



Alexey Bobylev. *Spring*, 2003. Oil on canvas, 61 × 91.5 cm. Courtesy of the St. Petersburg Art Salon, Russia.

Further research is needed to discover the mechanism of leukemogenesis and to develop a successful strategy for treating adult T-cell leukemia.

Human T-Cell Leukemia Virus Type I Induces Adult T-Cell Leukemia: From Clinical Aspects to Molecular Mechanisms

Jun-ichirou Yasunaga, MD, PhD, and Masao Matsuoka, MD, PhD

Background: *Human T-cell leukemia virus type I (HTLV-I) is a causative virus of adult T-cell leukemia (ATL), HTLV-I-associated myelopathy/tropical spastic paraparesis, and HTLV-I-associated uveitis. ATL is a neoplastic disease of CD4-positive T lymphocytes that is characterized by pleomorphic tumor cells with hypersegmented nuclei, termed “flower cells.” The mechanisms of leukemogenesis have not been fully clarified.*

Methods: *The authors reviewed the virological, clinical, and immunological features of HTLV-I and ATL and summarized recent findings on the oncogenic mechanisms of ATL and therapeutic advances.*

Results: *Multiple factors, such as viral genes, genetic and epigenetic alterations, and the host immune system, may be implicated in the leukemogenesis of ATL. Among them, viral genes, tax, and HBZ have been thought to play important roles. The prognosis of aggressive-type ATL remains poor, regardless of intensive chemotherapy. Effectiveness of allogeneic stem cell transplantation for ATL has been recently reported.*

Conclusions: *Although the precise mechanism of leukemogenesis of ATL remains unclear, recent progress provides important clues in oncogenesis by HTLV-I. Future research should focus on the composition of novel therapeutic strategies, including prevention, based on the evidence in the leukemogenic mechanisms.*

From the Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto, Japan.

Address correspondence to Jun-ichirou Yasunaga, MD, PhD, Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto 606-8507, Japan. E-mail: jyasunag@virus.kyoto-u.ac.jp
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Abbreviations used in this paper: HTLV-I = human T-cell leukemia virus type I, ATL = adult T-cell leukemia, HTLV-II = human T-cell leukemia virus type II, HBZ = HTLV-I bZIP factor, MST = median survival time, LTR = long terminal repeat, CTL = cytotoxic T lymphocyte.

Characteristics of HTLV-I

Epidemiology

About 10 to 20 million people worldwide are currently infected with human T-cell leukemia virus type I (HTLV-I).¹ HTLV-I is endemic in southwestern Japan, the Caribbean islands, the areas surrounding the Caribbean basin, and Central Africa. In addition, there are HTLV-I carriers in South America, Papua New Guinea, and the Solomon islands.²

Structure

HTLV-I belongs to the delta-type retroviruses, which also include bovine leukemia virus, human T-cell leukemia virus type II (HTLV-II), and simian T-cell leukemia virus.³ Bovine leukemia virus and simian T-cell leukemia virus have also been associated with neoplastic diseases. Like other retroviruses, the HTLV-I proviral genome has *gag*, *pol*, and *env* genes, flanked by long terminal repeat (LTR) sequences at both ends.⁴ A unique structure is found between *env* and the 3'-LTR and is known as the pX region. The plus strand of the pX region encodes the regulatory proteins p40^{tax} (Tax), p27^{rex} (Rex), p12, p13, p30, and p21, which are implicated in viral infectivity and proliferation of infected cells.⁵ HTLV-I b-ZIP factor (HBZ) was recently identified in the minus strand of the pX region.⁶ Among these, HBZ and Tax seem to play important roles in the pathogenesis of ATL.

