN-alpha, the expression of proto-oncogene c-Rel and interferon regulatory factor-4 (IRF-4) was examined. Resistant tumors exhibited c-Rel (6 of 10; 60%) more often than did sensitive variants (1 of 9; 11%). This finding was independent of the disease form. Elevated expression of the putative c-Rel target, IRF-4, was observed in 10 (91%) of 11 nonresponders and in all tested patients with c-Rel+ tumors and occurred in the absence of the HTLV-1 oncoprotein Tax. In contrast, tumors in complete responders did not express c-Rel or IRF-4. The expression of nuclear c-Rel and IRF-4 occurs in the absence of Tax in ATLL and is associated with antiviral resistance. [25].

10. Molecular biology of HTLV-1

Monoclonal integration of HTLV-1 proviral DNA is observed in all cases of ATL. Integration of defective HTLV-1 into ATL cells is observed in approximately one-third of ATL patients and is associated with clinical subtypes and prognosis. It is recommended to perform molecular analysis of HTLV-1 integration when possible. Either Southern blotting or polymerase chain reaction for HTLV-1 can be used to identify the presence of viral integration, although

the latter can also be used for quantitative purposes. Clinically, ATL is diagnosed on the basis of seropositivity for HTLV-1 and histologically and/or cytologically proven peripheral T-cell malignancy. [26].

11. Pathogenesis

Tax is a multifunctional protein that affects various cellular machinery and signaling pathways to mediate cellular transformation and viral replication.

The necessity of NF-κB, a transcription factor, in Tax-mediated transformation was confirmed in which a single point mutation in the Tax that disrupts to activate the NFκB pathway also eliminates the viral ability to transform [27].

11.1. Tax-independent NF-κB activation

However, Tax expression is lost in approximately 60% of all ATLs during the late stages of leukemogenesis stages. Notably, NF-κB pathways remain still strongly activated in HTLV-1-infected Tax-negative cells, suggesting the existence of Tax-independent mechanism. Reportedly, Tax-independent NF-κB activation occurs in Tax-positive cells. Several mechanisms are speculated in Tax-independent NF-κB activation, such as IKKB activation and the NF-κB member c-Rel [28-31].

HTLV-1 infection induces expression of many NF-κB stimulators and signaling molecules such as TNF, CD40, CD30, and Bcl-3. TNF is the prototypic stimuli of NF-κB activation, while CD40 and CD30 are potent activators of NF-κB pathways. Bcl-3 binds to p50 or p52 homodimers and transforms them from transcription repressors into activators [32-35].

11.2. Persistent NF-κB activation by HTLV-1

Tax binds to and increases the stability and activity of NF-κB and/or prevents NF-κB from binding to its inhibitors, resulting in a prolonged and elevated activation of NF-κB. NF-κB activation is aberrantly persistent, irrespective of whether it is Tax-dependent or -independent. A main reason for this abnormal activation is the co-existence and cross-activation of different NF-κB and NF-κB-related signaling pathways. [36-40].

In addition to NF-κB, Tax induces many other signaling pathways such as the phosphatidylinositol 3-kinase (PI3K)/AKT and DNA damage signaling pathways, leading to reciprocal enhancement of these pro-oncogenic pathways with NF-κB. Most of the mechanisms activate Tax-independent and -dependent NF-κB pathway. [41.42].

11.3. Differences between tax-dependent and tax-independent NF-κB activation by HTLV-1

NF-κB signaling pathways are persistently activated in HTLV-1-infected cells regardless of Tax expression. Tax-dependent and -independent NF-κB pathways also involve activation of common and distinct NF-κB members. NF-κB members activated in Tax-ex-

pressing T cells are predominantly RelA, c-Rel, p50 and p52, and those in Tax-negative T cells are mainly RelA and p50. Consistent with the role of positive feedback mechanisms in persistent NF-κB activation, expression of c-Rel and p100/p52 expression is induced in Tax-expressing cells, whereas p105/p50 mRNA expression is enhanced in ATL cells [43,44].

11.4. NFκB and apoptosis

Lymphoma cell lines including ATL cells, that were constitutively activated NFκB are resistant to various inducers of apoptosis including irradiation, etoposide, and combinations of cycloheximide and TNF or TRAIL, and resist the activation of both the intrinsic and extrinsic apoptotic pathways [45].

Although mutations that delete or inactivate p53 are common in ATLL, Tax can bypass p53-dependent cell-cycle checkpoints.

