SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 4: 262-264, 2012

# Bortezomib-based treatment for relapsed and refractory angioimmunoblastic T-cell lymphoma: Case report and literature review

SHUYAN LIU*, ZHENGANG YUAN*, CHUNYANG ZHANG, WEIJUN FU and JIAN HOU

Department of Hematology, Shanghai Changzheng Hospital, The Second Military Medical University, Shanghai 200003, P.R. China

Received February 15, 2012; Accepted May 14, 2012

DOI: 10.3892/ol.2012.724

**Abstract.** Angioimmunoblastic T-cell lymphoma (AITL) is a distinct peripheral T-cell lymphoma (PTCL) subtype, accounting for 15-20% of PTCL and 2% of all non-Hodgkin lymphoma (NHL), with a poor prognosis. In the present study, we describe a 76-year-old patient with AITL who failed to respond to conventional chemotherapy but responded to bortezomib-based treatment and demonstrated persistent clinical improvement at the 18-month follow-up. These data suggest that bortezomib-based treatment may be a reliable, safe and effective alternative for treating relapsed/refractory AITL.

## Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a distinct peripheral T-cell lymphoma (PTCL) subtype with uncommon clinical and pathological features, accounting for 15-20% of PTCL and 2% of all non-Hodgkin lymphoma (NHL). However, there is no consensus with regard to the best approach for treating patients with AITL and the disease often follows an aggressive clinical course. AITL portends a poor prognosis, the median survival time is less than three years and the five-year overall survival (OS) rate is only approximately 30% in most studies, even when treated intensively. However, AITL is not always lethal, with 30% of patients being long-term survivors (1,2).

In the present study, the first case in which a relapsed and refractory AITL patient is successfully treated with a combination of bortezomib, mitoxantrone and dexamethasone (PAD regimen) is reported. The diagnosis, clinical features and bortezomib-based treatment of AITL according to this case are described and previously published data are also discussed. The study was approved by Ethical Principles for Conducting Research With Humans and Other Animals committee of The Second Military Medical University, Shanghai.

*Correspondence to:* Dr Jian Hou, Department of Hematology, Shanghai Changzheng Hospital, The Second Military Medical University, 415 Fengyang Road, Shanghai 200003, P.R. China
E-mail: houjian167@sohu.com

*Contributed equally

*Key words:* bortezomib, treatment, relapsed, refractory, angioimmunoblastic T cell lymphoma

## Case report

In September 2008, a 76-year-old female individual first visited an otorhinolaryngology clinic with the chief complaints of dyspnea and painful swelling of the throat. Physical examination revealed that her bilateral tonsils were projected beyond the midline with an irregular surface. Pharyngeal stenosis and lymphoid follicular hyperplasia were observed in the posterior wall of the pharynx. The bilateral cervical, axillary and inguinal lymph nodes were enlarged with moderate hardness and limited motion, as well as splenomegaly. A computed tomography (CT) scan of the chest showed multiple swollen lymph nodes in the mediastinal and bilateral axillary areas. Bone marrow cytomorphological examination and biopsy at that time were normal. A diagnosis of AITL was confirmed by biopsy of the enlarged cervical lymph node and bilateral tonsils. Immunohistochemical staining of the tumor cells showed CD4(+), CD8(+), CD10(±), Ki-67(+), CD15(+), CD30(-), CD3(+), $CD31^+$ (vascular), $CD34^+$ (vascular), CXCL13(+) and follicular dendritic cell meshworks expressing CD21 (Fig. 1). T-cell receptor (TCR) γ gene rearrangement (+) and immunoglobulin (Ig) genes rearrangement (-) of the lymph nodes were detected by the polymerase chain reaction (PCR).