Transmission

Although HTLV-I infects target cells mainly through cell-to-cell contact, it appears that infection by free virions is inefficient.⁷ When HTLV-I is transmitted, HTLV-I-infected cells attach and form virological synapses with uninfected cells. Viral proteins and viral genome RNA are then transferred into the target cells.⁸ After transmission of viral RNA, it is reverse transcribed to cDNA by the reverse transcriptase, and the provirus DNA is integrated into the host genome. Thus, living HTLV-I-infected cells are required for infection. There are three major routes of HTLV-I infection: (1) mother-to-infant transmission (mainly through breast milk), (2) parenteral transmission, and (3) sexual transmission. Since HTLV-I can infect a variety of cell types, it has been suggested that its receptor is a ubiquitously expressed molecule. The glucose transporter GLUT-1 has been recently reported to be a receptor for HTLV-I.⁹

Clonal Expansion of HTLV-I-Infected T-Cells

Another human retrovirus — human immunodeficiency virus (HIV) — increases its progeny by replication of the virus itself, whereas HTLV-I increases its copy number by proliferation of the infected cells.³ Since HTLV-I provirus is randomly integrated into the host genome,^{4,10} the

integration site is specific to each HTLV-I-infected cell. The inverse polymerase chain reaction (PCR) assay is useful in identifying the HTLV-I integration sites by amplifying part of the LTR and flanking genomic DNAs. Use of this assay has shown that some clones persist for more than 7 years in the same HTLV-I carriers.¹¹ Analysis of HTLV-I provirus integration sites suggests that HTLV-I-infected cells can survive for a long time and finally transform to malignant leukemic cells.

Clinical Features of ATL

Latency and Incidence

Among individuals in Japan infected with HTLV-I, a small proportion of carriers (6% for males and 2% for females) develop ATL.¹² Most HTLV-I carriers do not develop HTLV-I-associated diseases. The latency period from the initial infection until onset of ATL is about 60 years in Japan¹³ and 40 years in Jamaica.¹⁴ These findings imply a multistep leukemogenic mechanism in the genesis of ATL.

Diagnosis and Disease Subtypes

Three diagnostic criteria for ATL have been defined.² The first is the presence of morphologically proven lymphoid malignancy with T-cell surface antigens (typically CD4+, CD25+). These abnormal T lymphocytes have hyper-lobulated nuclei in acute ATL and are known as “flower cells.” On the other hand, in the indolent types of ATL, smoldering and chronic types, the abnormality of the nuclear shape is generally milder than that in the acute form of the disease. The second is the presence of antibodies to HTLV-1 in the sera, and the third is the demonstration of monoclonal integration of HTLV-1 provirus in tumor cells by Southern blotting.

Four clinical subtypes of ATL have been established according to clinical features¹⁵: acute, lymphoma, chronic, and smoldering types. The acute type is the prototypic ATL in which patients exhibit an increased number of ATL cells, frequent skin lesions, systemic lymphadenopathy, and hepatosplenomegaly. The lymphoma type is characterized by prominent systemic lymphadenopathy, with few abnormal cells in the peripheral blood. These two subtypes have a poor prognosis since they are aggressive and the patients with these types are resistant to intensive chemotherapy. The median survival time (MST) of the patients with these aggressive types is about 1 year. In chronic ATL, the white blood cell count is mildly increased, and skin lesions, lymphadenopathy, and hepatosplenomegaly are sometimes exhibited. Smoldering ATL is characterized by the presence of a few ATL cells in which monoclonal integration of HTLV-I provirus is confirmed in the peripheral blood. In general, the chronic type of ATL progresses to the aggressive types (acute and lymphoma) within a

few years. It has been reported that MST of the patients with chronic type was about 2 years.¹⁵

