

ADULT T CELL LEUKEMIA LYMPHOMA

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1. ABSTRACT

Adult T cell leukemia lymphoma (ATLL) is a CD4+ lymphoproliferative malignancy resulting from human T-cell leukemia virus type 1 (HTLV1) infection. It includes differing clinical forms classified as smoldering, chronic, lymphomatous, and acute ATLL. The Tax protein of HTLV-1 has been implicated as a viral oncoprotein which enhances virus replication and alters cellular gene expression, including activation of nuclear factor kappa B (NF kB), to result in lymphoid transformation. Chemotherapy for ATLL has had limited efficacy with median survivals of about 1 yr. Antiviral therapy employing zidovudine and interferon has shown promising results, as have antibody-based therapies to the interleukin 2 (IL2) receptor. Novel approaches employ a combination of chemo/antiretroviral therapy, hematopoietic stem cell transplantation, or inhibitors of NF kB activation.

2. INTRODUCTION

Adult T cell leukemia lymphoma (ATLL) is a post thymic lymphoproliferative disorder that predominates in areas of the world in which the virus is endemic including southern Japan, the Caribbean basin, and many parts of Africa. Smoldering ATLL accounts for approximately 5% of ATLL cases and is characterized by 1-5% abnormal peripheral blood lymphocytes and limited skin lesions but no lymphadenopathy, visceral involvement, or hypercalcemia (1, 2). The median survival is estimated at 5 yrs, and it occasionally progresses to more advanced forms of disease. Chronic ATLL accounts for about 15% of ATLL cases, has a median survival of 2 yrs, and can also progress to more advanced forms of ATLL. It is characterized by lymphocytosis (absolute lymphocyte count >4000/mm³), as well as skin, liver, lung, or lymph node involvement but an absence of hypercalcemia, central nervous system, or other visceral involvement. The lymphomatous form of ATLL accounts for 20% of ATLL cases and the median survival is 6 mo to 2 yr. It is a non-Hodgkin's lymphoma presenting with frequent

involvement of the blood and skin, lytic bone lesions, but hypercalcemia is rare (Figure 1). It results from clonal proliferation of mature, activated CD3+CD4+CD5+CD25+ T cells that do not express CD7 or CD8 (3). Acute ATLL accounts for 60% of ATLL cases, and includes a high number of circulating leukemia cells, hypercalcemia, lytic bone lesions, lymphadenopathy, visceral or leptomeningeal involvement, opportunistic infection, and has a median survival of 6 mos. Opportunistic infections may occur at any time during the course of ATLL, including bacterial sepsis, cytomegalovirus, candida, *Pneumocystis carinii*, and *Strongyloides stercoralis* infections.

In the Revised European/American Lymphoma (REAL) classification, ATLL is listed as a type of peripheral T-cell neoplasm. It presents at an advanced stage with hepatosplenomegaly and diffuse lymphadenopathy without mediastinal enlargement. The malignant cells are polymorphous, and range from small to intermediate to large cells, and have lobulated nuclei, characteristic of activated T cells, often assuming a flower-like shape. The malignant T cells have clonal rearrangements of the T cell receptor gene and clonal integrated human T-cell leukemia virus type 1 (HTLV-1) provirus.

3. PATHOGENESIS

ATLL is caused by HTLV-1, but occurs only in the subset of HTLV-1 infected individuals who acquired the virus as a result of breast feeding (4). It has been conjectured that this is a result of infection of a susceptible thymus-derived CD4+ precursor or to an impaired immune response to the virus. Nevertheless, the infection remains clinically latent for decades and only 3-10% of infected individuals develop ATLL.

HTLV-1 infection is required for the development of ATLL. It has been hypothesized that there is an initial stage of polyclonal infection due to virus replication