The patient was diagnosed with AITL IIIB. The patient achieved a partial response to the initial treatment with two cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and three cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone). However, after four months the disease had progressed. The patient then received two cycles of salvage therapy with EDCP (cisplatin, etoposide, cyclophosphamide and dexamethasone). The patient also received cyclosporine and thalidomide for two months. No response was observed. Between March 2009 and July 2009, the patient received

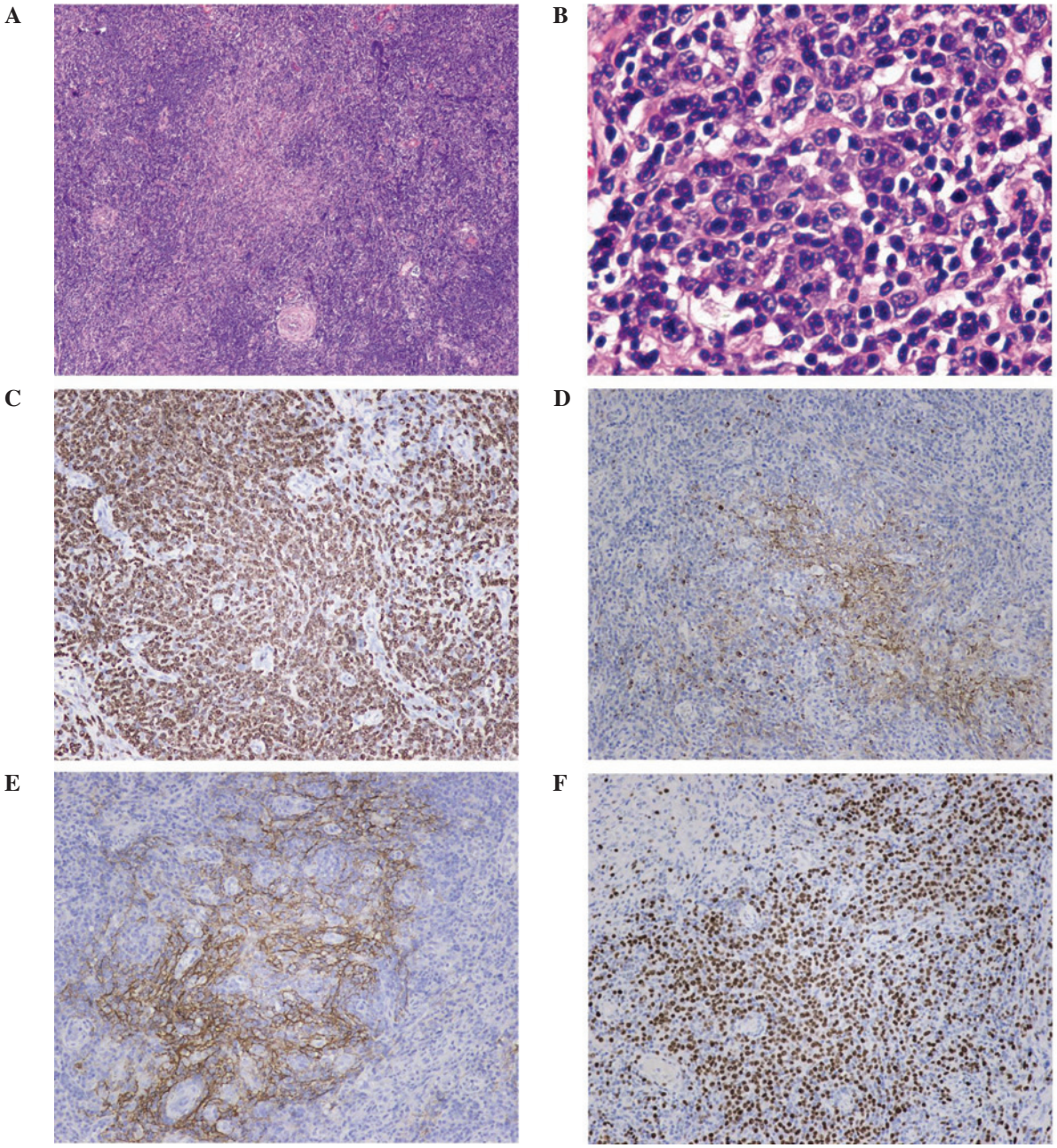


Figure 1. Lymph node biopsy. (A) Classical morphology with effacement of normal architecture and marked vascular proliferation associated with aggregates of atypical lymphoid cells (H&E staining; x40 magnification). (B) The infiltrate is composed of medium to large lymphoid cells with abundant clear cytoplasm (H&E staining; x400 magnification). (C and D) The characteristic phenotype of tumor cells expressing (C) CD3, (D) CXCL13. (E) CD21 immunostaining emphasizes marked follicular dendritic entrapping high endothelial venules. (F) Immunohistochemistry shows homogeneous staining for Ki67.