Immunological Features

Patients with ATL are profoundly immunocompromised and often have opportunistic infections caused by various pathogens such as *Pneumocystis jiroveci*, cytomegalovirus, *Strongyloides*, and *Mycobacterium*. This indicates that cell-mediated immunity is severely impaired in these patients.¹⁶ The incidence of infections is more frequent in patients with ATL than in patients with other hematopoietic malignancies.¹⁷ The similarity between ATL cells and the regulatory T cells (Tregs) has been suggested as a reason for the immunodeficiency. Tregs express CD4 and CD25 on their surface and have immunosuppressive functions. ATL cells show the same phenotype (CD4+, CD25+). Forkhead box P3 (FOXP3) is a key immunoregulatory molecule in Tregs and has been detected in 8 (47%) of 17 ATL cases.¹⁸ Such a Treg phenotype of ATL cells is considered to suppress the immune response and may be implicated in immunodeficiency. In addition to the FOXP3-expressing Tregs, antigen-induced, interleukin-10-secreting, T-regulatory type 1 (Tr1) cells have been identified as another subset of Tregs, which are FOXP3 negative.¹⁹ Although FOXP3 expression is not detected in about half of all ATL cases, ATL cells have been reported to produce interleukin-10,²⁰ suggesting that FOXP3-negative ATL cells also have a regulatory contribution.

Hypercalcemia

The high frequency of hypercalcemia is the most striking feature of ATL. About 70% of patients with ATL have high serum Ca²⁺ levels during the clinical course of the disease, particularly during the aggressive stage of ATL.²¹ Several pathologic studies of ATL patients with hypercalcemia have indicated that the high serum Ca²⁺ levels are due to an increased number of osteoclasts and accelerated bone resorption. Macrophage colony-stimulating factor (M-CSF) and receptor activator nuclear factor kappa B ligand (RANKL) are critical factors for the differentiation of osteoclasts, which are physiologically produced by stromal cells and osteoblasts.²² ATL cells with hypercalcemia aberrantly express RANKL, and M-CSF is elevated in their sera, resulting in the induced differentiation of precursor cells into osteoclasts.²³ It was also reported that the increased level of macrophage inflammatory protein-1 α (MIP-1 α) is associated with hypercalcemia in ATL.²⁴

Molecular Mechanisms of ATL Leukemogenesis

It has been suggested that multiple factors (eg, virus, host cell, and immune factors) are implicated in the

leukemogenesis of ATL.³ Therefore, a long latent period is needed before the onset of ATL. The factors associated with leukemogenesis are summarized below.

Viral Genes

Tax: This is the most extensively studied viral product among HTLV-I-encoded proteins due to its pleiotropic actions on viral and cellular genes.^{25,26} Tax potentially increases the expression of viral genes through viral LTRs, and it also stimulates the transcription of cellular genes through cellular signaling pathways of nuclear factor kappa B (NF- κ B), serum responsive factor (SRF), cyclic AMP response element-binding protein (CREB), and activated protein 1 (AP-1). Tax does not bind to promoter or enhancer sequences by itself, but it interacts with cellular proteins that are transcriptional factors or modulators of cellular functions. In addition to this transcriptional regulation, it is also known that Tax can functionally inactivate p53, p16^{INK4A}, and mitotic arrest deficient (MAD) 1. The PDZ domain-binding motif (PBM) in the C terminus of Tax was recently shown to be important for the transformation of a rat fibroblast cell line²⁷ and the induction of interleukin-2-independent growth of a mouse T-cell line.²⁸ HTLV-II is not associated with human malignancies like ATL, and HTLV-II-encoded Tax2 does not have a PBM. Since the addition of PBM augments transforming activity of Tax2, it is possible that this motif plays an important role in transformation by Tax. Further studies on PBM will contribute the identification of the alternate Tax functions.

On the other hand, Tax expression induces an immune response since it is the major target of cytotoxic T lymphocytes (CTLs).²⁹ Thus, the expression of Tax in HTLV-I-infected cells provides advantages and disadvantages for their survival. To escape from CTLs, ATL cells frequently lose the expression of Tax by several mechanisms. The 5'-LTR is a viral promoter for the transcription of viral genes, including the *tax* gene. The 5'-LTR is reported to be lost in 21 (39%) of 54 cases examined, indicating that ATL cells with such a provirus can no longer produce Tax.³⁰ The second mechanism is the nonsense or missense mutation of the *tax* gene in fresh ATL cells. Interestingly, in some cases, ATL cells have mutations in the class I MHC recognition site of the Tax protein, resulting in an escape from immune recognition.³¹ The third mechanism is an epigenetic change in the 5'-LTR, where DNA hypermethylation and histone modification silence the transcription of viral genes.^{32,33} With these mechanisms, ATL cells suppress Tax expression and can escape the host immune surveillance system. It is speculated that Tax plays an important role in the persistent proliferation of HTLV-I-infected cells during the carrier state, and the mutator phenotype of Tax accumulates genetic and epigenetic changes in the host genome that finally lead to Tax-independent proliferation and escape from the host immune system by inactivation of Tax.

