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 have been involved in the disease. ATLL occurs predominantly in adults, and is slightly more common in males (male:female ratio is 1.5:1). 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.

**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 than 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.

**Keywords:** ATLL, HTLV-1, Allogeneic bone marrow transplantation

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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 have been involved in the disease. ATLL occurs predominantly in adults, and is slightly more common in males (male:female ratio is 1.5:1). 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.

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). The seroprevalence in the United States and Europe is < 1%, and increases up to 20% in intravenous drug users. The lifetime risk of developing ATLL is 5%, if infected with HTLV-1 before the age of 20 years.

Acute T-cell leukemia/lymphoma may consist of an acute (60%), lymphomatous (20%), chronic (15%), or smoldering (5%) type of presentation. 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.

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.

The chronic variant frequently presents with exfoliative skin rash and less impressive peripheral blood findings. Finally, the smolder-
Hyper-CVAD for Adult T-Cell Leukemia/Lymphoma

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, and increased urinary tract infections. He was noted to have bilateral hilar lymphadenopathy predominantly in the superior aspect of the 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 cells were CD3+, CD4+, CD5+, CD99+, and lacked CD7 expression and, by immunohistochemistry, the neoplastic cells were CD3+, CD4+, CD5+, and CD7–, 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)(q31.2;q24.1),+3,+3, del(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 × 10⁹/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 1.34–1.86 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. LDH was 616 IU/L. Abdominal CT scans revealed extensive retroperitoneal lymphadenopathy predominantly in the superior aspect of the retroperitoneum, between the aorta and infrarenal inferior vena cava. A retroperitoneal lymph node biopsy showed a mononuclear infiltrate of medium-to-large-sized lymphoid cells with angulated nuclei, finely granular chromatin, and inconspicuous nucleoli. By flow cytometry, the neoplastic cells were CD3+, CD4+, CD5+, and lacked CD7 expression and, by immunohistochemistry, the lesional cells were CD3+ and negative for CD34, TdT, CD99, CD1a, ALK-1, CD30, EMA, CD10, and CD21. The proliferation...
rate as highlighted with the MIB-1 antibody was nearly 95%. An initial EIA study was reactive for HTLV-I/II, and the presence of HTLV-I was confirmed by Western Blot. Molecular studies identified T-cell receptor B gene rearrangements in both the peripheral blood and lymph node biopsy. A diagnosis of lymphomatous ATLL was made. The patient’s bone marrow was only minimally involved by the neoplastic process. The patient was in intense abdominal pain secondary to her tumor; hence, she was treated with 1 cycle of CHOP chemotherapy before a formal diagnosis. Her abdominal pain persisted for the following 3 weeks. After the diagnosis of ATLL was made, the treatment was then revised, and the hyper-CVAD regimen was begun on day 21. Trophoblastic medications, valacyclovir, trimethoprim-sulfamethoxazole, and fluconazole accompanied the chemotherapy. After the initial cycle of hyper-CVAD her abdominal pain rapidly resolved. She underwent a total of 8 cycles of hyper-CVAD. Four doses of intrathecal methotrexate for central nervous system (CNS) prophylaxis were given. The patient had restaging studies after her fourth cycle and her abdominal pain persisted for the following 3 weeks. After the diagnosis of ATLL was made, the treatment was then revised, and the hyper-CVAD regimen was begun on day 21. Trophoblastic medications, valacyclovir, trimethoprim-sulfamethoxazole, and fluconazole accompanied the chemotherapy. After the initial cycle of hyper-CVAD her abdominal pain rapidly resolved. She underwent a total of 8 cycles of hyper-CVAD. Four doses of intrathecal methotrexate for central nervous system (CNS) prophylaxis were given. The patient had restaging studies after her fourth cycle and was in a complete remission. She remains in remission 12 months after her treatment.

**Discussion**

The therapeutic approach of aggressive ATLL is hampered by the increased risk for development of lethal opportunistic infections because of a profound T-cell immunodeficiency. Because HTLV-I preferably infects CD4+ T-cells,6,15,16 most patients have an associated immunodeficiency, and opportunistic infections such as bacterial sepsis, *Pneumocystis carinii*, disseminated herpes zoster, cryptococcal meningitis, *Candida sepsis*, cytomegalovirus, and *Strongyloides stercoralis* are common cause of morbidity and mortality.