A Tax transgenic mouse model was analyzed for study the contribution of p53 inactivation to Tax-mediated tumorigenesis. The mice develop primary, peripheral tumors consisting of large granular lymphocytic (LGL) cells, which infiltrate the lymph nodes, bone marrow, spleen, liver, and lungs. Tax-induced tumors exhibited functional inactivation of the p53 apoptotic pathway; such tumors were resistant to an apoptosis-inducing stimulus. Experiments with mating Tax transgenic mice with p53-deficient mice demonstrated minimal tumor acceleration, but significantly accelerated disease progression and death in mice heterozygous for p53. The studies suggest that inactivation of p53 by Tax, whether by mutation or another mechanism, is not critical for initial tumor formation, but contributes to late-stage tumor progression [46,47]..

11.5. Telomerase

Telomerase is compsed of hTR, a 451 nucleotide stretch of RNA, which serves as a template for the RNA-dependent DNA polymerase, telomerase(hTERT).

Telomere length is also regulated by several positive and negative regulators These proteins can them prevent telomerase extension by blocking access of the reverse transcriptase to the now “closed”ends of telomeric DNA.

AZT is a thymidine analog, that has been shown to inhibit cancer growth and telomerase activity. Long-term treatment of HTLV-1 infected cells with AZT inhibits telomerase activity induces telomere attrition and promotes cellular senescence, in absence of apoptosis, due to the reactivation of tumor suppressor p53 transcriptional activities

Analysis of ATLL patients was done to examine the relationship between the responsiveness for antiviral therapy and p53 mutation. Those patients with a mutated p53 did not respond to AZT treatment, demonstrating that AZT treatment causes telomere attrition leading to the reactivation of a functional p53. [48.49].

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12. Response criteria

Complete remission (CR) is defined as a normalization of the complete blood count associated with a disappearance of all measurable tumors. The effect has to last for at least 1 month. However, patients with a persistence of < 5% of atypical lymphocytes are considered in CR because this situation may be observed in healthy carriers of HTLV-I. Patients who achieve CR with persistence of > 5% of atypical lymphocytes are considered in very good partial response. Partial response is defined as a decrease of > 50% in the number of leukemic cells and in the size of all measurable tumors. The effect has to last for at least 1 month. No response is defined as < 50% decrease in the number of leukemic cells or in the size of any measurable tumor or as disease progression. Patients who meet the CR or partial-response criteria but with the effect lasting < 1 month are classified as nonresponders.

13. Prognostic factors

Major prognostic indicators for ATL were analyzed in 854 patients; advanced performance status (PS), high LDH level, age ≥ 40 years, more than three involved lesions, and hypercalcemia are prognostic factors that have been identified by multivariate analysis. These factors were used to construct a risk model.5

For the chronic type of ATL, high LDH, high blood urea nitrogen, and low albumin levels have been identified as poor prognostic factors by multivariate analysis. Univariate analysis has revealed that neutrophilia,*p16* deletion, and chromosomal deletion detected by comparative genomic hybridization are associated with poor prognosis in chronic ATL.

In contrast, chronic lymphoid leukemia (CLL)–like morphology of ATL cells was associated with longer transformation-free survival of chronic ATL. Primary cutaneous tumoral type, although generally included among smoldering ATL, was a poor prognostic factor by univariate analyses [50].

The prognosis of acute- and lymphoma-type adult T-cell leukemia/lymphoma (ATL) is poor, but there is marked diversity in survival outcomes.

Data from 807 patients newly diagnosed with acute- and lymphoma-type ATL were evaluated and developed a PI using a multivariable fractional polynomial model. The Ann Arbor stage (I and II v III and IV), performance status (0 to 1 v 2 to 4), and three variables (age, serum albumin, and soluble interleukin-2 receptor [sIL-2R]) were identified as independent prognostic factors. Using these variables, a prognostic model was devised to identify different levels of risk. In the validation sample, MSTs were 3.6, 7.3, and 16.2 months for patients at high, intermediate, and low risk, respectively (P <.001).

A total of 854 ATL patients were analyzed for prognostic factors. Patients were 466 males and 388 females with a mean age of 57.1. A Cox proportional hazards model analysis revealed that five factors, advanced performance status, high lactic dehydrogenase value, age of 40 years or

more, increased number of total involved lesions and hypercalcemia, were associated with shortened survival(P<0.01).

