Published in final edited form as:
Curr Opin Oncol. 2005 September ; 17(5): 469–473.

Human T cell lymphotropic virus-associated leukemia/lymphoma

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Abstract

Purpose of review—This article summarizes the current pathophysiologic basis for human T cell lymphotropic virus-associated leukemia/lymphoma as well as past, present, and future therapeutic options.

Recent findings—New studies have been published on allogeneic stem cell transplantation, arsenic trioxide, and bortezomib for this condition.

Summary—Studies of the molecular biology of human T cell lymphotropic virus-1-induced T cell leukemia/lymphoma have defined a critical role for oncoprotein, Tax, and activation of nuclear factor κB transcription pathways, which have provided rational approaches to improved therapy for T cell leukemia/lymphoma as well as a model for other hematopoietic malignancies characterized by nuclear factor κB activation.

Keywords

human T cell leukemia/lymphoma; lymphoma; T cell leukemia/lymphoma

Introduction

Several reviews of human T cell leukemia/lymphoma (HTLV)-1)-associated leukemia/lymphoma (ATLL) have been published in the past year [1•,2,3]. Therefore, the emphasis of this review will be new developments in its pathogenesis, diagnosis, prognostication, and treatment, emphasizing findings from manuscripts published in the past year.

Considerable data support the etiologic role of HTLV-1 in ATLL [4]. Patients with ATLL are infected with HTLV-1, as evidenced by serologic and nucleic acid assays, and infection precedes disease development. Moreover, HTLV-1 transforms CD4+ lymphocytes in culture, resulting in a cell surface phenotype and gene expression profile similar to that of ATLL. In addition, HTLV-1 is clonally integrated into CD4+ lymphocytes. Last, a related virus, bovine leukemia virus, induces an analogous lymphoproliferative malignancy of B cells in cattle. A distinct clinical syndrome, HTLV-1–associated myelopathy, is also a result of infection (Table 1).

In southern Japan, the Caribbean Basin, many parts of Central and South America, Africa, and Middle Eastern Asia, HTLV-1 is endemic. It is transmitted by contaminated blood products, by sexual means, or by breast feeding. Although HTLV-1–associated myelopathy can result from any of these forms of transmission, ATLL seems to occur only after breast feeding, but several decades later in life.

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Four subtypes of ATLL have been described: smoldering, chronic, leukemic and lymphomatous ATLL (Table 1) [1•,2]. Smoldering ATLL is characterized by 1 to 5% abnormal peripheral blood lymphocytes or limited skin lesions. Chronic ATLL may include lymphocytosis, skin lesions, or liver, lung, or lymph node involvement. Leukemic ATLL is characterized by lymphocytosis, hypercalcemia, lytic bone lesions, lymphadenopathy, visceral or leptomeningeal involvement, and opportunistic infections. Lymphomatous ATLL is a post-thymic T cell non-Hodgkin's lymphoma with frequent blood, skin, and bone involvement.

Pathogenesis

There is strong evidence implicating the transcriptional transactivator protein, Tax, as the critical oncoprotein of HTLV-1 [5•,6]. Proviral deletions in ATLL patients are common, but the *tax* gene is generally conserved. Tax is capable of transforming Rat 1 fibroblasts. Tax expression in a *Herpesvirus samirii* or retrovirus vector results in CD4+ cell immortalization. Tax expression in transgenic mice results in various neoplasms, including lymphoma.

Tax is a pluripotent transcriptional activator that does not independently bind DNA but rather enhances the activity of cellular transcription factors and chromatin modeling determinants (Table 2) [7]. Tax activates the viral promoter though cAMP-response element binding proteins (CREB), and CREB-binding protein and the related p300. Tax activates the nuclear factor κB (NFκB) family of proteins by binding to the regulatory inhibitor kinase kinase γ subunit, and by enhancing phosphorylation and activity of inhibitor kinase kinase α and β subunits through interactions with mitogen activated protein kinase kinase. Activation of NFκB is critical for HTLV-1 immortalization in culture, and for tumorigenesis in Tax transgenic mice [8–10]. NFκB enhances the expression of proteins that promote cell proliferation and angiogenesis, and resistance to apoptosis.

Tax has multiple effects on the cell cycle progression through transcriptional or post-transcriptional effects (Table 2). The effects on G1 progression result from the effects of Tax on the tumor suppressor, p53, Rb, on inhibitors of cyclin-dependent kinases (INK proteins), and on cyclins and cyclin-dependent kinases. Tax induces phosphorylation of p53 and represses its transcriptional activity [11]. Tax affects INK proteins, through direct binding and suppression of p16-INK4A, transcriptional repression of p18-INK4C, decreased transcription of p19-INK4D, and increased expression of p21 [12,13]. In addition, Tax binds cyclin-dependent kinase-4 and cyclin D2, resulting in activation, enhanced phosphorylation of cyclin D3, and enhanced transcription of the cyclin D2 gene [5•,14–16]. Tax also modulates the G2 phase of the cell cycle by binding and inhibiting mitotic arrest defect 1 protein, the Cdc20 anaphase-promoting complex, and the checkpoint kinases, Chk1 and 2, disrupting the G2-M checkpoint [17–19].