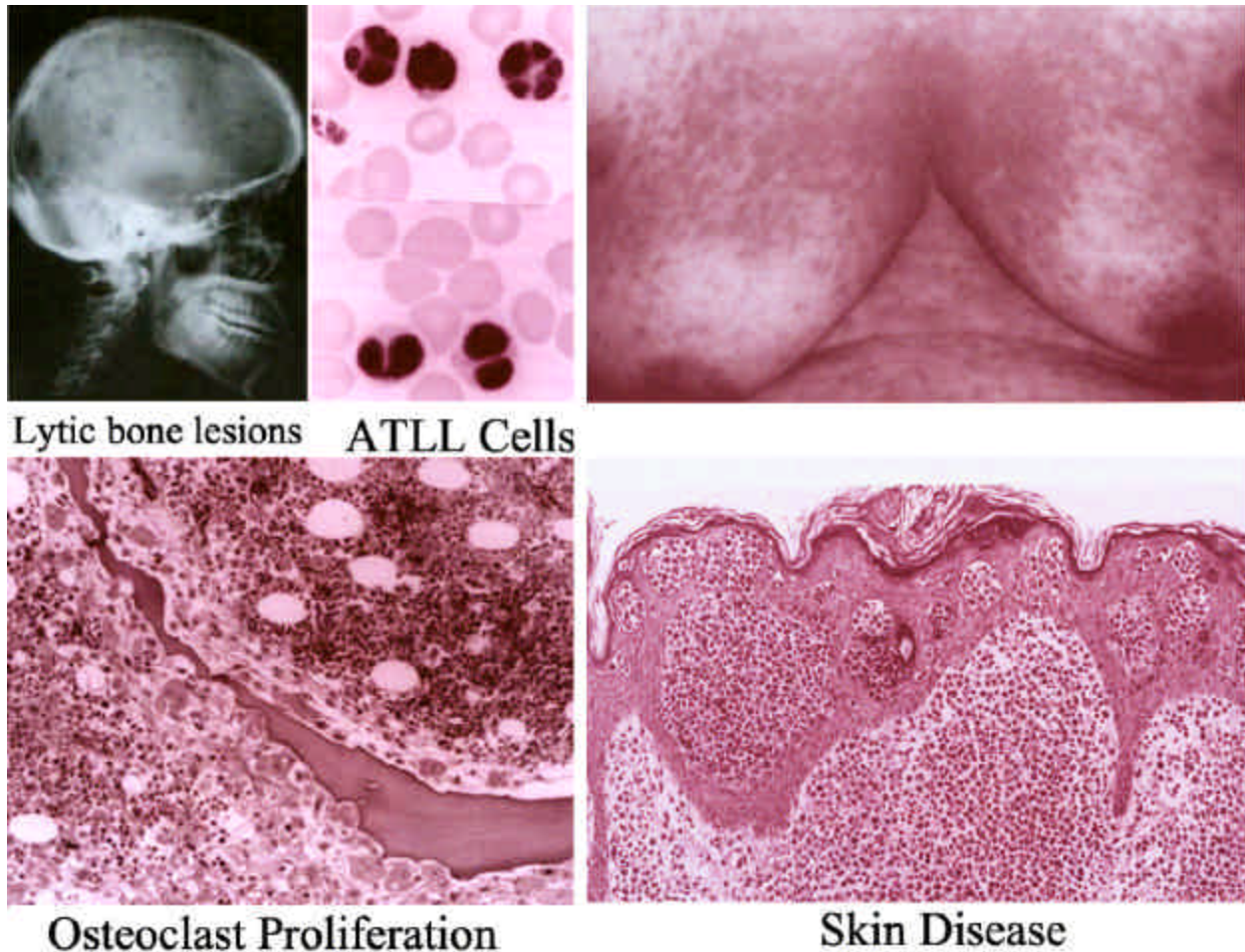


Figure 1. Clinical Manifestations of ATLL Modified with permission from (81).

and spread, and a subsequent stage of clonal expansion of infected cells (5). It appears that HTLV-1 replication is critical during the polyclonal infection stage, but not in the clonal expansion stage (6). It is unclear whether any virus gene expression is required during the latter stage, and whether secondary genetic events are irreversibly triggered.

The transcriptional activator (Tax) protein, is a multifunctional oncogenic protein that is pivotal in both of these processes (4, 7, 8). Tax is important for virus replication due to its ability to transcriptionally transactivate the viral promoter through activities mediated via the cyclic AMP response element binding(CREB)/activating transcription factor (ATF) family and their co-activators, CREB binding protein (CBP) and p300. Moreover, Tax also activates the transcription of cellular genes, via effects on the NF κ B family of proteins, and other pathways. This results in the induction of cell proliferation through cytokines such as IL2 and 15 and receptor subunits, as well as resistance to the induction of apoptosis (9, 10).

