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CLINICAL VIGNETTE

Possibly Improving Treatment Options for a Rare Disease: A Case of Adult T Cell Leukemia (ATL)

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Adult T Cell Leukemia (ATL) is an unusual T cell malignancy with a wide spectrum of clinical presentations. ATL is caused by Human T Cell Leukemia Virus type 1 (HTLV 1) infection. HTLV 1 is a retrovirus, or RNA virus, that replicates by reverse transcribing the RNA genome into double stranded DNA, which integrates randomly into the infected cell genome. HTLV 1 infection is endemic in southern Japan and the Caribbean. Infection can rarely result in a disease, either a multiple sclerosis like partial paraplegia, known as tropical spastic paraparesis (TSP), or ATL.[1]

When ATL develops, the condition ranges from low grade with multi-year survival to acute with survival median of months. Smoldering ATL is characterized by skin rashes with less than 5% of circulating peripheral blood mononuclear cells (PBMCs) being ATL cells and median survival over 5 years. Chronic ATL generally has skin involvement and adenopathy with elevated white blood counts (WBCs) due to circulating ATL cells with median survival of significantly under 5 years. Lymphomatous ATL has extensive adenopathy and liver and spleen involvement with median survival of 2-3 years. Acute ATL presents as an acute leukemia with cytopenia, bone lesions, and hypercalcemia and median survival of less than one year.[1]

Many different chemotherapy regimens and anti-retroviral therapies have been used to treat ATL, particularly the acute and lymphomatous presentations. Most studies have been done in Japan, which has the largest population of patients. The mixed anti-viral and anti-neoplastic regimen, zidovudine (AZT) and alpha interferon (IFN), had significant clinical activity in early studies and improved overall survival (OS) in a large meta-analysis.[2] However in acute ATL, the overall results remain poor, even with multi-agent chemotherapy followed by autologous stem cell transplant.

This case describes a woman diagnosed with chronic ATL at age 71 who received AZT and IFN and then a series of newer therapies for peripheral T cell lymphomas. She achieved a clinical near complete remission on therapy and has been off all treatment for over 2 ½ years without symptoms and without imaging or blood test evidence of progression.

She presented with a pruritic popular rash on her torso approximately 2 months after an episode of shingles on her left neck. She was referred to dermatology and multiple punch biopsies were performed, which showed an abnormal lymphoid infiltrate with CD 3 and CD 4 positive but aberrantly CD 7 and bcl-2 negative T cells. T cell receptor (TCR) gene rearrangement studies were positive for a clonally rearranged TCR. A PET/ CT demonstrated PET + and mildly enlarged axillary, right internal mammary and pericecal adenopathy. A bone marrow biopsy revealed 10% abnormal CD 3 + cells and peripheral blood flow cytometry revealed a mild lymphocytosis with 93% abnormal circulating cells with lobulated nuclei. The patient was then discovered to be HTLV 1 +, supporting the diagnosis of ATLL and HIV negative. On further questioning, she disclosed that her ex-husband had had frequent extramarital affairs. He never agreed to be tested for HTLV.

She was suffering from intense pruritis requiring at least 20 mg of prednisone daily and had lost 14 lbs. over the prior 2 months. She was started on treatment with zidovudine (AZT), a reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus (HIV), and alpha-interferon (IFN),[2] which represent both anti-cancer and anti-viral medications. The AZT and IFN regimen caused fatigue and mild pancytopenia and some improvement in her rash. After several months with a persistent requirement for prednisone for the rash, she was switched to denileukin diftitox (ONTAK),[3] an anti-CD 25/interleukin 2 receptor antibody linked to a diphtheria toxin protein synthesis inhibitor. She received ONTAK for over one year with resolution of the rash and improvement of PET findings, but she experienced increasing fatigue and fluid retention despite diuretics and dose modification. She was then switched to pralatrexate (FOLOTYN),[4] a new anti-metabolite type of chemotherapy targeting the folate cycle DNA synthesis pathway. She received FOLOTYN for 10 months before progressive mucositis and fatigue prompted switching therapy again. She then received romidepsin (ISTODAX),[5] a histone deacetylase inhibitors (HDACs), which are thought to induce cell cycle arrest by altering acetyl group patterns on histones and transcription factors. She received ISTODAX for approximately one year with normalization of the PET scan and blood tests and the persistent absence of a rash. She had progressive fatigue despite dose modification and decided to stop therapy and follow her disease clinically. She has been off all ATL therapy for over 2 ½ years and remains in a clinical complete remission with occasional PET scan and blood test follow-up. She is alive and free of clinically

evident disease for over 6 years, substantially better survival and markedly better disease control than is reported in the literature.

ATL is a rare virus-associated malignancy with a variable natural history. Past studies, performed primarily in Japan, have shown only modest effectiveness of anti-ATL therapy but with some overall survival improvement. T cell lymphomas tend to be less responsive to chemotherapy and have overall poorer outcomes than with their much more common B cell lymphoma counterparts. This difference in clinical outcome may be shifting with the development of multiple new therapies, particularly targeted therapies like the denileukin diftitox and romidepsin described above. In addition, the older regimen of AZT and IFN suggest possible efficacy of targeting the transforming virus, HTLV 1, even though it is thought to be no longer actively replicating. Continued research on ATL and HTLV 1 will likely shed further light on targeted therapies and potentially anti-viral therapies for T cell and transforming virus associated malignancies

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