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Bortezomib-based chemotherapy to treat refractory angioimmunoblastic T-cell lymphoma: A case report and review of the literature

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Abstract. The peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of aggressive neoplasms that account for <15% of all non-Hodgkin's lymphoma cases in adults. Angioimmunoblastic T-cell lymphoma (AITL) is a specific subtype of PTCL. The tumor is frequently aggressive and there is currently no general consensus regarding an effective treatment strategy. The present study reports a case in which bortezomib combined with dexamethasone was used to treat refractory AITL. A 63-year-old woman was admitted to Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Zhejiang, China) on August 17, 2013. The patient had been diagnosed with AITL for 4 months and had experienced a relapse of symptoms for the 4 days prior to admission. The patient demonstrated fever and dyspnea, accompanied by severe edema in the face and lower limbs, which later spread to the right upper limb. The patient was treated with bortezomib plus dexamethasone, which rapidly relieved the symptoms. The patient was subsequently administered an additional 2 cycles of bortezomib-based chemotherapy and survived for an additional 4 months, prior to succumbing to the disease. Only a small number of studies have reported the use of bortezomib in the treatment of T-cell lymphoma. The present study suggested that bortezomib-based treatment may be a reliable, safe and effective alternative for the treatment of relapsed/refractory PTCL. The efficacy of bortezomib as a treatment for PTCL requires additional evaluation in future studies.

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Introduction

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of aggressive neoplasms that account for <15% of all non-Hodgkin's lymphoma (NHL) cases in adults (1). The incidence of PTCL varies geographically, with the highest incidence in regions of Asia (2,3). The incidence in the USA has increased by 7.9% annually between 1992 and 2005 (4). In total, there are 23 types of PTCL defined by the 2008 World Health Organization classification (5), including extranodal nasal-type natural killer/T-cell lymphoma, enteropathy-associated T-cell lymphoma, subcutaneous panniculitis-like cell lymphoma, angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL) and peripheral T-cell lymphomas not otherwise specified (PTCL-NOS). There are clear variations in incidence and survival rates in the subtypes according to age, gender, ethnicity and geographical distribution (2,6). A diagnosis of PTCL is based on the results of a tissue biopsy, usually a lymph node biopsy. The disease stage and prognosis of the patient at diagnosis are determined by the International Prognostic Index (IPI) score, similarly to other NHLs (7,8). PTCL is frequently aggressive and there is currently no general consensus regarding an effective treatment strategy; therefore, regimens that treat aggressive B-cell NHL are commonly used (4). Among all the subtypes anaplastic lymphoma kinase positive ALCL may have the best survival rate, while patients with other PTCLs have poor outcomes (1). The tendency for poor survival rates in PTCL suggests that the regimens used in patients with aggressive B-cell lymphomas may not be equally efficacious in T-cell lymphomas. Therefore, patients are encouraged to attend clinical trials whenever available (9).

PTCL-NOS is the most common subtype of PTCL, accounting for ~26% of T-cell lymphoma cases worldwide, and AITL is the second most common subtype accounting for ~19% (6). The majority of patients with AITL have a median age of 59-64 years without any gender predilection (10). Patients typically present with generalized lymphadenopathy, fever, night sweats and weight loss (10). AITL may manifest following the administration of drugs, particularly antibiotics, or a viral infection, and may occasionally be associated with various bacterial or fungal infections, possibly reflecting the

consequences of immune deregulation in AITL patients (9). The course of AITL is variable, and the overall prognosis is poor; however, there is occasional spontaneous remissions in a few cases (9). The best treatment for AITL is unknown. Anthracycline-based chemotherapy, administered following induction therapy, may achieve a 46% complete remission rate; however, intensive combination chemotherapy, including CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), hyper-CVAD (cyclophosphamide, doxorubicin, vincristine and dexamethasone) and mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone) did not improve complete remission rates when used with various chemotherapeutics during randomized studies, including stem cell transplantation (10). Univariate analysis demonstrated that men, mediastinal lymphadenopathy and anemia are poor prognostic factors for the overall survival rate of patients (10). No therapy has increased the long-term survival rate to >30% (6).