Tax is responsible for many of the cardinal manifestations of malignancy, including proliferation, growth factor independence, resistance to tumor

suppressors, genetic instability, angiogenesis, tumor dissemination, immune evasion, and chemotherapy resistance (5, 7). Tax induces lymphoproliferation and resistance to apoptosis through activation of NF κ B and anti-apoptotic proteins Bcl-XL, inhibitor of apoptosis (IAP), Fas-associated death domain-like interleukin (IL)-1 β -converting enzyme-inhibitory protein (FLIP), survivin, and chemokine I-309, and transcriptional activation of other cell cycle regulatory proteins such as E2F expression through CREB/ATF and Jun and early growth factor response gene expression through the serum response factor (11-13). Tax causes transcriptional repression of repair enzyme DNA polymerase β , tumor suppressors alternative reading frame protein (ARF) and p53, cell cycle inhibitor p18 INK4C, signaling kinase Lck, and pro-apoptotic protein Bax and post-transcriptional effects through direct binding of cell cycle inhibitor p16 INK4A, cyclin D3, cyclin dependent kinase 4, and phosphorylation, stabilization, and functional inactivation of p53 (14-16). Tax induces genetic instability due to defects in DNA repair and cell cycle checkpoint proteins such as proliferating cell nuclear antigen (PCNA) and mitotic arrest defect-1 (MAD-1) protein which also results in resistance to microtubule inhibitors (17, 18). Tax induces angiogenesis by activating the expression of matrix metalloproteinase 9 and vascular endothelial growth factor

(19-21). Tax blocks tumors suppressor responses by inhibiting transforming growth factor beta (TGFbeta) signaling (22). Tax promotes tumor invasion into bone by inducing expression of receptor activator of NF kB ligand (RANKL) and macrophage colony-stimulating factor as well as osteoclast activation and hypercalcemia by inducing expression of IL1, parathyroid-related protein and TGFbeta (23-25)

Other viral gene products are involved in virus replication and regulation of latency, but it is unclear whether they have a specific role in lymphoid proliferation and immortalization (26). Several of these events can be modeled in tissue culture and in animal models. For example, HTLV-1 infection of PBMCs or Tax expression from retrovirus or gamma herpes virus vectors results in immortalized CD4+ cell lines. Moreover, Tax expression in Rat-1 fibroblasts results in transformation. In addition, Tax expression in transgenic mice results in a variety of malignancies as well as leukemia-lymphoma (27).

4. DIAGNOSIS, STAGING, AND PROGNOSTIC MARKERS

The diagnosis of ATLL is generally considered to require HTLV-1 infection, a CD4+CD25+ lymphoid proliferation, and the pathological trademarks of lymphoma or leukemia. Currently, serological assays are the most rapid means for diagnosis of HTLV infection and differentiating HTLV-1 from -2 (28). Advances in HTLV diagnosis in the future, as well as those for other viruses, may involve use of gene chips to detect specific viral sequences (29).

ATLL is subdivided into smoldering, chronic, and acute forms (1). Acute forms are further subdivided into leukemic and lymphomatous subtypes. It is likely that these variant clinical manifestations are different manifestations or stages of the same disease process.

Age, serum level of lactate dehydrogenase (LDH), hypercalcemia, and performance status have been reported as prognostic factors (30). In addition, expression of drug resistance protein, lung-resistance related protein (LRP) has also been associated with poor prognosis (31). Proviral load may also serve as a measure of tumor burden (32-36)

Several groups have initiated gene expression studies to identify new prognostic markers for ATLL, and critical mediators of transformation. In studies of HTLV-1 infected cells in culture cell cycle regulated kinases and DNA repair genes were found to be over expressed (37). In studies of HTLV-1 transformed cells, deregulation of genes involved in control of apoptosis were found (38), whereas studies of Tax expressing cell lines showed differential expression of gene associated with apoptosis, cell cycle regulation, DNA repair, signaling, immune modulators, cytokines and growth factors, and adhesion molecules (39). In a study of mRNAs in peripheral blood mononuclear cells of ATLL patients, T-cell differentiation antigen, MAL, lymphoid-specific G-protein coupled receptor CCR7, and a

subunit of the ubiquinone oxidoreductase complex were up regulated in acute versus chronic ATLL, whereas fibrinogen-like protein hPT49 was down regulated in acute compared to chronic ATLL (40).

