



Lenalidomide in patients with Relapsed or Refractory HTLV-1 Related Adult T cell Leukemia/Lymphoma (ATLL)

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Abstract

Adult T-cell Leukemia/Lymphoma (ATLL) is resistant to chemotherapy and the acute and lymphomatous subtypes of disease have a dismal prognosis. There is no standard therapy for relapsed or refractory disease in Western countries and new agents are being explored. Lenalidomide is an immunomodulatory agent with promising activity in hematologic malignancies, including non-Hodgkin's lymphoma and represents a novel therapeutic option. We investigated the safety and efficacy of lenalidomide (25 mg once daily) on Days 1 to 21 of every 28-day cycle in a phase two study of patients with relapsed or refractory ATLL. The study was closed early due to limited patient accrual. Of 4 patients enrolled, no response was observed in two patients evaluable for response. No grade 3 or 4 toxicity was noted. In this small single institution experience, lenalidomide showed no clinical activity and manageable toxicity in two evaluable patients with relapsed or refractory ATLL. This experience highlights the need for collaborative studies of this rare disease and enrolling patients on clinical trials promptly.

Keywords

HTLV-1, ATLL, Non-Hodgkin's Lymphoma, Therapy

Case Presentation

Adult T-Cell Leukemia/Lymphoma (ATLL) is a rare and aggressive peripheral T-cell neoplasm caused by the Human T-cell Lymphotropic Virus Type-I (HTLV-I), a type C human retrovirus endemic in parts of Japan, sub-Saharan Africa, the Caribbean basin, as well as the United States where immigrants of endemic countries reside. Patients with the acute and lymphomatous subtypes of ATLL have a poor prognosis with a median survival of only 6 to 13 months despite aggressive chemotherapy [1,2]. There is no standard of care for relapsed or refractory disease in Western countries; however novel therapies are under investigation.

Lenalidomide is an immunomodulatory agent with demonstrated efficacy in several hematologic malignancies. Hypothesized mechanisms of action include immunomodulatory effects, direct cytotoxicity to tumor cells, enhanced natural killer and T-cell function and anti-angiogenic activity [3]. Lenalidomide is approved for myelodysplastic syndrome and multiple myeloma and has shown promising efficacy in chronic lymphocytic leukemia, non-Hodgkin's lymphoma and cutaneous T cell lymphoma [4]. A phase 2 study of lenalidomide in ATLL is ongoing in Japan [5]. We conducted a prospective study of lenalidomide in North American patients with relapsed or refractory ATLL. The study was closed early due to limited patient accrual, however we report the experience of the four enrolled patients.

For this phase II study, key inclusion criteria were age ≥ 18 years, a confirmed diagnosis of relapsed or refractory ATLL of the acute or lymphomatous subtype, Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 , and acceptable laboratory parameters. Women of childbearing potential required a negative serum or urine pregnancy test and agreed to commit to abstinence from heterosexual intercourse or to begin two acceptable methods of birth control. Men agreed not to father a child and to use a condom with partners of child-bearing potential even after successful vasectomy. Key exclusion criteria were any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent signing the informed consent form, known hypersensitivity to thalidomide, known positivity for HIV or infectious hepatitis, type B or C and recent deep venous thrombosis/pulmonary embolism requiring dose adjustments of anticoagulation within two months. The study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Columbia University.

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Table 1: Patient characteristics

Characteristics	N=4
Median age (range), years	54 (36-56)
Sex M/F	1:3
Ethnic origin	All Caribbean
Clinical subtype of ATLL	Acute 3 Lymphoma 1
Median ECOG performance status (range)	1 (0-2)
Median number of prior therapies (range)	4 (2-9)
Response	0/4

Eligible patients received oral lenalidomide (25 mg once daily) on Days 1 to 21 of every 28-day cycle. Treatment was continued until evidence of progressive disease, intolerable side effects, patient choice to withdraw, or death. The primary endpoint was overall response rate (ORR) as defined by the Japanese Clinical Oncology Group (JCOG) response criteria for ATLL [6]. Secondary endpoints were tumor control rate, duration of response, time to progression, progression-free survival, and safety.