These factors were used to construct a model to identify patients at three different risks for shortened survival. A group of 178 patients (21.8%) with a hazard ratio of less than 0.5 were classified into the low risk (LR) group, 492 (60.4%) with hazard ratio of less than or equal to 0.5 and less than 2.5 into standard high risk (SHR) group, and 145 (17.8%) with hazard ratio of 2.5 or more extremely high risk (EHR) group. MST, and projected 2- and 4-year survival rates were 37 months, 66.3% and 41.2% for LR, 8 months 20.6%, and 4.5% for SHR, and 2.4 months, 5.6% and 0% for EHR, respectively.

14. Classification

The following diagnostic criteria are proposed to classify four clinical subtypes of ATL(Table I); 1) Smouldering type, 2) Chronic type, 3) Lymphoma type, and 4) Acute type.

1. Smouldering type, 5% or more abnormal lymphocytes of T-cell nature in PB, normal lymphocyte level (less than 4 x 10(9)/l), no hypercalcaemia (corrected calcium level less than 2.74 mmol/l), lactate LDH value of up to 1.5 x the normal upper limit, no lymphadenopathy, no involvement of liver, spleen, central nervous system (CNS), bone and gastrointestinal tract, and neither ascites nor pleural effusion. Skin and pulmonary lesion(s) may be present. In case of less than 5% abnormal T-lymphocytes in PB, at least one of histologically-proven skin and pulmonary lesions should be present.

2. Chronic type, absolute lymphocytosis (4 x 10(9)/l or more) with T-lymphocytosis more than 3.5 x 10(9)/l, LDH value up to twice the normal upper limit, no hypercalcaemia, no involvement of CNS, bone and gastrointestinal tract, and neither ascites nor pleural effusion. Lymphadenopathy and involvement of liver, spleen, skin, and lung may be present, and 5% or more abnormal T-lymphocytes are seen in PB in most cases.

3. Lymphoma type, no lymphocytosis, 1% or less abnormal T-lymphocytes, and histologically-proven lymphadenopathy with or without extranodal lesions.

4. Acute type, remaining ATL patients who have usually leukaemic manifestation and tumour lesions, but are not classified as any of the three other types.

A total of 818 ATL patients with a mean age of 57 years, newly diagnosed from 1983 to 1987, were analysed by this criteria. 253 were still alive with a median follow-up time of 13.3 months from diagnosis, while 565 were dead with a median survival time (MST) of 5.4 months. MST was 6.2 months for acute type, 10.2 months for lymphoma type, 24.3 months for chronic type, and not yet reached for smouldering type. 2- and 4-year survival rates were 16.7% and 5.0% for acute type, 21.3% and 5.7% for lymphoma type, 52.4% and 26.9% for chronic type, 77.7% and 62.8% for smouldering type, respectively. Distinct clinical features and laboratory findings of each clinical subtype are described [51].

	Smouldering	Chronic	Lymphoma	Acute
Lymphocyte count	Less than 4	4 or more	less than 4	more than 4
(10 9 lympho/liter)				
% of atypical lympho	5 or more	5 or more	1 or less	more than 5
LDH	1.5x NUL	2x NUL		
Ca	less than 2.74	less than 2.74		more than 2.74
Lyphoadenopathy	No	No	Yes	-
Mean survival time(Mo)		24.3	10.2	6.2
2 year survival (%)	77.7	52.4	21.3	16.7
4 year survival (%)	62.8	26.9	5.7	5
	NUL	Normal upper	limit	

Table 1. Classification of subtypes

15. Treatment options

The treatment of ATL usually depends on the subtype. Patients with aggressive forms have a very poor prognosis due to intrinsic chemoresistance, a large tumor burden, and frequent infectious complications because of immune deficiency.

In multiple Japanese trials for aggressive ATL, data clearly demonstrated that combinations of chemotherapy did not have significant effect on long-term survival. Indolent ATL patients(chronic or smoldering) have a better prognosis. However, recent data from Japanese showed poor long-term results when these patients were managed with a watchful-waiting policy until progression or with chemotherapy [52].

15.1. Conventional chemotherapy

The clinical trials in Japan(protocols LSG1-VEPA and LSG2) demonstrated that first-generation chemotherapy, such as CHOP type, ie, cyclophosphamide, hydroxydaunorubicin,

oncovin (vincristine), and prednisone has little impact in ATL, especially in the acute type. Only a 16% to 36% patients achieved CR.

New-generation agents such as deoxycoformycine, a nucleoside analog, irinotecan hydrochloride (CPT-11: a topoisomerase I inhibitor), and MST-16(a topoisomerase II inhibitor), have also been tested in pilot phase II studies of refractory or relapsed ATL patients, however the results have been uniformly disappointing.