5. CHEMOTHERAPY

Over the last 25 yrs, improved combination chemotherapy regimens and supportive care have improved median survivals to about 12 months, but long-term survival is quite rare (41, 42). Complete remission rates in lymphomatous ATLL were significantly better than the leukemic variant. In a recently published clinical trial of combination chemotherapy in 93 eligible patients, the response rate was 81% with 35% complete remissions, median survival time of 13 months, and 31% 2 yr survival (43). Deoxycoformycin was identified as an active agent, whereas other agents whose activity was limited by toxicity included chlorodeoxyadenosine, etoposide, and carboplatin (44). High levels of multidrug resistant (MDR) gene expression on ATLL cells suggest that MDR inhibitors may be required to enhance the activity of chemotherapeutic agents for ATLL (45).

6. ANTIVIRAL THERAPY

Promising results with the use of zidovudine and interferon alpha were reported in 1995 by an American group and a French group (46, 47). However, lower response rates were described in a cohort treated at the National Institutes of Health, as well as cohorts treated in Great Britain, France, and Japan (48-51). There is general agreement that relapses occur in the majority of individuals after discontinuation of therapy. The mechanism of activity of this combination remains unclear. This regimen may be functioning through antiviral mechanisms on virus replication in a small proportion of tumor cells or non-malignant supporting cells, antiproliferative effects such as those described for interferon alpha, induction of apoptosis of malignant cells, and/or immunomodulatory effects (52, 53). HTLV replication is quite sensitive to interferon alpha, as a result of inhibition of virus assembly at the level of Gag targeting to lipid microdomains in the plasma membrane, known as rafts (54). In contrast to the results with chemotherapy, activity of this combination appears to be greater with leukemic variants than lymphomatous ATLL. It remains unclear whether other nucleoside analogues with greater activity for HTLV-1 RT can substitute for that of zidovudine, such as tenofovir (55). The activity towards ATLL of long-lasting and potentially more active pegylated interferon remains to be examined. It is also unclear whether this combination therapy should be combined with chemotherapy. If the combination is to be employed, it is unlikely that interferon and chemotherapy can be given simultaneously, due to myelosuppression, and thus, the sequencing of therapies is also unclear. Lamivudine has also been reported to have activity in HTLV-associated myelopathy patients, despite the finding that HTLV-1 RT is relatively insensitive to this nucleoside analogue (55-58). Non-nucleoside analogues and protease inhibitors, active against HIV-1, are inactive at inhibiting HTLV replication.

Table 1. Phase II Trial of Induction Therapy with EPOCH Chemotherapy and Maintenance Therapy with combivir/Interferon Alpha-2a for HTLV-1 Associated T-cell non-Hodgkin's Lymphoma

EPOCH chemotherapy
Etoposide 50 mg/m ² /day given as a continuous 96 hr IV infusion on days 1-5.
Vincristine 0.4 mg/m ² /day given as a continuous 96 hrs IV infusion on days 1-5, maximal dose 2 mg. Doxorubicin 10 mg/m ² /day given as a continuous 96 hrs IV infusion on days 1-5. Cyclophosphamide 750 mg/m ² given IV on day 5 over 30 minutes.
Prednisone 60mg/m ² given orally on days 1-5.
Cycles are repeated every 21-28 days, for two cycles beyond best response, and a maximum of 6 cycles. "Best response" is the response achieved when 1 or more additional cycles of chemotherapy are given and no additional tumor shrinkage is noted. That may include stable or progressive disease after 2 cycles chemotherapy.
All patients will receive G-CSF at a dose of 5ug/kg subcutaneously daily beginning 24 hours after the administration of prednisone for 10 days beginning on day 6 or until the absolute neutrophil count has recovered to >4,000 cell/mm ³
<u>Antiretroviral therapy:</u> Antiviral therapy for one year will begin one month after completion of EPOCH: Combivir (zidovudine 300 mg + lamivudine 150 mg) 1 tablet po bid. Interferon Alpha-2a 9 mU SQ qd.