The present study reports a case of refractory AITL, which was treated with bortezomib combined with dexamethasone.

Case report

A 63-year-old woman was admitted to the Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (Zhejiang, China) on August 17, 2013. The patient had been diagnosed with AITL for 4 months and had experienced a relapse of symptoms for the preceding 4 days prior to admission.

A total of 4 months prior to admission, the patient presented with enlarged bilateral cervical, axillary and inguinal lymph nodes, which exhibited moderate hardness and limited motion. Computed tomography (CT; SOMATOM Definition AS and SOMATOM Sensation 16; Siemens AG, Munich, Germany) revealed hepatosplenomegaly and lymphadenopathy at the mediastinal, retroperitoneal and mesenteric regions.

Pathological assessment of a left lymph node biopsy led to a diagnosis of AITL, with the following immunohistochemical results (all antibodies were mouse anti-human monoclonal, unless otherwise stated): Negative staining for cluster of differentiation (CD)20 (catalog no., M0755; dilution, 1:1,500; Dako, Glostrup, Denmark) and CD8 (catalog no., NCL-L-CD8-295; dilution, 1:50; Leica Biosystems Nussloch GmbH, Nussloch, Germany); positivity for CD3 (catalog no., A0452; dilution, 1:400; Dako), Ki-67 (80%; catalog no., M7240; dilution, 1:1,000; Dako), B-cell lymphoma 6 (catalog no., NCL-L-BCL-6-564; dilution, 1:400; Leica Biosystems Nussloch GmbH), CD4 (catalog no., M7310; dilution, 1:50; Dako), programmed cell death protein 1 (catalog no., ZM-0381; dilution, 1:1,500; Beijing Zhongshan Biological Technology Co., Ltd., Beijing, China) and CD5 (catalog no., M3641; dilution, 1:50; Dako); partial positivity for CD7 (catalog no., NCL-L-CD7-580; dilution, 1:400; Leica Biosystems Nussloch GmbH) and chemokine (C-X-C motif) ligand 13 (goat polyclonal; catalog no., ZG-0601; dilution, 1:100; Beijing Zhongshan Biological Technology Co., Ltd.); focal staining for CD10 (catalog no., M7308; dilution, 1:50; Dako); positivity for CD21 (catalog no., M0784; dilution, 1:1,000; Dako) indicating dendritic cell hyperplasia; and Epstein-Barr virus positivity in scattered cells. T-cell receptor rearrangement was positive. Furthermore, bone marrow biopsy revealed abnormal T-cell infiltration. The patient was diagnosed with stage IV AITL and B-group, and experienced night sweats and weight loss (6). The patient demonstrated an IPI (7) score of 2, due to the presence of stage IV disease and being >60 years of age.

The patient was treated with cyclophosphamide (1,000 mg/dl; Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China), doxorubicin (70 mg/dl; Shenzhen Main Luck Pharmaceuticals Inc., Shenzhen, China), vincristine (2 mg/dl; Zhejiang Hisun Chemical Co., Ltd., Taizhou, China) and prednisone (30 mg/dl; Zhejiang Xianju Pharmaceutical Co., Ltd., Hangzhou, China) (CHOP) plus L-asparagine (L-ASP; 3,600 IU day 1; Jiangsu Hengrui Medicine Co., Ltd.) chemotherapy on May 8, 2013. However, L-ASP treatment was subsequently ceased due to a severe skin rash. Subsequently, the patient was administered 2 cycles of CHOP chemotherapy. The enlarged lymph nodes were observed to shrink following the first cycle of chemotherapy, but became larger again and were accompanied by fever prior to the next cycle of chemotherapy; therefore, the therapy was changed to a gemcitabine (1,400 mg/dl; Faulding Pharmaceuticals, Ltd., Adelaide, Australia), dexamethasone (40 mg/dl on days 1-4; Jiangsu Hansoh Pharmaceutical, Co., Ltd., Lianyungang, China) and platinum (Jiangsu Hansoh Pharmaceutical, Co., Ltd.) regimen. Subsequently, the lymph nodes were observed to have decreased in size.