HBZ: As described above, the 5'-LTR is often deleted or hypermethylated in ATL cells. Therefore, transcription of viral genes encoded on the plus strand of HTLV-I is frequently suppressed. Conversely, the 3'-LTR is conserved and hypomethylated in all ATL cases, suggesting its significance in leukemogenesis. In 2002, HBZ was identified in the complementary strand of HTLV-I as a protein that interacts with CREB-2 and suppresses Tax-mediated viral transcription.⁶ We found that HBZ was transcribed from the 3'-LTR, and it was expressed in all ATL cells that we analyzed.³⁴ Moreover, there is no abortive genetic alteration, such as nonsense mutation or deletion, in their HBZ sequences. These findings suggest that HBZ is a critical gene in leukemogenesis. Therefore, we focus on its functions in ATL cells. Suppression of HBZ gene transcription by short interfering RNA inhibits proliferation of ATL cells. In addition, HBZ gene expression promotes proliferation of a human T-cell line. Analysis of T-cell lines transfected with mutated HBZ genes shows that HBZ supports T-cell proliferation in its RNA form by regulation of the E2F-1 pathway, while HBZ protein suppresses Tax-mediated viral transcription through the 5'-LTR, as reported previously.⁶ According to these results, we conclude that the single HBZ gene has bimodal functions in two different molecular forms and that the RNA form of HBZ is likely to be important in the transforming activity of HTLV-I. The molecular mechanisms of the functions of HBZ RNA are still uncertain, and further studies are needed to better understand ATL leukemogenesis and to develop new therapeutic strategies.

Changes of Host Cell Genes

Genetic Alterations: Various mutations of tumor suppressor genes have been demonstrated in cancer, and it has been established that multiple changes of such genes are necessary for the emergence of malignant cells. In ATL cells, previous studies have demonstrated mutations of the *p53* gene in approximately 30% of patients,³⁵⁻³⁷ while we observed such genetic changes (including mutations and insertion) in 9% of ATL cases (3 of 30 in acute type, 1 of 3 in lymphoma type, and 0 of 12 in chronic type). Deletion or mutation of the *p16^{INK4A}* gene has also been reported in ATL.³⁸⁻⁴¹ It is noteworthy that such genetic changes in the *p53* and *p16^{INK4A}* genes are detected in more aggressive disease states, indicating that somatic DNA changes in these two genes associated with the progression of ATL. The *p27^{KIP1}* gene is a cyclin-dependent kinase inhibitor and arrests cell proliferation. Genetic alterations of *p27^{KIP1}* have been identified in only 2 of 42 ATL patients.⁴² *RB1/p105* and *RB2/p130* are members of the retinoblastoma (*Rb*) gene family, and they regulate the cell cycle. Genetic changes in these genes in ATL cells have been also reported. Homozygous loss of *RB/p105* was detected in 2 of 40 ATL cases,⁴³ and a

mutation of *RB2/p130* gene was found in 1 of 41 cases.⁴⁴ Mutations in the *Fas* gene have also been reported in patients with ATL.^{45,46} However, such genetic changes have not been frequently detected.