7. CHEMO/ANTIRETROVIRAL COMBINATION THERAPY

A clinical trial has been started in the U.S. to investigate the combination of chemotherapy with antiviral therapy given sequentially. The chemotherapy regimen employs 2-6 cycles of an infusional chemotherapy regimen, EPOCH, consisting of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (Table 1). This regimen has shown excellent activity in relapsed lymphomas and in HIV-associated lymphomas (59, 60). After achieving maximal response, antiretroviral therapy is employed for up to 1 yr with zidovudine, lamivudine, and interferon. The primary objective of this trial is to determine if this regimen is effective and well tolerated in ATLL. Secondary objectives are to assess prognostic markers including HTLV-1 RNA and DNA load, Tax protein levels, HTLV-1 clonality, p53 levels and phosphorylation, HTLV-1 phenotypic and genotypic sensitivity to the antivirals,

8. ANTIBODIES

Radiolabeled antibodies directed against CD25, the alpha subunit of the IL2 receptor have led to promising results (61-63). In a study of 18 patients with ATLL Yttrium 90-labeled anti-Tac antibody, directed against the IL2 receptor alpha subunit, was administered in doses of 5-15 mCi, resulting in 7 partial and 2 complete remission (64). Significant toxicity was primarily to the hematopoietic system. Anecdotal reports of the use of other antibodies, such as anti-CD52 antibody (alemtuzumab, Campath) have also been described (65). Anti-CD2 antibody has shown activity in a severe combined immunodeficiency disease (SCID) mouse model of ATLL (66). In contrast, denileukin difitox (Ontak), an IL2-diphtheria toxin fusion protein has not shown significant activity in ATLL (O. Hermine, personal communication). Clinical trials of antibodies to the IL15 receptor have not been reported.

9. STEM CELL TRANSPLANTATION

Trials with autologous bone marrow or stem cell transplants for ATLL have been largely unsuccessful. In one study, 10 patients received allogeneic stem cell

transplants with mild if any immediate toxicity and engraftment in all cases (67). Median leukemia-free survival was more than 17 months, with 6 of 10 patients developing acute graft versus host disease (GVHD), and 3 patients developing extensive chronic GVHD. Four patients died of acute GVHD, pneumonitis, gastrointestinal bleeding, or renal insufficiency, and 2 patients relapsed with acute ATLL. Nevertheless, preliminary intriguing results with allogeneic transplants have been described, although toxicity remained problematic (68, 69). One study of allogeneic hematopoietic stem cell transplantation in 11 patients with ATLL included 6 patients with acute ATLL, 4 cases of lymphomatous ATLL, and 1 subject with chronic type ATLL (70). Five patients developed acute GVHD, and 3 developed chronic GVHD. All 10 patients who survived more than 30 d achieved complete remission, and estimated 1 yr disease-free survival rates were 45%. Four patients were reported to be alive and disease-free at a median follow-up of 25 mos, whereas the others died of transplant-related complications. It remains unclear whether there is an advantage to the use of seropositive donors. In one study presented at the 11th International Conference on Human Retrovirology, HTLV-1-specific CTL responses in ATL patients were found to be reactivated after non-myeloablative hematopoietic stem cell transplantation (71, 72). Effects of high dose chemotherapy and stem cell transplantation on virus load and HTLV reservoirs remain to be examined. Similar trials are underway in studies of patients with HIV-associated lymphoma.

10. OTHER APPROACHES

Arsenic has been employed as a therapy in acute promyelocytic leukemia. Arsenic downregulates Tax expression in culture by destabilizing the protein (73-75). The effects are enhanced by interferon, perhaps through the effect of PML, an interferon inducible protein. A clinical phase II study is currently being performed in France.

Tax up regulation of the nuclear factor kappa B (NF kB) pathway appears to be critically important in ATLL proliferation and resistance to apoptosis (76, 77). An inhibitor of NF kB activation, Bay 11-7082 induced apoptosis of primary ATLL cells (11). A proteasome inhibitor, PS-341 (bortezomib, velcade) blocked I kB degradation, NF kB activation, and inhibited proliferation

and induced apoptosis of Tax transgenic tumor cells in culture and in mice (78). Both agents have activity against ATLL cells in SCID mouse models. (79, 80)

11. PERSPECTIVE

Advances in rapid and specific diagnosis of HTLV, and improvements in combination chemotherapy and supportive care have led to incremental advances in the treatment of ATLL. Incorporation of interferon alpha and antiretroviral nucleoside analogs, antibody conjugates directed against interleukin receptors, high dose chemotherapy coupled with stem cell transplantation, and inhibitors of NF kB activation remain promising approaches to combine with chemotherapy programs. Other targeted therapies can now be evaluated in animal models, especially SCID and transgenic models of ATLL. Translational research studies of provirus load and clonality, virus and cell gene expression, virus mutations and treatment-resistance, and alterations in apoptosis, genetic stability, lymphoid proliferation dynamics, and parameters of tumor invasiveness, angiogenesis, and dissemination will identify critical determinants of response.

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