A phase III study in Japan demonstrated that the LSG15 regimen consisting of VCAP (vincristine, cyclophosphamide, doxorubicin, prednisolone), AMP (doxorubicin, ranimustine, prednisolone), and VECP (vindesine, etoposide, carboplatin, prednisolone) is superior to biweekly CHOP for newly diagnosed acute, lymphoma, or unfavorable chronic ATL. The CR rate and 3-year overall survival(OS) were greater as 40% vs 25%, 24% vs 13%, respectively, however,the median 13 months survival was disappointing [53].

The poor prognosis of ATL after chemotherapy is probably the consequence of several factors. The cellular immune deficiency observed at the early stages may lead to a high frequency of opportunistic infections. Overexpression of the multidrug resistant gene and p53 gene mutations is a feature of ATL cells and results in intrinsic resistance to chemotherapy.

15.2. Monoclonal antibodies

15.2.1. CC Chemokine Receptor 4 (CCR4)

CC chemokine receptor 4 (CCR4) is a chemokine receptor expressed on T-helper type 2 and regulatory T cells. Because CCR4 is expressed on most ATL cells, KW-0761, a humanized anti-CCR4 monoclonal antibody, which markedly enhances antibody-dependent cellular cytotoxicity, was evaluated in the treatment of patients with relapsed ATL. [54].

A multicenter phase II study of KW-0761 for patients with relapsed, aggressive CCR4-positive ATL. Patients received intravenous infusions of KW-0761 once per week for 8 weeks at a dose of 1.0 mg/kg. Of 28 patients enrolled in this study, responses were noted in 13 of 26 evaluable patients, including CR in 8, with an overall response rate of 50%. The median progression-free time and overall survival were 5.2 and 13.7 months, respectively. The most common adverse events were infusion reactions (89%) and skin rashes (63%), which were manageable and reversible in all the cases.

Because monoclonal antibodies were tried as single agents, trials are needed to define in combination therapies with chemotherapy in the lymphoma form or with antiretroviral therapy in the acute form. Following on a phase III study(JCOG9801(Japan Clinical Oncology Group 9801) for untreated aggressive ATL promote to conduct a randomized trial of VCAP-AMP-VECP chemotherapy with or without KW-0761 for untreated ATL.

15.2.2. CD52

CD52 is also the candidate target. A monoclonal antibody against CD52(Alemtuzumab) has demonstrated good results: however, the results are scanty and limited to case reports. with

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or without nucleoside analogs such as pentostatin may be promising. However, the associated immunosuppression is a concern in patients with viral-mediated disease. [55-57].

15.3. HSC transplantation

The several retrospective studies have confirmed that allogeneic SCT(allo SCT) with the use of either myeloablative conditioning or reduced-intensity conditioning conditioning as a promising treatment option for ATL.

The number of ATL patients eligible for allo SCT is quite limited because of the older age at presentation (>60 years), poor performance status, the severe immunosuppression, and the low CR rate, in particular in the acute form.

Although selection criteria for patients and sources of stem cells remain to be resolved, allo-SCT may be considered as a treatment option for patients with aggressive ATL.

For treating aggressive ATL, LSG15 is the standard chemotherapy, however, its efficacy of LSG15 is transient. Improved outcome after allo-SCT, despite a high incidence of graft-versus-host disease, has been reported.

To evaluate whether allo-SCT is more effective than LSG15 for aggressive ATL, an up front phase II clinical trial is now being planned. [1].

15.3.1. Donor selection

Total 386 patients with ATL who underwent allo-SCT using different graft sources were evaluated [58].

154 received human leukocyte antigen (HLA)-matched related marrow or peripheral blood; 43 received HLA-mismatched related marrow or peripheral blood; 99 received unrelated marrow; and 90 received single unit unrelated cord blood. After a median follow-up of 41 months (range, 1.5-102), the 3-year OS for the entire cohort was 33% (95% confidence interval, 28%-38%). Multivariable analysis showed that 4 recipient factors were significantly associated with lower survival rates: older age (> 50 years), male sex, status other than CR, and the use of unrelated cord blood compared with use of HLA-matched related grafts. Treatment-related mortality rate was higher among patients given cord blood transplants; disease-associated mortality was higher among those given transplants not in remission. Among transplants, donor HTLV-I seropositivity adversely affected disease-associated mortality.