The characteristics of the four patients who consented for the study between February 2011 and June 2013 are presented in Table 1. There were 3 women and 1 man with a median age at diagnosis of 54 years (range 36 to 56). All had emigrated from the Caribbean, three had the acute subtype of disease, one had the lymphomatous subtype of disease, and the median ECOG performance status was 1 (range 0-2). The median number of prior therapies was 4 (range 2 to 9). Of the 4 patients enrolled, one progressed before receiving therapy and the remaining three patients received lenalidomide for one day, 15 days and 21 days respectively. In the two patients evaluable for response after a 28 day cycle, no therapeutic response was observed. In addition, no grade 3 or 4 toxicity was observed, with the most common toxicities being grade 1 fatigue (3/4), and grade 1 thrombocytopenia (2/4). All patients ultimately expired of relapsed disease, with overall survival ranging from 7 to 62 months. The trial was closed early due to limited patient accrual.

In this small single institution experience, lenalidomide showed no clinical activity and manageable toxicity in two evaluable patients with relapsed or refractory ATLL. Two additional patients progressed shortly after enrolling in the study. It is challenging to interpret the lack of clinical activity observed as this was a highly refractory, heavily pretreated patient population and only two patients were evaluable for response; however, this experience highlights the need for collaborative studies of this rare disease and enrolling patients on clinical trials promptly.

Lenalidomide was selected for this study because preclinical and early clinical studies suggest that lenalidomide has anti-tumor activity against relapsed or refractory T-cell lymphomas, including ATLL, even though its mechanism is not well understood. ATLL derived cells secrete high levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF), induce endothelial tube formation in vitro and establish functional gap junction-mediated communication with endothelial cells suggesting a potential role for anti-angiogenesis [7]. Lenalidomide enhanced the cytotoxicity of HTLV-I positive cells without a direct anti-proliferative effect on those cell lines, an effect possibly mediated through CD56 positive cells stimulated by lenalidomide [8]. The antimyeloma activity of lenalidomide and pomalidomide has recently been attributed to Cereblon (CRBN), although further studies are necessary to elucidate the role it may have in other hematologic malignancies, including ATLL [9]. A tumor flare reaction following lenalidomide has been described in a number of hematologic malignancies and can easily be mistaken for disease progression. The pathophysiology of tumor flare is unclear although it is likely some form of immunomodulatory mechanism [10]. Future studies of ATLL patients on lenalidomide therapy for longer durations should take this into consideration.

The optimal therapeutic strategy for relapsed ATLL is unknown, primarily because it has been challenging to conduct prospective, randomized and multi-institutional trials. A low overall incidence and prevalence of ATLL combined with the aggressive nature of the disease, difficulty with response assessments because of complex presentations with leukemic, lymphomatous and skin compartments, and the immunocompromised nature of patients who frequently have multi-organ system dysfunction preventing cytotoxic therapy, all contribute to the challenge. The largest study of relapsed ATLL enrolled 28 patients in multiple centers in Japan and led to the approval of mogamuluzimab in Japan based on an overall response rate of 50%, and median progression-free survival and overall survival of 5.2 and 13.7 months, respectively [11]. The most common adverse events included infusion reactions (89%) and skin rash (63%). Mogamuluzimab is an investigational agent in the U.S. and has not been approved for any indication by the FDA however current trials in ATLL, cutaneous T cell lymphoma, and non-Hodgkin's lymphoma are ongoing.

Outside of Japan, the AIDS Malignancy Consortium treated 19 patients with aggressive ATLL (N=19) with EPOCH chemotherapy followed by antiviral therapy and interferon for up to one year resulting in an ORR of 58% (CR 10.5%) and a median duration of response of 13 months. Although this regimen appeared active, viral replication during therapy coincided with disease progression, which likely contributed to treatment failure [12]. A number of small studies and cases have reported the activity of combination zidovudine and IFN-alpha and demonstrated a high response rate in previously untreated and treatment refractory patients. A retrospective meta-analysis suggests this therapy is most effective for all subtypes but lymphoma [13]. A randomized trial has not been conducted. Novel agents for the potential application to the treatment of ATLL include pralatrexate, bortezomib, forodesine, and histone deacetylase inhibitors [5].

Clinical trial participation continues to be a desirable option and multi-center collaborative efforts should evaluate patients promptly before deterioration of performance status, opportunistic infection and multi-system organ dysfunction set in. This phase II study was closed prematurely but showed no clinical activity in two patients evaluable for response.

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