Survivin(g) Adult T-cell Leukemia/Lymphoma

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In this issue of ONCOLOGY, Tobinai reviews the management of human T-cell lymphotropic virus type 1 (HTLV-1)–associated adult T-cell leukemia/lymphoma (ATL). Although rare in the United States, an estimated 10 to 20 million people are infected with HTLV-1 worldwide and 2% to 5% will develop ATL.[1]

In this issue of ONCOLOGY, Tobinai reviews the management of human T-cell lymphotropic virus type 1 (HTLV-1)–associated adult T-cell leukemia/lymphoma (ATL). Although rare in the United States, an estimated 10 to 20 million people are infected with HTLV-1 worldwide and 2% to 5% will develop ATL.[1] The prevalence of HTLV-1 infection and the consequent poor prognosis of ATL mark the disease as a public health issue in many countries. Prevention of transmission will ultimately eliminate disease associated with HTLV-1 infection.

The knowledge that HTLV-1 is often transmitted early in life through breast-feeding led to prenatal screening programs in Japan. Substitution of infant formula for breast milk from seropositive mothers has been successful in reducing the rate of transmission from 20% to 3%.[2] This approach is often not practical in poor countries that lack funds for screening and the purchase and distribution of commercial infant formula. Other approaches such as using HTLV-1–negative “wet nurses” to breast-feed infants of infected mothers may offer affordable alternatives. Blood donor screening has shown near-uniform effectiveness in removing blood transfusion as a source of HTLV-1.

Slow Progress in New Therapies

To date, there are no demonstrated effective antiviral therapies for HTLV-1. The role of antiretroviral drugs in the prevention of clinical disease is unknown and is not likely to be studied due to the requirements for a large patient cohort, long follow-up times, lack of surrogate disease markers, and lack of funding. HTLV-1 vaccination may eventually play a role in preventing viral transmission and ultimately ATL, but no successful vaccine has yet been developed. Currently, we are unable to detect individuals at high risk for developing ATL, and there is little understanding of the factors that lead to ATL in an HTLV-1–infected individual, although there appears to be some genetic predisposition. In some infected families, multiple members have developed ATL. Investigators have found a weak association with HLA subtype.[3] Genome-wide association studies may provide insights into these factors.

Progress in developing new therapies for ATL has been slow due to its relative infrequency, its differing clinical phenotypes and the variability of outcome within these subtypes, and a lack of a consensus on optimal treatment. A meta-analysis of the combination of zidovudine (azidothymidine) and interferon-alpha for the treatment of ATL was provocative and suggested that this combination should be further evaluated for therapy of the acute and chronic forms of ATL.[4] The lymphoma subtype is not responsive to this drug combination, and standard chemotherapy remains the mainstay of treatment. This combination is most effective as initial therapy but relatively ineffective after prior treatment, likely due to the acquisition of p53 mutations in the tumor cells.[5] In our limited experience, this approach was not promising. Poor tolerance and its use as second-line therapy may have been responsible. A major drawback to this combination is toxicity associated with long-term therapy.

The Japanese Lymphoma Study Group has performed admirably in moving the research forward through a series of historically controlled clinical trials and recently completed a randomized phase III study.[6] As summarized, the investigators randomized patients to the eight-drug LSG15 regimen (VCAP-AMP-VECP, consisting of vincristine, cyclophosphamide, doxorubicin, prednisone, ranimustine, vindesine, etoposide, and carboplatin) or to biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). A significantly higher response was seen in the LSG15 group (40% vs 25%), but 1-year progression-free survival (28% vs 16%) and overall survival at 3 years (24% vs 13%) were not significantly different. Importantly, many surviving patients still had evidence of
disease. In addition, these results are difficult to interpret because of the mixture of the acute, lymphoma, and aggressive chronic disease subtypes that were included, the different durations of the treatments (24 weeks for LSG15 and 16 weeks for CHOP), and an imbalance in prognostic features between the treatment groups. Over the past 25 years, the National Cancer Institute has evaluated and treated over 200 patients with ATL. Although a variety of novel approaches have yielded responses, with rare exceptions, the disease inevitably recurs.

**Other Treatment Options**

Outside of a clinical trial, until more effective therapies are developed, patients with the acute and lymphoma subtypes of ATL should be considered for allogeneic stem cell transplantation (ASCT) at initial diagnosis. The patient and family members should undergo HLA typing, and ASCT should be employed at first remission. The availability of alternative stem cell sources including a matched-unrelated donor, umbilical cord blood transplants, and reduced-intensity conditioning regimens now make this an option for an increasing number of patients. In the LSG15 trial, 14 patients underwent ASCT, but half had progressive disease before ASCT was initiated, emphasizing the necessity for advance planning.[6] For this approach to be successful, it is important that patients achieve a period of disease control that lasts for 3 to 4 months. This provides time for the graft to achieve immunologic maturity and develop a graft-vs-leukemia/lymphoma effect. The LSG15 regimen may allow for longer response durations, permitting the patient to go to transplant and providing a rationale for adoption of this approach.

The introduction of monoclonal antibodies particularly in combination with chemotherapy has been one of the major advances in the past decade and has significantly improved the outcome of patients with lymphoma and other cancers. T cells express a rich array of receptors, and a number of monoclonal antibodies targeting these molecules are in clinical trials.[7] We and others have evaluated antibodies directed at CD25, CD2, and CD52 alone and in combination with chemotherapy, with some success. Additional trials will be required to clarify the roles of antibodies.

**Molecular Mechanisms**

Gene-expression profiling has been used to characterize ATL cells in the peripheral blood and has demonstrated pathways that may lead to malignant transformation of infected T cells.[8,9] A major oncogenic pathway appears to result from the increased expression of the transcription factor TCF4 and beta-catenin, which in turn drive the expression of the antiapoptotic protein BIRC5 (survivin). TCF4 downregulation in vitro by RNA interference resulted in decreased TCF4 and survivin RNA levels and was associated with a decrease in ATL cell viability. Downregulation of survivin RNA alone also decreased cell viability. Survivin is a member of the family of proteins that suppress apoptosis. It can be induced by various stimuli and exists in the cytoplasm and in the nuclei of both tumor and normal proliferating cells. In addition to its role as an apoptosis inhibitor, survivin acts as a subunit of the chromosomal passenger complex that corrects attachment errors between chromosomes and the mitotic spindle, regulates the quality-control checkpoint, and ensures the correct completion of cytokinesis. Survivin is expressed in many tumors and has been correlated with resistance to therapy-induced apoptosis. Elevated survivin mRNA levels inversely correlated with survival in ATL patients; higher expression was associated with a worse prognosis.[10] Pharmaceutical companies have identified survivin as a therapeutic target, and several approaches to inhibit its action are being evaluated.[11] However, it may be necessary to simultaneously deliver an apoptotic signal in conjunction with survivin inhibition for this approach to be successful.

**Recommendations**

Due to the low incidence of ATL in many developed countries and the limited resources available in regions where HTLV-1 infection and ATL are more common, investigators and public health agencies will need to take advantage of international collaborations to define treatment standards for ATL. Care should be taken distinguishing between the subtypes of ATL because of their differing prognoses and responses to therapy. Choices of therapy should be driven by biologic studies that define targets and markers that signal benefit from a particular therapeutic approach. The ability to sequence the genome of the cancer cell may soon be economically feasible and will help define the specific mutations associated with this malignancy to help generate individualized therapy. The ease of obtaining tumor cells from leukemic patients provides an opportunity to better understand ATL.
and improve outcome in the disease.

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