Between August 13-17, 2013, the patient exhibited a fever (39˚C) and dyspnea. Physical examination revealed severe edema in the face and lower limbs. The symptoms were not relieved following 1 week of antibiotic treatment with imipenem and caspofungin, and diuretic treatment (20 mg intravenous furosemide; Shanghai Harvest Pharmaceutical, Co., Ltd., Shanghai, China). The patient was weak and was confined to bed rest. The facial edema became more severe and spread to the right upper limb. The patient additionally exhibited abdominal distention. Chest and abdominal CT revealed a small amount of pleural, mediastinal and abdominal effusion. Mediastinal, supraclavicular and peripancreatic lymph nodes were enlarged. The patient's condition became increasingly worse, and the patient was considered to exhibit superior vena cava (SVC) syndrome, which is one complication of lymphoma. On August 21, 2013, the patient was administered bortezomib plus dexamethasone [2.4 mg bortezomib on days 1 and 4 (Xi'an Janssen Pharmaceutical., Co., Ltd., Xi'an); and 20 mg dexamethasone on days 1-4 (Tianjin Kingyork Group, Tianjin, China)]. Following chemotherapy, the patient no longer exhibited a fever and the antibiotic treatment was ceased. The symptoms improved and 1 week later the patient was discharged from hospital. On September 9, 2013, the patient was followed-up and demonstrated no fever or edema, with no requirement for bed rest. CT indicated that the pleural effusion had decreased and that the peripancreatic, retroperitoneal and mesenteric lymph nodes had reduced in size. The patient was administered another regimen of bortezomib plus dexamethasone on September 11, 2013. However, 1 month later the patient exhibited a red itching rash on the neck and face. The patient was administered bortezomib and a hyper-CVAD A regimen (2.4 mg bortezomib on days 1 and 4; 400 mg cyclophosphamide twice a day, on days 1-3; 60 mg Adriamycin on day 4; 2 mg vincristine on days 4 and 11; and 40 mg dexamethasone on days 1-4 and 11-14). Due to bone marrow suppression, the patient developed a severe infection

Table I. Bortezomib-based chemotherapy to treat T-cell lymphoma.

First author, year	Study type	Drug regimen	Patients, n	Patient type	CR, %	PR, %	ORR, %	PFS	3-year OS	Ref.
Liu *et al*, 2012	Case report	PAD	1	Relapsed AITL	-	-	-	18 months	-	(18)
Hourigan *et al*, 2013	Case report	V-EPOCH	1	Refractory ATL	-	-	-	-	36 months	(19)
Kim *et al*, 2012	Multicentre single-arm phase 2 trial	V+CHOP	46	PTCL-NOS, ENKTL, ALCL, CTCL, HSTL	65	-	76	35%	47%	(21)
Lee *et al*, 2008	Phase 1	V+CHOP	13	Advanced, aggressive T-cell lymphoma	61.5	-	-	-	-	(22)
Zinzani *et al*, 2007	Phase 2	Bortezomib	12	Relapsed, refractory PTCL-NOS, CTCL	17	50	67	7-14 months	-	(23)

PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; ENKTL, extranodal natural killer/T-cell lymphoma, nasal type; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic lymphoma kinase-negative anaplastic large-cell lymphoma; CTCL, cutaneous T-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma; ATL, acute adult T-cell leukemia/lymphoma; OS, overall survival; PFS, progression-free survival; PAD, bortezomib, mitoxantrone and dexamethasone regimen; CR, complete response; PR, partial response; ORR, overall response rate; V+CHOP, bortezomib plus cyclophosphamide, doxorubicin, vincristine and prednisone regimen; V-EPOCH, bortezomib plus etoposide, prednisone, vincristine, doxorubicin and cyclophosphamide.

following chemotherapy. Therefore, chemotherapy was ceased and the patient succumbed to the disease on January 6, 2014. Written informed consent was obtained from the patient's family for the publication of the present study.