Epigenetic Changes: In addition to genetic alterations, epigenetic changes such as DNA hypermethylation and histone modification have been analyzed in the context of oncogenesis, since these alterations dysregulate gene transcription. DNA hypermethylation in the promoter regions of tumor suppressor genes is commonly observed in various cancer cells. As well as other malignancies, DNA methylation of the *p16^{INK4A}* promoter is common in ATL cells and accumulates according to the progression of the disease.⁴¹ Using the methylated CpG island amplification/representational difference analysis (MCA/RDA) method, we recently isolated hypo- and hyper-methylated genes in ATL cells, compared with peripheral blood mononuclear cells from an HTLV-I carrier.^{47,48} The *MELIS* gene was hypomethylated and aberrantly transcribed in ATL cells.⁴⁷ *MELIS* is an alternatively spliced form of *MEL1* lacking the PR (PRDI-BF1 and RIZ1) domain and is associated with dysregulation of TGF- β -mediated signaling. Since ATL cells are resistant to TGF- β , aberrant expression of *MELIS* by hypomethylation might be responsible for this phenotype. On the other hand, 53 hypermethylated DNA regions in ATL cells, compared with cells in the carrier state, have been isolated using the MCA/RDA method, and it has been found that the methylation density of these regions increases with disease progression.⁴⁸ Near these hypermethylated regions, the Kruppel-like factor 4 (*KLF4*) gene and the early growth response 3 (*EGR3*) gene have been identified. They are expressed in normal T cells but are suppressed in ATL cells, and they are reactivated with 5-aza-2'-deoxycytidine treatment, indicating that their silencing is associated with DNA hypermethylation. *KLF4* is a cell-cycle regulator,⁴⁹ and *EGR3* is a critical transcriptional factor for induction of Fas ligand expression.⁵⁰ Enforced expression of these in ATL cells induces apoptosis, suggesting that they are candidates for the tumor suppressor genes of ATL. Other than those above, hypermethylation of several genes (eg, *APC*⁵¹, *CD26*⁵², and *PMS1*⁵³) have been reported in ATL cells. The accumulation of these epigenetic changes is thought to play a part in multistep leukemogenesis.

Genetic Predisposition to ATL: Familial clustering of ATL cases suggests that genetic background influences the onset of ATL.⁵⁴ Polymorphism of the promoter region of tumor necrosis factor alpha (TNF- α) has been shown to be associated with ATL, in comparison with asymptomatic carriers, suggesting that the genetic polymorphism that increases the production of TNF- α is associated with susceptibility to ATL.⁵⁵

HLA is also a candidate genetic factor that controls the immune response against viral antigens presented

by antigen-presenting cells. Specific HLA alleles have been reported to be associated with an increased risk of ATL onset. The allele frequencies of HLA-A*26, HLA-B*4002, HLA-B*4006, and HLA-B*4801 are significantly higher in patients with ATL than in patients with HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and asymptomatic HTLV-I carriers in southern Japan. It has been reported that ATL developed 12.6 years earlier in patients with these alleles compared with patients with other alleles.⁵⁶ Since these HLA alleles are genetically defective in their recognition of HTLV-I Tax peptides and are incapable of generating anti-Tax CD8+ CTLs, individuals with such an HLA haplotype allow the proliferation of HTLV-I-infected cells.

Interaction Between HTLV-I-Infected Cells and the Host Immune System

Immunosuppression and the Acceleration of the Onset of ATL: Host immune responses, especially CTLs against HTLV-I, control the number of HTLV-I-infected cells. It is assumed that CTLs in asymptomatic carriers control the proliferation of HTLV-I-infected cells and suppress the development of ATL.⁵⁷ In a case report of a liver allograft recipient who developed ATL during immunosuppressive treatment,⁵⁸ the recipient was an HTLV-I carrier and underwent liver transplanta-

tion 2 years before the onset of ATL. The patient achieved complete remission by the discontinuance of immunosuppressive therapy and combined chemotherapy but died of graft rejection. In addition, among 24 patients with posttransplantation lymphoproliferative disorders (PT-LPDs) after renal transplantation in Japan, 5 had ATL.⁵⁹ Considering that most of the PT-LPDs are of B-cell origin in Western countries, this frequency of ATL was high. These findings indicate that the immunodeficient state supports the onset of ATL.