Severe hypercalcemia also contributes to the morbidity in treating patients with ATLL. Hypercalcemia is most commonly seen in the acute subtype and is typically because of increased osteoclasts and accelerated bone resorption.12,16

However, most patients with ATLL will die of their disease. The VCAP-AMP-VECP regimen is superior to biweekly CHOP despite its higher toxicity with newly diagnosed acute, lymphomatous, and unfavorable chronic types of ATLL. In a phase III study, the rate of complete response (CR) was higher in the VCAP-AMP-VECP arm (40%) than in the biweekly CHOP arm (25%). The overall survival (OS) at 3 years was 24% in the VCAP-AMP-VECP arm and 13% in the CHOP arm.14 The proposed explanation for the improved CR and OS with the VCAP-AMP-VECP regimen is the incorporation of ranimustine and carboplatin, which are not affected by MDR-related genes. Also, it is a more complex chemotherapeutic drug combination of longer duration and higher intensity.

We report here 2 patients with aggressive ATLL who achieved a rapid complete and durable remission when treated with the hyper-CVAD regimen. Neither patient appeared to have had a brisk response to their initial CHOP chemotherapy.

Hyper-CVAD achieves similar dose intensity as VCAP-AMP-VECP but has not been formally studied in this disease. In fact, surprisingly there have only been limited reports of this regimen in ATLL. Table 1 summarizes the published experience with hyper-CVAD in ATLL.17-19 The number of patients is small and prolonged follow-up is absent. Furthermore, there may be a publication bias toward reporting only successful outcomes. However, based on this limited number of patients, this regimen may be effective as 4 of the 5 cases in which outcomes were reported documented CRs with the fifth case documenting a CR except for persistent hepatosplenomegaly of undetermined cause for 18 months.

Moreover, hyper-CVAD, which is used commonly in other high-grade hematologic malignancies such as Burkitt lymphoma, lymphoblastic lymphoma, and acute lymphoblastic leukemia, incorporates 2 therapeutic agents that have not been previously studied together in ATLL, high-dose cytarabine and high-dose methotrexate. Both of these agents are ideally suited for ATLL as they both have activity in the CNS (often a site of relapse in ATLL) and are active against other aggressive T-cell lymphomas.

With improvement in the CR rate seen with more intense chemotherapy regimens, allo-SCT has become an increasingly popular treatment option for young patients with aggressive ATLL. An estimated OS of 45% at 3 years has been recorded with this modality, likely attesting to a graft-versus-ATLL effect. In fact, the consensus report on ATLL has recommended consideration of allo-SCT for unfavorable prognostic suitable patients with chronic, acute and lymphomatous ATLL after an induction regimen.20 In light of this recent success with allo-SCT in patients with ATLL, obtaining a rapid durable CR is important in this aggressive malignancy before transplantation.

**Conclusion**

The present report adds to the body of literature suggesting a more intensive chemotherapy regimen other than CHOP is needed.

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**Table 1** Summary of the Published Experience With Hyper-CVAD and ATLL (Including Current Report)

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen, Number of Cycles</th>
<th>Response</th>
<th>Last Reported Outcome</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiVenuti, et al7</td>
<td>Hyper-CVAD, 4</td>
<td>CR</td>
<td>Remission at 1 year</td>
<td>Denileukin Diftitox maintenance used</td>
</tr>
<tr>
<td>Arat, et al7</td>
<td>Hyper-CVAD, NR</td>
<td>CR</td>
<td>Remission at 2 months</td>
<td>–</td>
</tr>
<tr>
<td>Michalis, et al18</td>
<td>Hyper-CVAD, 5</td>
<td>Near CR</td>
<td>Remission at 18 months</td>
<td>Maintenance interferon/acyclovir used</td>
</tr>
<tr>
<td>Petersen, et al9</td>
<td>Hyper-CVAD, 6</td>
<td>NR</td>
<td>Death from sepsis, 2 months after therapy</td>
<td>–</td>
</tr>
<tr>
<td>Current Report</td>
<td>Hyper-CVAD, 6</td>
<td>CR</td>
<td>Remission at 18 months</td>
<td>Allo-BMT used</td>
</tr>
<tr>
<td>Current Report</td>
<td>Hyper-CVAD, 8</td>
<td>CR</td>
<td>Remission at 12 months</td>
<td>–</td>
</tr>
</tbody>
</table>

*Resolution of bone marrow and circulating leukemia cells as well as lymphadenopathy and marked reduction in hepatosplenomegaly but not completely back to normal size.
Abbreviations: allo-BMT = allogeneic bone marrow transplantation; ATLL = Acute T-cell leukemia; CVAD = cyclophosphamide/vincristine/doxorubicin/dexamethasone; CR = complete response; NR = not reported*
to effectively treat ATLL. Furthermore, hyper-CVAD, a commonly used regimen for aggressive hematologic malignancies, may be a reasonable induction regimen.

Disclosures

References