15.3.2. Conditioning regimen

A retrospective study of allo SCT for ATL were conducted in Japan for the effects of the preconditioning regimen [59].

The median OS and 3-year OS of bone marrow or peripheral blood transplantation recipients (n=586) were 9.9 months (7.4-13.2 months) and 36% (32-41%), respectively.

The values for recipients of myeloablative conditioning (MAC: n = 280) and reduced-intensity conditioning (RIC: n = 306) were 9.5 months (6.7-18.0 months) and 39% (33-45%) and 10.0 months (7.2-14.0 months) and 34% (29-40%), respectively.

Multivariate analysis showed that 5 variables significantly contributed to poorer OS; older age, male gender, not in CR, poor performance status, and transplantation from unrelated donors. Although no significant difference in OS between MAC and RIC was observed. Regarding mortality, RIC was significantly associated with ATL-related mortality compared with MAC.

15.3.3. Graft-Versus-ATL(GVL) effect

The effects of acute and chronic GVHD on overall survival, disease-associated mortality, and treatment-related mortality among 294 ATL patients who received allo HCT were analyzed [60].

The occurrence of GVHD demonstrated that the development of grade 1-2 acute GVHD (aGVHD) was significantly associated with higher overall survival (P = 0.018) compared with the absence of aGVHD. Occurrence of either grade 1-2 or grade 3-4 aGVHD was associated with lower disease-associated mortality compared with the absence of aGVHD, whereas grade 3-4 aGVHD was associated with a higher risk for treatment-related mortality (P < 0.001). The development of extensive chronic GVHD (cGVHD) was associated with higher treatment-related mortality (P = 0.006) compared with the absence of cGVHD. These results indicate that the development of mild-to-moderate aGVHD attribute a lower risk of disease progression and a beneficial effect on the survival of ATL patients with allografts.

Clinical studies have suggested that allo SCT improves the clinical course of ATL with a graft-versus-ATL effect. It is speculated that donor-derived HTLV-1 Tax-specific CD8(+) cytotoxic T cells (CTLs) contribute to the graft-versus-ATL effect after HSCT.

The frequencies, differentiation, functions and clonal dynamics of Tax-specific CTLs in peripheral blood (PB) and bone marrow (BM) from an ATL patient were analyzed after HSCT [61]. Donor-derived Tax-specific CTLs effectively suppressed HTLV-1 replication in both PB and BM at least during chronic graft-versus-host disease after HSCT.

Tax-specific CTLs persistently existed as less-differentiated CD45RA(-)CCR7(-) effector memory CTLs based on predominant phenotypes of CD27(+), CD28(+/-) and CD57(+/-). Two predominant CTL clones persistently existed and maintained strong cytotoxic activities against HTLV-1 in both PB and BM over three years after HSCT.

To study the GVL effects after allo-HSCT, 21 ATL patients(18 acute, 2 lymphoma and 1 chronic) were examined [62]. allo-HSCT, seven patients were in CR, one was in PR, five had stable disease(SD) and eight had progressive disease(PD). The disease after allo-HSCT was CR in 14, PR in 3, SD in one and PD in 3 patients. Among 15 patients who survived longer than 100 days, ATL relapsed in 10 patients. After the discontinuing of immunosuppressant therapy in these 10 patients, 8 manifested GVHD; ATL was ameliorated to CR in 6 patients. Donor lymphocytes were infused into 2 patients who did not show GVHD; 1 obtained CR. In 5 patients with skin relapse alone, 4 patients achieved CR following the discontinuation of the immunosuppres-

sants. From these results, Gv-ATL effects played an important role in the outcome of allo-HSCT for ATL. [63].

15.4. Antiviral therapy

15.4.1. Zidovudine (AZT) and Interferon(INF)

Zidovudine (AZT) and interferon(INF) are known to be as antiviral agents.

Phase II studies with the combination of AZT and IFN treatment showed a high response rate. For acute ATL, first-line antiviral therapy alone resulted in a significant survival advantage (5-year overall survival [OS] of 28%) compared with first-line chemotherapy with or without maintenance antiviral therapy (5-year OS of 10%). Achieving CR with antiviral therapy resulted in a 5-year survival rate of 82%.

A study of worldwide meta-analysis on 254 ATL survival treated in the United States, the United Kingdom, Martinique, and France (116 acute ATL, 18 chronic ATL, 11 smoldering ATL, and 100 ATL lymphoma) was performed. Five-year OS rates were 46% for 75 patients who received first-line antiviral therapy, 20% for 77 patients who received first-line chemotherapy, and 12% for 55 patients who received first-line chemotherapy followed by antiviral therapy.