Influence of the Route of HTLV-I Transmission on Anti-HTLV-I Immune Responses: Since ATL is considered to develop among carriers vertically infected by HTLV-I, it is possible that the route of HTLV-I transmission might be associated with the host anti-HTLV-I immune responses and the onset of ATL. It has been reported that host anti-HTLV-I immunity is influenced by the conditions of the primary infection in rat models.⁶⁰ When inoculated with HTLV-I donor cells (MT-2) orally, intravenously, or intraperitoneally, immunocompetent rats became persistently infected. However, none of the orally inoculated rats but all of the intravenously or intraperitoneally inoculated rats produced significant levels of anti-HTLV-I antibodies. Moreover, T-cell proliferative response against HTLV-I was hardly detected in orally inoculated rats. The lack of immune response in orally infected subjects could result in the

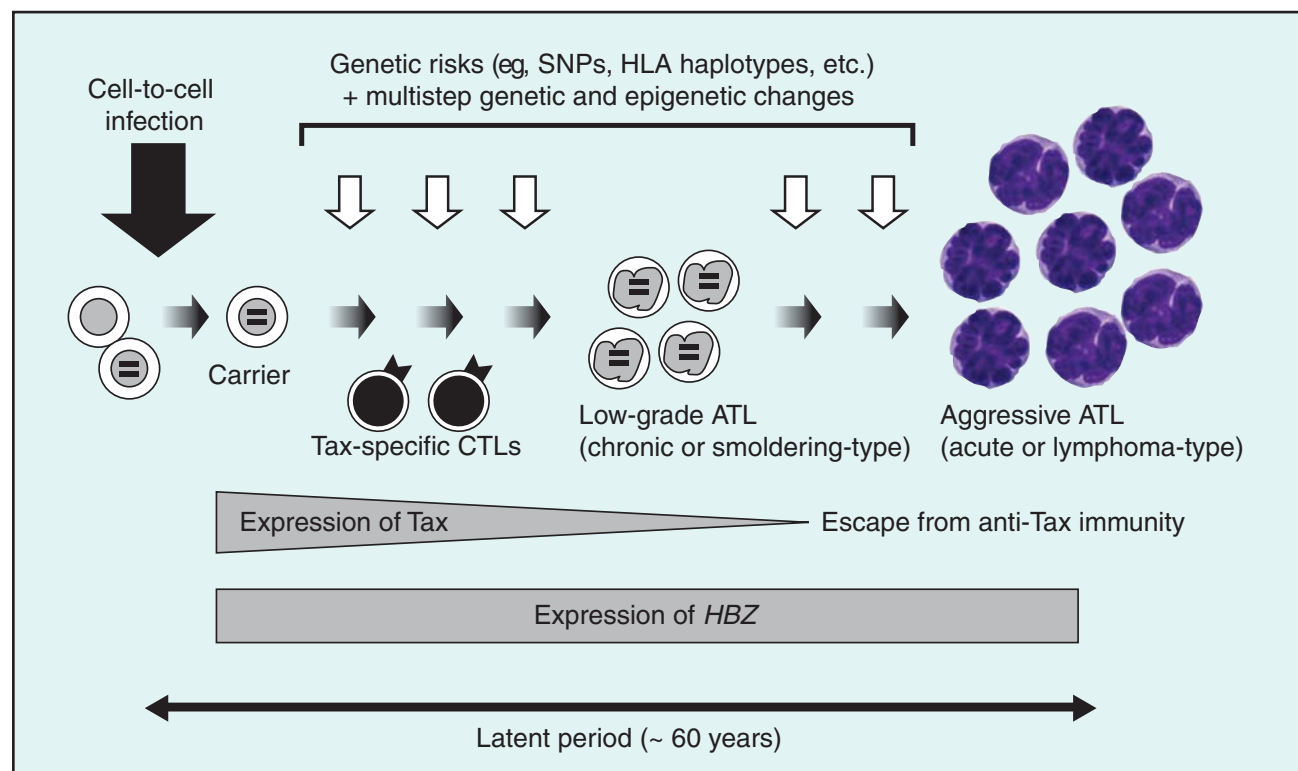


Figure. — Schematic model of the natural course from HTLV-I infection to the onset of ATL. HTLV-I is transmitted by cell-to-cell contact of HTLV-I-infected cells. After infection, HTLV-I promotes clonal proliferation of infected cells by Tax and HBZ. However, proliferation of HTLV-I-infected cells is also controlled by CTLs in vivo. During the latency period, the genetic and epigenetic alterations accumulate in the host genomes. In late phase, the expression of Tax is inactivated, suggesting that Tax is not always necessary in this stage. On the other hand, HBZ is important in all phases. This Figure is reprinted by courtesy of the *International Journal of Hematology*. From Yasunaga J, Matsuoka M. Leukemogenesis of adult T-cell leukemia. *Int J Hematol*. 2003;78:312-320.

survival and eventual transformation of HTLV-I-infected cells, which might explain why ATL has developed in vertically transmitted carriers.

Multistep Process in Leukemogenesis of ATL

In the carrier phase, HTLV-I-infected cells are conferred growth advantages by viral genes such as *tax* and *HBZ*. However, since Tax is a target of the host immune system, the number of Tax-expressing cells is regulated, and selected HTLV-I-infected clones survive by clonal proliferation for a long time. During this incubation time, genetic and epigenetic alterations accumulate in the host genome, and a fully malignant cell eventually appears. In the late step of leukemogenesis, silencing of Tax expression is advantageous for the cells that acquire a transformed phenotype without Tax; therefore, the tumor cells that do not express Tax are selected and frequently observed in cases of ATL. On the other hand, *HBZ* seems to be important in all phases because it is expressed throughout at all stages and conserves its sequences in all cases.