Complete Remission in Two Cases of Adult T-Cell Leukemia/Lymphoma Treated With Hyper-CVAD: A Case Report and Review of the Literature

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Abstract

Background: Acute T-cell leukemia/lymphoma (ATLL) is a post thymic (peripheral) T-cell neoplasm caused by human T-cell lymphotropic virus type 1 (HTLV-1). Historically, the chemotherapy regimen CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) has been the standard treatment of this rare malignancy. However, its prognosis is poor and median survival in the aggressive variants of ATLL is only 6-10 months. Recently, a more aggressive regimen piloted in Japan, vincristine/cyclophosphamide/doxorubicin/prednisone (VCAP)- doxorubicin/ranimustine/prednisone (AMP)- vindesine/etoposide/carboplatin/prednisone (VECP), has been reported to yield better survival results over biweekly CHOP in a phase III trial. However, the hyper- cyclophosphamide/vincristine/doxorubicin/dexamethasone (CVAD) regimen is a much more frequently used regimen for the treatment of aggressive hematologic malignancies, and has a higher intensity then CHOP. Yet, there is little reported experience with hyper-CVAD regimen in ATLL. **Case Reports:** We present 2 patients diagnosed with ATLL who were treated with hyper-CVAD chemotherapy and have achieved a durable complete remission. One of the patients has gone on to receive an allogeneic bone marrow transplantation and has been in complete remission for over 18 months. The other has been in a continuous remission for approximately 12 months. We also review the past published experience with the hyper-CVAD regimen in patients with ATLL. **Conclusion:** A commonly used chemotherapy regimen for aggressive hematologic malignancies, hyper-CVAD, can induce durable remissions in patients with ATLL.

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Introduction

Acute T-cell leukemia/lymphoma (ATLL) is a malignant post thymic (peripheral) T-cell neoplasm caused by human T-cell lymphotropic virus type 1 (HTLV-1). Takatsuki and colleagues described the first ATLL cases in 1976. They reported a series of 16 patients who were born in the same region of Japan, suggesting that a transmissible agent may involved in the disease.[1-3] ATLL occurs predominately in adults, and is slightly more common in males (male:female ratio is 1.5:1).[4] The ATLL distribution is linked to the endemic areas of HTLV-1 such as southern Japan, the Caribbean, Melanesia, sub-Saharan Africa, and Central and South America.[5,6] There are 15-20 million people infected with HTLV-1 worldwide and the common modalities of transmission are sexually, vertically (mother-child), breast feeding, or parenteral (intravenous drug use or blood transfusion).[3,7-10] The seroprevalence in the United States and Europe is < 1%, and increases up to 20% in intravenous drug users.[2,11] The lifetime risk of developing ATLL is 5%, if infected with HTLV-1 before the age of 20 years.[6,9,10]

Acute T-cell leukemia/lymphoma may consist of an acute (60%), lymphomatous (20%), chronic (15%), or smoldering (5%) type of presentation.[4,12] Acute ATLL usually presents as a leukemic phase with an elevated leukocyte count, skin lesions, generalized lymphadenopathy, hypercalcemia in 70% of patients with or without lytic lesions, hepatosplenomegaly, elevated lactate dehydrogenase (LDH), and eosinophilia.[4]

The lymphomatous variant usually presents with marked lymphadenopathy but without peripheral blood involvement, a high LDH and skin involvement is usually present. Hypercalcemia is less common.[4,13]

The chronic variant frequently presents with exfoliative skin rash and less impressive peripheral blood findings. Finally, the smolder-

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ing variant usually has normal leukocyte counts and < 5% of circulating neoplastic cells, and there is no hypercalcemia.

The lymphomatous and acute variants have the worst prognosis, 10 months and 6 months, respectively. This is felt to be due to the multidrug resistance (MDR) phenotype of malignant cells, and its aggressive clinical features such as its rapid proliferation rate, large tumor burden, frequent associated multiorgan failure, hypercalcemia, and/or frequent infectious complications.[14]

The current chemotherapy approach for newly diagnosed acute, lymphomatous, and unfavorable chronic types of ATLL, as proposed at the International Consensus Meeting published in 2009, uses vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP). The VCAP-AMP-VECP regimen is superior to biweekly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) despite its higher toxicity.[14]

However, possibly because of its unfamiliarity and the fact that ranimustine is not available in the United States, VCAP-AMP-VECP is not a widely used anti-lymphoma regimen. In the United States and elsewhere, a commonly used intensive regimen for aggressive hematologic malignancies is hyper-CVAD. However, there is little published currently on the efficacy of this more intensive regimen in patients with ATLL.[7] In this paper, we report 2 patients with ATLL who were treated with the hyper-CVAD regimen. Both patients obtained a rapid complete and durable remission. We also review the past published experience with the hyper-CVAD regimen in patients with ATLL.