Patients with acute, chronic, and smoldering ATL significantly benefited from first-line antiviral therapy, whereas in ATL lymphoma, first-line antiviral therapy resulted in a significant survival disadvantage (median and 5-year OS of 7 months and 0%, respectively) compared with first-line chemotherapy with or without maintenance antiviral therapy (median and 5-year OS of 16 months and 18%, respectively). Finally, a multivariate analysis confirmed that first-line antiviral therapy significantly improves overall survival of ATL patients (hazard ratio 0.47; 95% confidence interval 0.27-0.83; P =.021). [64,65].

Virus expression has been reported to be limited or absent when ATLL is diagnosed, and this has suggested that secondary genetic or epigenetic changes are important in disease pathogenesis.

Nineteen patients were prospectively enrolled in a phase II clinical trial of infusional chemotherapy with etoposide, doxorubicin, and vincristine, daily prednisone, and bolus cyclophosphamide (EPOCH) given for two to six cycles until maximal clinical response, and followed by antiviral therapy with daily zidovudine, lamivudine, and alpha interferon-2a for up to one year [66].

Seven patients were on study for less than one month due to progressive disease or chemotherapy toxicity. Eleven patients achieved an objective response with median duration of response of thirteen months, and two complete remissions. Viral reactivation(median 190-fold) was observed during EPOCH chemotherapy.

Alternative therapies are sorely needed in this disease that simultaneously prevent virus expression.

15.4.2. Arsenic trioxide

Arsenic trioxide synergizes with IFN to induce cell-cycle arrest and apoptosis in HTLV-I–infected and freshly isolated leukemia cells from ATL patients.

The arsenic/IFN combination kills ATL cells through rapid reversal of the constitutive activation of NF-κB and delayed shut down of cell cycle-regulated genes secondary to Tax degradation by the proteasome that was concomitant with cell death induction [67]. It was speculated that that leukemia initiating activity(LIC) is dependent on continuous NF-κB expression. [68]. Other phase II study, the efficacy and safety of the combination of arsenic, IFN, and AZT in 10 newly diagnosed chronic patients was evaluated [69]. 100% response rate was observed, including 7 CR, 2 PR but with > 5% circulating atypical lymphocytes, and 1PR. Side effects were moderate and mostly hematologic.

The addition of arsenic to AZT/IFN, through elimination of LIC activity, may result in long-term disease eradication and potential cure. Treatment of arsenic/IFN/AZT combination was a suboptimal 5-days-per-week treatment, 3 of 6 patients remained in continuous complete remission for 7-18 months after discontinuation of maintenance therapy, whereas 5 patients with chronic ATL previously treated with IFN/AZT alone all relapsed, on average before 5 months. Similarly, in an ongoing trial of ATL lymphoma patients, ie, maintenance therapy with arsenic/IFN after complete remission with chemotherapy, resulted in all assessable patients remaining in complete remission for 23-44 months, a distinctly uncommon finding in these diseases. These observations suggest that in ATL patients arsenic/IFN efficiently targets ATL LIC activity and may be useful as a consolidation therapy.

The results of another phase II trial in which arsenic was added to the combination of AZT and IFN in newly diagnosed chronic ATL were reported. All 10 patients enrolled responded, including seven patients who achieved CR, two patients who achieved very good PR, and one patient achieved PR. Side effects were moderate and no relapse was noted at the time of reporting.

These encouraging results suggest that the triple combination of arsenic, AZT and IFN is a promising even for the first line therapy of ATL.

15.5. Targeting NFκB in ATLL patients

In ATLL cells the NFκB pathway remains activated even after Tax expression is repressed. Thus NFκB remains a therapeutic target even when Tax is not expressed.

To determine if NFκB blockade is tolerated in these patients, and whether or not it improves response rates and overall survival, multicenter trial combines infusional chemotherapy (EPOCH) with bortezomib. This trial includes treatment with integrase inhibitor raltegravir, which was found to inhibit HTLV-1 integration. The addition of an antiviral agent to this ATLL treatment regimen is based clinical trial in which chemotherapy was found to markedly enhance virus expression in a subset of patients.