Discussion

PTCLs are a heterogeneous group of aggressive neoplasms and patient survival depends, at least partially, upon the subtype identified. In general, survival time is measured in months without treatment. The International Peripheral T-cell Lymphoma Project reported 5-year overall survival rates of 32% and 5-year relapse-free survival of only 20% in subtypes of PTCL not otherwise specified (PTCL-NOS), while the survival rates were 33 and 18% in AITL, respectively (11,12). It is clear that patients with T-cell lymphoma possess inferior rates of response to chemotherapy, and demonstrate poorer progression-free survival (PFS) and overall survival compared with patients with B-cell lymphoma (13). There is no general consensus regarding the preferred chemotherapeutic treatment for PTCL, and patients should be encouraged to participate in clinical trials whenever possible (14).

Bortezomib, a proteasome inhibitor, is a novel agent approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma and relapsed or refractory mantle cell lymphoma (15-17). However, only a few studies have reported the use of bortezomib to treat T-cell lymphoma (Table I).

A study by Liu *et al* (18) described the case of a 76-year-old female patient with AITL, who did not respond to conventional chemotherapy, but responded to bortezomib-based treatment. The treatment regimen was PAD, comprising 1.3 mg/m^2 bortezomib, 2 mg/m^2 mitoxantrone and 40 mg dexamethasone on days 1, 4, 8 and 11 for 5 cycles of 28 days each (18). The patient demonstrated persistent clinical improvement, weight gain, disappearance of lymphadenopathy, improvement of performance status and no systemic symptoms of fever, night sweats or weight loss at the 18-month follow-up visit (18). Hourigan *et al* (19) also used bortezomib accompanied by an EPOCH regimen (etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone) as a salvage therapy for the treatment of a 48-year-old man who was diagnosed with refractory acute adult T-cell leukemia/lymphoma (ATL). Bortezomib (1 mg/m^2) was administered on days 1, 4, 8 and 11 of each cycle (19). Following a single cycle of V-EPOCH (bortezomib plus EPOCH) (20), the lymphadenopathy resolved and the patient's lactate dehydrogenase levels became normalized (19). Following 4 cycles of V-EPOCH, peripheral blood flow cytometry and a bone marrow examination demonstrated no evidence of residual leukemia (19). Subsequent to 5 cycles of V-EPOCH, the patient received a consolidative non-myeloablative haploidentical bone marrow transplant and continued to demonstrate a complete response (CR) 36 months after the completion of treatment (19).

There have been a number of prospective phase II trials of bortezomib in patients exhibiting relapsed or refractory PTCL. Kim *et al* (21) performed a phase II study on 46 patients with stage III/IV PTCL, to investigate the efficacy of bortezomib in combination with CHOP as a first-line treatment. Patients were administered bortezomib on days 1 and 8