There is also evidence suggesting that secondary genetic or epigenetic events are required for ATLL development, because the Tax protein is not usually evident in uncultured ATLL tissues. Moreover, only approximately 10% of individuals infected by breast feeding, and few if any individuals infected by other routes, experience ATLL, and only several decades later in life. DNA methylation is an epigenetic determinant of gene expression that can modulate oncogenesis. In an analysis of hypermethylated sequences in ATLL, 53 hypermethylated DNA sequences were identified, of which 7 resulted in repressed gene expression in ATLL compared with normal T cells [20]. The downregulated genes included the Kruppel-like factor 4 gene, a cell cycle regulator, and early growth response 3 gene, a regulator of Fas ligand expression, both of which resulted in resistance to induction of apoptosis. These studies may provide insights into factors that determine which infected individuals remain asymptomatic compared with those in whom ATLL develops.

Prognostic markers

The diagnosis of ATLL requires evidence of HTLV-1 infection by serologic or nucleic acid techniques, a CD4+ CD25+ lymphoid proliferation, and clinicopathologic characteristics of leukemia or lymphoma. Clonality is a critical feature of ATLL and may be demonstrated by clonal Tcell receptor gene rearrangements or a proviral integration pattern [21]. In a recent study of 50 persons infected with HTLV-1 with clonal integration, 21 experienced ATLL, with an incidence rate of 48 per 1000 person-years [22•]. Another 10 patients experienced opportunistic infections or other malignancies, resulting in death. A leukocyte count higher than 9000/μl was predictive of ATLL development. In established ATLL, the patient's age, serum level of LDH, hypercalcemia, and performance status have been reported as prognostic determinants.

Provirus load may be a prognostic marker for ATLL as well as a measure of tumor burden in established ATLL. This assay measures the number of integrated and unintegrated copies of viral DNA in cells. Studies of viral RNA in cells or plasma have not been reported. A recent study examined proviral load in individuals infected with HTLV-1 and HTLV-2 [23]. The proviral load in HTLV-1–infected patients ranged from 3.1 to 1.8×10^5 copies per 10^6 peripheral blood mononuclear cells (PBMCs) and was detectable in 94% of asymptomatic individuals. The HTLV-2 proviral load ranged from 1.1 to 1.0×10^6 copies per 10^6 peripheral blood mononuclear cells (PBMCs) and was detectable in 91% of asymptomatic individuals. In this study, however, there was no information on ATLL development.

Gene expression studies of ATLL may also provide information of prognostic importance. In comparison of tumorigenic and non-tumorigenic ATLL cell lines, an adhesion protein OX40 and a regulator of G protein signaling, RGS1, were overexpressed in tumorigenic ATLL cells [24]. Other studies of cells transformed by HTLV-1 infection, Tax-expressing cell lines, or ATLL cells have identified overexpression or underexpression of genes associated with apoptosis, cell cycle regulation, DNA repair, signaling, immune mediation, and cytokine or growth factor production compared with activated uninfected lymphocytes [25–28].

Chemo-antiretroviral therapy

A variety of combination chemotherapy regimens have been used for leukemic or lymphomatous ATLL, but median survival remains at approximately 1 year, with a 5-year survival rate of less than 5% [29–35]. Promising results with the combination of interferon-α and zidovudine have been reported from some but not all groups of investigators [36–42]. Relapses occur in most individuals when treatment is discontinued. An infusional regimen, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, is currently being evaluated in combination with interferon-α and combivir in the National Cancer Institute—sponsored clinical study #AMC 033. The etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin regimen was chosen on the basis of its activity in refractory lymphomas and in HIV-associated lymphomas [43,44].

Stem cell transplantation

Autologous stem cell transplantation (SCT) is generally ineffective for leukemic or lymphomatous ATLL [45]. The role of allogenic SCT for ATLL remains unclear [46–52]. In a recent study of 16 patients over the age of 50 with ATLL who underwent allogeneic SCT, a reduced-intensity conditioning regimen with fludarabine, busulfan, and rabbit antithymocyte globulin was well tolerated [53]. Proviral load became undetectable in 8 patients, but remission rates are not yet available. A graft-versus-ATLL effect was found with this procedure. In a study of ATLL patients who obtained complete remission after non-myeloablative allogenic SCT from HLA-identical siblings, CD8+ cytotoxic T lymphocytes directed against the HLA-

A2 restricted dominant Tax epitope were found after, but not before, transplantation [54]. Cytotoxic T lymphocytes to HTLV-1 Env epitopes may also result in ATLL cytotoxicity [55].