Bortezomib is another non-specific inhibitor of the NFκB pathway that is capable of inhibiting proliferation of tumors cells [72]. Bay11-7082, an IKK inhibitor, inhibits the NFκB pathway in

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ATLL cells and sensitizes HTLV-1 infected cells lines as well as primary ATLL cells to apoptosis [73,74]. Over the past years several additional studies have therapeutically targeted the NFκB pathway in order to kill ATLL cells

Oridonin, NIK-333, curcumin, fucoidan, and histone-deacetylase inhibitors have all been reported to induce apoptosis in ATLL cells by repressing the NFκB pathway. The field now awaits successful clinical trials in vivo [75,76].

15.6. Watch-and-wait policy for indolent ATL

Patients with smoldering or chronic ATL subtypes have a better prognosis than those with aggressive variants of ATL. Therefore, these 2 ATL subtypes were considered indolent and were usually managed with a watchful-waiting policy until disease progression. However, the reported median survival of chronic and smoldering types was only 18 months and 58 months, respectively, and the OS rates were < 20% at 5 years in both types. From Japanese study with longer follow-up period, that indolent ATL had a poor prognosis: patients with smoldering ATL had an estimated 15-year survival rate of 12.7% with a median survival of 2.9 years, whereas patients with chronic ATL had an estimated 15-year survival rate of 14.7% with a median survival of 5.3 years. Importantly, patients who received chemotherapy had a significantly lower survival compared with patients treated on a watch-and-wait policy.

From 1974 to 2003, newly diagnosed indolent ATL in 90 patients (65 chronic type and 25 smoldering type) was analyzed. The median survival time was 4.1 years; The estimated 5-, 10-, and 15-year survival rates were 47.2%, 25.4%, and 14.1%, respectively, with no plateau in the survival curve. Kaplan-Meier analyses showed that advanced PS, neutrophilia, high concentration of lactate dehydrogenase, more than 3 extranodal lesions, more than 4 total involved lesions, and receiving chemotherapy were unfavorable prognostic factors for survival. Multivariate Cox analysis showed that advanced PS was a borderline significant independent factor in poor survival (P =.06). The prognosis of indolent ATL in this study was poorer than expected.

15.7. Telomerase inhibitors

AZT is a thymidine analog that has been shown to inhibit cancer growth and telomerase activity. HTLV-I infected cells undergo senescence during long-term AZT treatment, du to the reactivation of tumor suppressor p53 transcriptional activities. This effect is dependent upon telomere shortening. In vivo patient samples of AZT-treated ATLL patients show decreases in telomerase activity and telomere lengths [48].

16. Treatment strategy

16.1. Acute ATL

As summarized in Fig. 3, in Japan, at present, LSG15 is the standard chemotherapy for the treatment of aggressive ATL, but the efficacy of LSG15 in most patients is transient.