at a dose of 1.6 mg/m (22), in addition to CHOP every 3 weeks for a total of 6 cycles (21). Overall, three subtypes of PTCL (PTCL-NOS, AITL and anaplastic lymphoma kinase-negative anaplastic large-cell lymphoma) demonstrated an 87% overall response rate (ORR) and a 73% CR rate (21). However, the treatment efficacy for extranodal natural killer (NK)/T-cell lymphoma, nasal type was poor with a CR rate of only 30% (3/10) (21). In total, 30 patients achieved a CR (65%) and the ORR was 76% (12). The 3-year overall survival and progression-free survival rates were 47 and 35%, respectively, due to frequent relapse following remission. However, bortezomib plus CHOP appears to be superior to treatment with CHOP alone or CHOP-like regimens (21). Lee *et al* (22) also investigated bortezomib in combination with CHOP as a first-line therapy for advanced, aggressive T-cell lymphoma. A total of 13 patients received 55 cycles of treatment. The overall CR rate in all patients was 61.5% (22). Zinzani *et al* (23) used bortezomib as a single agent to treat cutaneous T-cell lymphoma, at a dose of 1.3 mg/m^2, intravenously on days 1, 4, 8 and 11, every 21 days for a total of 6 cycles. The ORR was 67%, with 2 (17%) and 6 (50%) patients achieving a CR and a partial response (PR), respectively (23). All responses were enduring, lasting for 7-14 months (23). In all the aforementioned studies, bortezomib was well-tolerated. The most common toxicities were peripheral sensory neuropathy, neutropenia and thrombocytopenia.

The primary mechanism underlying the anticancer activity of bortezomib is via the activation of nuclear factor-κB (NF-κB) and inhibition of the degradation of inhibitory-κB, which leads to the suppression of the NF-κB signaling pathway, followed by downregulation of anti-apoptotic target genes (24). Another important anticancer mechanism occurs via upregulation of NOXA, which is a pro-apoptotic protein that may interact with the anti-apoptotic proteins of the B-cell lymphoma 2 (Bcl-2) subfamily, leading to the apoptotic death of malignant cells. Bortezomib-induced apoptosis has been demonstrated in T and NK lymphoma cells, implying that bortezomib may have a significant therapeutic role in the treatment of T-cell lymphoma (25-27).

The patient in the present study was diagnosed with stage IV refractory PTCL, and appeared to exhibit primary drug resistance. Classical chemotherapy was not effective. The patient subsequently developed severe edema of the face and lower limbs. CT scans revealed enlarged lymph nodes in the mediastinal and supraclavicular regions. It was considered that the patient may by exhibiting SVC syndrome, despite negative indications on the CT scan. SVC syndrome is a condition caused by the obstruction of blood flow through the SVC (28,29). Obstruction may be caused by invasion or external compression of the SVC by an adjacent pathological process involving the right lung, lymph nodes or other mediastinal structures, or by thrombosis. Dyspnea is the most common symptom, and patients also frequently exhibit facial swelling or head fullness, arm swelling, a cough, chest pain or dysphagia. Patients with cerebral edema may experience headaches, confusion or possibly become comatose. Upon physical examination, the most common findings are facial edema, and distension of the veins in the neck and on the chest wall. The most frequent cause of SVC syndrome is intrathoracic malignancy, which is responsible for 60-85% of cases. Among all malignancies, lung cancer and NHL are responsible for ~95% of cases of SVC syndrome (28,29). Non-malignant conditions account for 15-40% of SVC obstructions in contemporary retrospective series. Among these cases, SVC thrombosis cases, which are associated with the presence of intravascular devices, including central venous catheters and cardiac pacemaker leads, have increased rapidly (29,30). The goal of management for SVC syndrome is to alleviate symptoms and treat the underlying disease. For patients with malignancy, chemotherapy is the initial choice of treatment. The edema symptoms of the present patient were relieved soon after chemotherapy, indicating the effectiveness of the treatment.

For the present patient, who exhibited refractory and aggressive T-cell lymphoma, bortezomib with dexamethasone achieved rapid and favorable effects. The symptoms caused by SVC syndrome were completely relieved and the lymph nodes reduced in size. The results of the present study suggest that bortezomib-based treatment may be a reliable, safe and effective alternative for the treatment of relapsed/refractory PTCL. However, the efficacy of bortezomib should be additionally evaluated in larger controlled clinical trials, with an extended follow-up period. Further investigation is required to observed whether bortezomib is more favorable for the treatment of AITL than other drugs.

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