Antibodies

Anti-Tac antibody, which recognizes CD25, the α subunit of the interleukin-2 receptor, has been shown to have therapeutic efficacy for ATLL cells in patients and in a murine xenograft model [56]. A recent study showed that antitumor activity depended on Fc receptor-mediated clearance [57]. Improved activity is seen with radioimmunoconjugates, such as Yttrium90-labeled anti-Tac [58,59]. In one study of 18 ATLL patients given doses of 5 to 15 mCi, there were 7 partial and 2 complete remissions. A monoclonal antibody to human transferrin receptor, constitutively expressed at high levels on ATLL cells, blocked ATLL cell growth in culture [60]. Similarly, anti-CD2 antibody has activity in the severe combined immunodeficiency mouse model of ATLL. Anti-CD52 antibody (Alemtuzumab, Campath) has also been reported to be active in one ATLL patient [61]. Denileukin difitox (Ontak), an interleukin-2—diphtheria toxin fusion protein, has not been reported to be active in ATLL, however. A recent manuscript describes Tax activation of CD40; thus, antibodies to CD40 that are in current clinical trials could be of interest for ATLL [62].

Tax is a critical target for cytotoxic T lymphocyte—mediated killing [63]. Downregulation of Tax with small interfering RNAs resulted in resistance to cytotoxicity in culture and in a rat model system [64]. Studies of therapeutic Tax vaccines would therefore be of great interest.

Novel therapies

Arsenic trioxide has been shown to synergize with interferon-α in inducing growth arrest and apoptosis of ATLL cells in culture [65–68]. A phase II trial in seven patients with relapsed or refractory ATLL resulted in one complete remission and three partial remissions. [69]. Treatment was discontinued at a median of 3 weeks, however, because of toxicity or disease progression.

The critical role of NFκB in the transforming function of Tax has led to several studies in ATLL patients of inhibitors of this pathway. Bortezomib (PS341, Velcade), which blocks IκB degradation, inhibits NFκB activity in HTLV-1 immortalized cells and Tax transgenic tumor cell lines in culture in murine transplant models [70,71]. This blocked cell proliferation and resulted in apoptosis. There have been several anecdotal reports of the successful use of bortezomib in patients with refractory ATLL.

Retinoids and angiogenesis inhibitors have also been explored for anti-ATLL activity [72, 73].

Conclusion

No specific therapeutic recommendations can be made for smoldering ATLL or chronic ATLL at this time, in light of their variable course and duration. The leukemic and lymphomatous forms of ATLL are best treated with interferon-α and zidovudine with or without conditioning with chemotherapy. Subsequent therapy with allogeneic SCTor radioimmunotherapy could be useful for consolidative therapy. Monitoring proviral load seems to be helpful in assessing therapeutic efficacy. Further clinical trials are warranted to define the mechanism of action of these therapies and prognostic markers, and the optimal timing and doses or different agents. The role of other agents such as bortezomib, arsenic trioxide, and alemtuzumab remains to be further defined.

Acknowledgements

The author thanks Dr L. Mizrachi-Bernal for critiquing the manuscript.

Supported by NIH grants CA105218, CA70062, CA10073, and CA63417

Abbreviations

ATLL
T cell leukemia/lymphoma

HTLV
human T cell leukemia/lymphoma

NFκB
nuclear factor κB

SCT
stem cell transplantation

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Table 1
HTLV-1 disease associations

Nonmalignant conditions	
Asymptomatic infection	
HTLV-associated myleopathy (HAM), tropical spastic paraparesis (TSP)	
HTLV-associated arthropathy	
HTLV-associated uveitis	
Malignant disorders	
Smoldering ATLL	Atypical lymphocytes, limited skin lesions
Chronic ATLL	Lymphocytosis, skin lesions, liver, lung, lymph node involvement
Acute ATLL, lymphomatous form	T-cell non-Hodgkin's lymphoma with frequent blood, skin, bone lesions
Acute ATLL, leukemia form	T-cell leukemia with hypercalcemia, lytic bone lesions, lymphadenopathy, visceral or leptomeningeal involvement, opportunitistic infections

HTLV, human T cell leukemia/lymphoma virus; ATLL, HTLV-1-associated leukemia/lymphoma.

Table 2

Tax oncoprotein activities

Transcriptional activities
Serum-response factor
cAMP-response factor–activation of viral promoter
Nuclear factor κB–activation of cytokines, anti-apoptosis genes, cell proliferation genes, and angiogenesis
Posttranscriptional activities
Proliferation–inhibition of p16 cell cycle inhibitor, activation of cyclin-dependent kinase 4 and cyclin 2
Apoptosis–inactivation of p53
Genetic instability defect in G2/M checkpoint caused by binding mitotic arrest defect 1 protein, Cdc20 anaphase-promoting complex, and checkpoint kinases Chk1 and 2