³⁴ The Figure shows the schematic model of multistep leukemogenic mechanisms of ATL.

Current State and New Strategies of ATL Treatment

In general, patients with aggressive types of ATL need to be treated immediately at diagnosis, whereas patients with indolent types can be followed without treatment. Despite intensive chemotherapy, aggressive ATL is a disease with a poor prognosis. The effectiveness of hematopoietic stem cell transplantation and new molecular-targeted drugs has been reported, and establishment of the novel therapeutic strategies is expected. This section reviews extant therapy and the candidates for more effective drugs to improve the prognosis of this aggressive disease.

Combination Chemotherapy

Intensive combination chemotherapy has been used to treat the aggressive forms of ATL, such as the acute and lymphoma types. Since ATL is a neoplasm of mature T cells, it has been treated with chemotherapies for non-Hodgkin's lymphoma. CHOP therapy, consisting of a combination of cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisolone, has been the standard regimen for aggressive-type ATL. Granulocyte colony-stimulating factor-supported biweekly CHOP is an intensified therapy. The Japan Clinical Oncology Group recently reported that the response rate of biweekly CHOP was 66%, with 25% complete response rate and 41% partial response rate. The overall survival rate at 3 years was 12.7% and MST was 10.9 months, as reported at the 47th American Society of Hematology

Annual Meeting.⁶¹ It was also reported that the more potent chemotherapy, consisting of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisolone), AMP (doxorubicin, ranimustine [MCNU], and prednisolone), and VECF (vindesine, etoposide, carboplatin, and prednisolone), improves the prognosis of ATL (response rate, 72%; complete response rate, 40%; partial response rate, 32%; overall survival rate at 3 years, 23.6%; and MST, 12.7 months). However, the survival of ATL patients is still poor regardless of these intensive chemotherapies.⁶¹