Case Reports

Patient 1

Patient 1 is a 60-year-old male of Caribbean descent with a past medical history remarkable for mild coronary artery disease, hyperlipidemia, hypertension, chronic onychomycosis, benign prostatic hypertrophy, and gastroesophageal reflux who presented with fevers, night sweats, fatigue, and anorexia. His white blood cell count (WBC) was 91.1 × 10^9/L (normal range: 3.5-11.0 × 10^9/L), with 83% lymphocytes. His hemoglobin was 14.3 g/dL (normal range: 13.5-16 g/dL) and platelet count was 154 × 10^9/L (normal range: 150-400 × 10^9/L). Physical examination showed multiple bilateral palpable small neck lymph nodes and hepatosplenomegaly. The remainder of the laboratory values were significant for elevated transaminases, aspartate aminotransferase (AST), 160 IU/L (normal range: 10-42 IU/L); alanine aminotransferase (ALT), 245 IU/L (normal range: 6-45 IU/L); LDH, 574 IU/L (normal range: 50-175 IU/L); alkaline phosphatase, 323 IU/L (normal range: 40-130 IU/L); total bilirubin, 2.8 mg/dL (normal range: 0.2-1.3 mg/dL); direct bilirubin, 1.8 mg/dL (normal range: 0.0-0.3 mg/dL); and calcium, 15.5 mg/dL (normal range: 8.5-10.5 mg/dL). A contrast-enhanced computed tomography (CT) scan showed a markedly enlarged liver consistent with diffuse involvement with leukemia with small mesenteric lymphadenopathy. A subset of the lymphoid cells examined in peripheral blood had markedly lobulated "flower-like" nuclei. On the bone marrow examination, approximately 25%-35% neoplastic lymphoid cells with a similar morphology were identified. There was prominent osteoclastic activity noted. Flow cytometry immunophenotypic analysis of peripheral blood, identified a predominant (95%) population of $CD2^+$, surface CD3–, cytoplasmic $CD3^+$, $CD5^+$ T-lymphoid cells that were CD7–, $CD4^+$, $CD25^+$, had partial expression of HLA-DR and CD56, and minimal expression of CD30. They were negative for CD34, CD8, CD16, and CD57. Molecular studies detected T-cell receptor *B* gene rearrangements in both peripheral blood and bone marrow. The presence of HTLV-1 was confirmed by polymerase chain reaction. Cytogenetics performed on the bone marrow aspirate showed a complex karyotype: 48XY,t(1;3)(q31;24),+3,+3, add(8)(q11.1),–10, del(13)(q12q22), del(16)(q22), +mar[10]/46,XY[11]. On hospital day 4, the patient's total bilirubin rose to 4.4 mg/dL and he was treated urgently with CHOP chemotherapy at standard doses for 1 cycle before his formal diagnosis. By day 21, his WBC responded only minimally with decrease to 27 × 10^9/L with 72% abnormal lymphocytes. He had persistence of his hepatomegaly. His treatment course was complicated by difficult-to-control hypercalcemia during the first 21 days of his treatment, requiring multiple doses of intravenous pamidronate and aggressive diuresis. After the diagnosis of acute ATLL was determined, the patient's treatment was changed to the hyper-cyclophosphamide/vincristine/doxorubicin/dexamethasone (CVAD) regimen starting on cycle 2 with prophylactic valacyclovir, trimethoprim-sulfamethoxazole, and fluconazole. Within 10 days of his initial cycle of hyper-CVAD, his WBC and lymphocyte number normalized and his calcium level normalized. His hepatomegaly resolved as well. His course was also remarkable for a decrease in his ejection fraction to 37% with a clinical episode of congestive heart failure. It was felt that this was because of a coronary artery event and not doxorubicin related. He also developed a persistent mild renal insufficiency, creatinine level 1.34-1.80 mg/dL (0.4-1.3 mg/dL). As a consequence of these complications, his treatment regimen was shortened to 6 cycles (he received 3 cycles of hyper-CVAD part A and 3 cycles of hyper-CVAD part B) instead of 8 total planned cycles. The patient achieved a complete clinical remission with this regimen. He then underwent allogeneic hematopoietic stem cell transplantation (allo-SCT) from his matched brother and remains in clinical remission over 18 months after diagnosis.

Patient 2

Patient 2 is a 59-year-old Caribbean woman with a medical history remarkable for total abdominal hysterectomy with bilateral oophorectomy for cervical cancer, hypertension, and hypercholesterolemia, who presented with a history of 2 months of intermittent abdominal pain. Physical examination showed a palpable midepigastric abdominal mass, but no hepatosplenomegaly or peripheral lymphadenopathy. Laboratory studies were remarkable for a normal creatinine and blood counts. Liver function tests including AST, alkaline phosphatase, and total bilirubin were normal with the exception of the ALT which was 58 IU/L. Lactate dehydrogenase was 616 IU/L. Abdominal CT scans revealed extensive retroperitoneal lymphadenopathy predominantly in the superior aspect of the retroperitoneum, between the aorta and infrahepatic inferior vena cava. A retroperitoneal lymph node biopsy showed a monotonous infiltrate of medium-to-large-sized lymphoid cells with angulated nuclei, finely granular chromatin, and inconspicuous nucleoli. By flow cytometry, the neoplastic