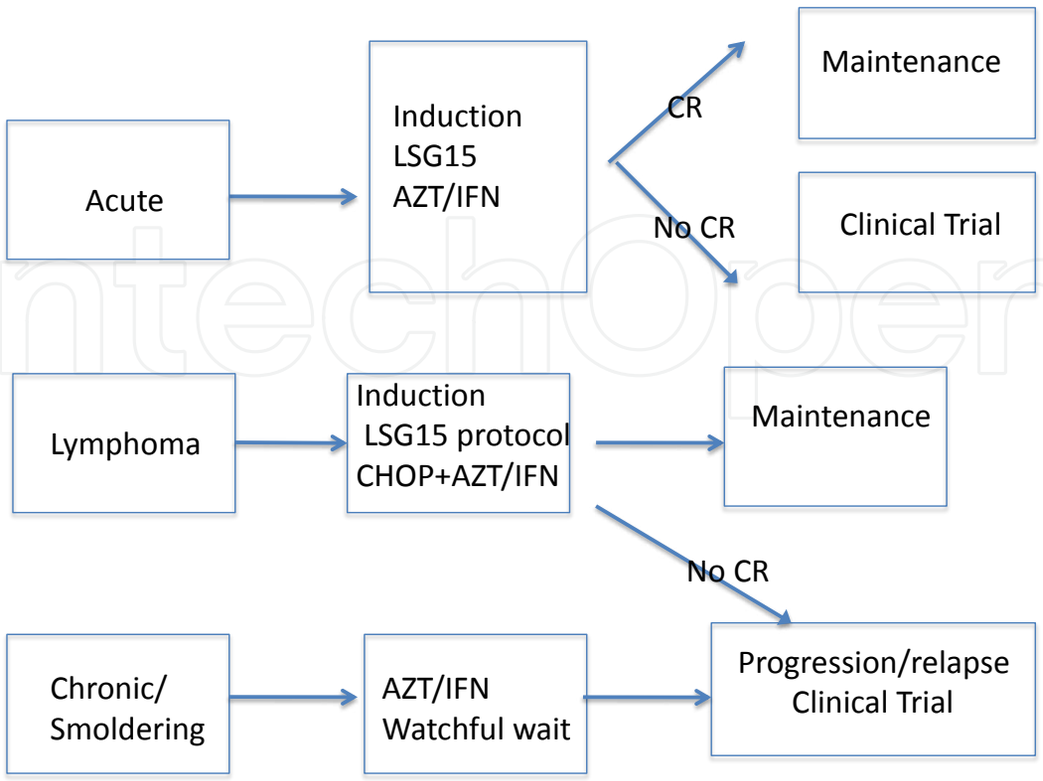


Figure 3. Treatment proposal

To evaluate whether allo-SCT is more effective than the standard chemotherapy (LSG15) for aggressive ATL, clinical trial are needed.

In United States, an antiviral therapy such as AZT+IFN is recommended [1].

16.2. Chronic and smoldering ATL

Although patients with chronic and smoldering ATL have a better prognosis compared with patients with acute ATL and ATL lymphoma, long-term survival is dismal when these patients are managed with a watchful-waiting policy until their disease progresses. Moreover, patients who received chemotherapy alone had even a poorer outcome.

It is one proposal that patients with chronic and smoldering ATL should be treated with antiviral therapy. In the worldwide meta-analysis on ATL survival, patients with chronic/smoldering ATL who received first-line antiviral therapy only had an excellent survival (100% OS beyond 5 years). The recommended starting dose is AZT 900 mg/d (in 3 divided doses) and IFN-α (5-6 million IU/m2/d). Usually, after 1 month, AZT dose can be titrated down to 600 mg/d in 2 divided doses, and the IFN dose can be reduced to 3-5 million IU/d or alternatively 1.5 μg/kg of pegylated IFN weekly. The addition of other antiretroviral agents, such as 3TC (lamivudine) or zalcitabine, has been tested by several centers. However, no clinical evidence of added benefit was demonstrated. On the basis of the preclinical data, clinical trials are testing the effect of adding arsenic to the AZT/IFN combination as a consolidation therapy with the

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aim of then stopping therapy and achieving cure by potential elimination of leukemia-initiating cells.

16.3. Lymphoma

In Japan, LSG protocol is generally tried. When treated with this LSG15 protocol, ATL lymphoma patients achieved a better CR rate (66.7%) than acute type (19.6%) or chronic type (40.0%) patients.

First-line antiviral therapy is less effective than first-line chemotherapy in ATL lymphoma. Probably, the combination of chemotherapy and AZT/IFN is recommended as front-line therapy in ATL lymphoma based on the reactivation of HTLV-1 virues.

Based on encouraging results from Japan, allo SCT is recommended for young patients with ATL lymphoma and sutable donor.

17. Supportive therapy in ATL

Infectious events are often fatal in ATL patients. Sulfamethoxazole-trimethoprim and anti-fungal agents were recommended for the prophylaxis of *Pneumocystis jiroveci* pneumonia and fungal infections, respectively, in the JCOG trials. Although cytomegalovirus infection commonly occurs in ATL patients, ganciclovir is not routinely recommended for prophylaxis. In addition, in patients not receiving chemotherapy, antifungal prophylaxis may not be critical.

18. Prevention

In 1980, investigation of mother-to-child transmission (MTCT) for explaining the infection of HTLV-1. Epidemiological data revealed the MTCT rate at ~20%. Cell-mediated transmission of HTLV-1 without prenatal infection suggested a possibility of milk-borne transmission. A prefecture-wide intervention study to refrain from breast-feeding by carrier fmothers, the ATL Prevention Program Nagasaki revealed a marked reduction of HTLV-1 MTCT by complete bottle-feeding from 20.3% to 2.5%, and a significantly higher risk of short-term breast-feeding (<6 months) than bottle-feeding (7.4% vs. 2.5%, $P < 0.001$) [77].

19. Conclusion

Further investigation on the ATL pathogenesis is crucial for the prevention and treatment of this refractory leukemia/lymphoma. Clinical trials to assess additional targeted therapies such as NF-kB-targeted therapy or monoclonal antibodies are mandatory after achieving CR. Allogeneic BMT with the use of conventional or non-myeloablative conditioning should be considered for suitable patients.

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