Allogeneic Stem Cell Transplantation

The first report of successful bone marrow transplantation for ATL was published in 1996.⁶² The patient was grafted with cells donated from an HTLV-I-uninfected sister. Subsequently, other cases treated with allogeneic stem cell transplantation (allo-SCT) have shown its effectiveness.^{63,64} Utsunomiya et al⁶⁵ reported that the median leukemia-free survival time of 10 ATL patients treated with allo-SCT was 17.5 months. It was also shown that two cases with no symptoms of graft-vs-host disease relapsed with ATL. It was reported that some relapsed ATL patients who had received SCT did achieve subsequent complete response after discontinuation of immunosuppressive therapy or donor lymphocyte infusion.⁶⁶ In addition, it was reported that Tax-specific CTLs were increased in some ATL patients after SCT, which might contribute to induction of remission.⁶⁷ These findings suggest that the graft-vs-leukemia effect is essential for its curative influence. In a report involving 16 patients aged >50 years with ATL who underwent allo-SCT with reduced-conditioning intensity (RIST), the efficacy of this regimen was demonstrated.⁶⁸ Since most ATL patients are older, RIST is considered to be safer and more useful. Based on these data, allo-SCT is becoming one of the standard therapies for ATL. However, a case of ATL developed from donor cells 4 months after allo-SCT.⁶⁹ The donor was an HTLV-I-infected sibling and asymptomatic. This indicates that the immunosuppressive status in recipients of allo-SCT also potentially contributes to the development of ATL in donor-derived T cells that are infected with HTLV-I.

Molecular-Targeted Agents

NF- κ B Inhibitors: NF- κ B activation has been reported in ATL cells, and it is strongly associated with oncogenesis. Therefore, NF- κ B is thought to be an attractive molecular target. Bortezomib is a proteasome inhibitor that blocks the degradation of I κ B, resulting in inhibition of NF- κ B activation. It has been shown that bortezomib is effective against ATL cells in vitro and in vivo,⁷⁰ and its effect could be enhanced by combined use of anti-CD25 antibody.⁷¹ Depsipeptide is a histone deacetylase inhibitor, and a clinical trial on its use in

cutaneous T-cell lymphoma has commenced. This drug also inhibits the activation of NF- κ B and AP-1 in ATL cells, and it induces apoptosis.⁷²

Monoclonal Antibodies: An alternative approach to the therapy of ATL is to target cell-surface markers on the malignant cells with monoclonal antibodies. Anti-CD25 (anti-Tac) monoclonal antibody, which was first administered to patients with ATL in the late 1980s,⁷³ was reported to be effective in some patients, with a complete response in 2 of 19 patients and a partial response in 4 of 19 patients.⁷⁴ Another antibody, anti-CD52 monoclonal antibody (Campath-1H), is being evaluated in a phase II clinical trial by the National Institutes of Health (Protocol 03-C-0194). Humanized anti-CD2 antibody (MEDI-507) has also been shown to be effective in vivo.⁷⁵

Zidovudine Plus Interferon Alpha

It has been reported that combination therapy with zidovudine (ZDV) and interferon alpha (IFN- α) is effective against ATL. The mechanism of its antitumor effect is still uncertain.⁷⁶ A phase II study in France has reported a response rate of 92% for patients who received ZDV/IFN- α as initial treatment (complete response rate, 58%; partial response rate, 33%).⁷⁷ However, it has also been reported that response and survival in patients treated with ZDV/IFN- α after initial chemotherapy was less impressive than in those treated with IFN- α as first-line therapy, and median overall survival was 11 months for the whole population.⁷⁷

Prevention of ATL

Since ATL seem to be associated with infection of HTLV-I in early life, the most important route of infection is vertical transmission through breast milk. Avoidance of breast-feeding by an HTLV-I-infected mother reduces transmission by 80% and helps to prevent ATL. Since high provirus load is a risk factor of ATL,⁷⁸ reducing provirus load by antiretroviral therapy or immunotherapy might prevent the onset of ATL in HTLV-I carriers. Tax-targeted vaccines in a rat model of HTLV-I-induced lymphomas showed promising antitumor effect,⁷⁹ so this strategy might contribute to the prevention of ATL development.

Conclusions

In the last quarter of a century, many aspects of HTLV-I and ATL have been demonstrated, and new discoveries are being made. However, the precise mechanism of leukemogenesis remains unknown, and more importantly, a successful therapy for ATL has not been established. Future research should focus on the composition of novel therapeutic strategies, including prevention, based on the evidence in the leukemogenic mechanisms.

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