five 28-day cycles of PAD regimen comprising 1.3 mg/m$^2$ bortezomib, 2 mg/m$^2$ mitoxantrone and 40 mg dexamethasone on days 1, 4, 8 and 11, after signed informed consent was obtained. At the 18-month follow-up, the patient showed persistent clinical improvement, weight gain, disappearance of lymphadenopathy, improvement of performance status and no B symptoms, and complete response was achieved. The patient did not receive therapy until October 2010 when the patient was diagnosed as relapsed by positron emission tomography (PET). Subsequently, one cycle of COP and PAD were performed. However, severe myelosuppression and minor therapeutic effects were observed. The patient succumbed to a severe pulmonary infection in March 2011.

## Discussion

AITL is a rare and aggressive malignancy which affects elderly adults at an age ranging from 59 to 65 years, clinically characterized by a sudden onset of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, skin rash, bone marrow involvement, anemia (often hemolytic and Coombs-positive), polyclonal hypergammaglobulinemia and hypereosinophilia. Using PCR techniques, the detection of monoclonal or oligoclonal rearrangement of the TCR was found to be present in the majority of cases. In addition, the rearrangement of the Ig gene(s) was observed in up to one-third of patients (3). As yet, the standard therapeutic option

for patients with AITL has not been clearly established. Various treatment strategies, which range from the CHOP or CHOP-like therapy to chemotherapy with autologous stem cell transplantation, even allogeneic transplantation, have proved to be largely unsuccessful in curing the disease. The lack of a demonstrated improvement in OS supports the development of novel approaches, including alemtuzumab (4), zanolimumab (5), denileukin diftitox (6), pralatrexate (7), histone deacetylase (HDAC) inhibitors (8), cyclosporine (9), thalidomide (10), gemcitabine (11) and bortezomib (12).

Bortezomib is a dipeptide boronic acid that selectively and potently inhibits the proteasome 26S complex, exerting anti-tumor activity mainly via the inhibition of the NF-κB pathway components correlated with cell proliferation, apoptosis and angiogenesis (13). It has been reported that abnormal PRDM1β expression reflected poor prognosis in T-cell lymphoma, and that bortezomib is able to downregulate PRDM1β through NF-κB inactivation (14). *In vitro* and *in vivo* studies demonstrated that bortezomib has the ability to eliminate tumor cell interaction with endothelial cells in T-cell leukemia/lymphoma by affecting the expression of genes associated with the adhesion cascades (15). Therefore, bortezomib may play a special therapeutic role and be safe from the emergence of acute toxicity, which is important considering that AITL patients tend to be elderly adults with a number of concomitant medical problems.

A PAD regimen is commonly used to treat patients with multiple myeloma. To the best of our knowledge, this is the first reported case of the successful management of relapsed and refractory AITL with a combination of bortezomib, mitoxantrone and dexamethasone (PAD regimen). This combination was well tolerated and induced a complete and relatively sustained remission in this patient. We believe bortezomib was involved in the therapy of this patient since no response to anthracyclines and high-dose glucocorticoid was observed. Martínez-Delgado *et al* differentiated two subgroups of PTCL characterized by a high or reduced expression of the NF-κB pathway genes (16). Furthermore, Martínez-Delgado *et al* observed that a low expression of the NF-κB pathway genes was significantly associated with short OS and may be an independent prognostic factor. Bortezomib not only acted on tumor cells themselves through NF-κB inactivation, but also removed tumor cell interaction with endothelial cells (14,15). Therefore, we suggest that NF-κB-positive AITL patients treated with bortezomib have better results to treatment than NF-κB-negative AITL patients.

Considering that heavy chemotherapy may cause serious adverse events in elderly adults, the use of the PAD regimen may be a reliable, safe and effective alternative for treating relapsed/refractory AITL. However, the efficacy of bortezomib should be elucidated in further larger-sized clinical trials with an extended follow-up. Furthermore, continued preclinical and clinical research is required to identify more effective treatment options for patients with relapsed/refractory AITL.

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