

Case Research

A Chinese patient with relapsed and refractory Hodgkin lymphoma treated with brentuximab vedotin

Zhi-Gang Cao, Hong-Wei Zhou, Chao-Jin Peng, Mo Liu, Yu Du and Qing-Ming Yang

Abstract

At present, approximately 20% of Hodgkin lymphomas (HL) are relapsed and refractory, and therapeutic methods including chemotherapy, radiotherapy, and even stem cell transplantation are unsatisfactory. Brentuximab vedotin, composed of CD30 antibody and a chemotherapeutic agent, is a new targeted drug that eradicates tumor cells by binding to the CD30 antigen on their surface. In clinical trials, the response rate and complete remission rate of this drug were 73% and 40%, respectively, for relapsed and refractory HL. Here we report a case of CD30-positive relapsed and refractory HL that was treated with brentuximab. Before the treatment with brentuximab, the patient underwent chemotherapy, radiotherapy, and autologous stem cell transplantation. However, the disease continued to progress, affecting multiple organs and prompting symptoms such as persistent fever. After the treatment with brentuximab, the patient's condition improved. Body temperature returned to normal after 4 days. Lung nodules were reduced in size and number after a single course of treatment, and PET/CT showed partial remission and complete remission after 3 and 6 courses of treatment, respectively. The entire treatment process progressed smoothly, though the patient experienced some symptoms due to chemotherapy, including peripheral neuritis of the limbs, irritating dry cough, and mild increase in aminotransferase. No serious adverse effects were observed. The current general condition of the patient is good; the continuous complete remission has amounted to 6 months.

Key words Hodgkin lymphoma, treatment, brentuximab vedotin

Hodgkin lymphoma (HL) is a malignant tumor derived from lymphatic tissue and is considered highly curable. Approximately 70% of patients can achieve long-term disease control with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) induction chemotherapy^[1]. The standard management for relapsed or refractory HL patients is salvage chemotherapy with second- or third-line regimens followed by autologous stem cell transplantation (ASCT). Unfortunately, this intensive therapy controls relapsed and refractory disease in only 50% of patients. Patients who experience HL relapse after ASCT have a poor prognosis, and treatment options

remain largely palliative^[2,3]. However, the antibody-drug conjugate brentuximab vedotin has shown promising efficacy in these patients^[4]. In a pivotal phase II, open-labelled, multi-center trial, patients with relapsed or refractory HL after ASCT had an overall response rate of 74%, with a complete remission rate of 34%, after the treatment with brentuximab^[5,6]. Brentuximab was approved by the US Food and Drug Administration for the treatment of relapsed or refractory HL and systemic anaplastic large cell lymphoma in August 2011.

Here we report a female patient with relapsed and refractory HL who underwent brentuximab treatment through the State Food and Drug Administration (SFDA)-approved named patient programs (NPP) project^[7]. To the best of our knowledge, this is the first case applying brentuximab for HL in the mainland of China.

Case Report

A 17-year-old girl presented with painless swelling of the right neck and supraclavicular lymph nodes accompanied with fever and fatigue in February 2007. The pathology report after lymph

Authors' Affiliation: Department of Hematology and Oncology, the First Affiliated Hospital of the People's Liberation Army General Hospital, Beijing 100048, P. R. China.

Corresponding Author: Qing-Ming Yang, Department of Hematology and Oncology, the First Affiliated Hospital of the People's Liberation Army General Hospital, Beijing 100048, P. R. China. Tel: +86-10-68989344; Fax: +86-10-68989344; Email: Yangqm@medmail.com.cn.

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node biopsy indicated that the normal lymph node structure had disappeared and scattered distributions of Reed-Sternberg (RS) cells and Hodgkin disease (HD) cells occurred. Immunohistochemical staining showed that these cells were positive for CD30 (**Figure 1A**), paired box protein 5 (PAX5) (**Figure 1B**), and Epstein-Barr virus (EBV), and negative for CD15 and anaplastic lymphoma kinase (ALK). The patient was diagnosed with stage IIa HL, mixed cellularity subtype. Treatment with 4 cycles of ABVD was conducted as induction chemotherapy followed by bilateral neck and supraclavicular radiation therapy (36 Gy). The patient achieved complete remission (CR) but, after about 1 year, relapsed with inguinal and mediastinal lymph node involvement, as detected by positron emission tomography (PET)/computed tomography (CT) scan. Afterwards, 8 cycles of salvage chemotherapy with cyclophosphamide, vinorelbine, epirubicin, and prednisone (CHOP) were performed, and the patient achieved CR again.

A PET/CT scan in April 2010 indicated relapse, with mediastinal, left axillary, retroperitoneal, pelvic cavity, and inguinal lymph node involvement and multiple nodules at the thoracolumbar vertebrae, right iliac crest, and right ischium. The patient was diagnosed with HL of nodular sclerosis subtype after a left inguinal lymph node biopsy. She then underwent 2 cycles of salvage chemotherapy with rituximab, cyclophosphamide, vinorelbine, epirubicin, prednisone, and etoposide (R-CHOPE) and underwent ASCT in December 2010. A PET/CT scan in June 2011 subsequently demonstrated relapse once more, with nodules in the liver, spleen, and lung (**Figure 2A**). The patient gradually developed pancytopenia during the treatment progress. Consequently, 2 cycles of salvage chemotherapy with gemcitabine, dexamethasone and nedaplatin (GDP) were given, but the disease persisted at the end of therapy. On October 20th, 2011, results of CT scan showed that the number and size of nodules in the lung significantly increased (**Figure 2B**). The patient exhibited persistent fever and systemic failure, and showed an Eastern Cancer

Oncology Group (ECOG) score of 3.

In October 2011, the patient began brentuximab monotherapy, with a dose of 1.8 mg/kg, once every 3 weeks. Following the first course of brentuximab, the patient's body temperature dropped gradually after 4 days of treatment and returned to normal 1 week later. Because of bone marrow involvement, white blood cell, hemoglobin, and platelet counts decreased markedly before treatment. However, the patient continued with brentuximab therapy without interruption under the support of granulocyte colony-stimulating factor (G-CSF), thrombopoietin (TPO), and interleukin-11 (IL-11). Following the first course of brentuximab, CT scan showed that the lung nodules were significantly reduced in size and number (**Figure 2C**). After the second treatment, the patient began to recover from pancytopenia and regain physical strength, and her condition improved significantly. After the third course of treatment, the patient was capable of self-care, indicating an ECOG score of 2. PET/CT scan suggested partial remission (PR). After the fourth course of treatment, anemia began to improve, with hemoglobin increasing from 60 to 100 g/L. After physical activity palpitations disappeared, the patient's heart rate fell from 110–130 to 70–80 beats/min. Shrinkage was noted in multiple nodular shadows in double lung fields (**Figure 2D**). After the sixth course of treatment, hemoglobin count had nearly returned to normal, and lesions in the lungs, liver, spleen, bones, mediastinum, and abdomen significantly decreased. A PET/CT scan showed that the lung nodules had disappeared, and the maximum standard uptake values (SUVmax) of thoracolumbar vertebral nodules and liver and spleen nodules had decreased to normal (**Figure 3**). The patient achieved CR, and the ECOG score was 1. The patient encountered reversible adverse reactions during treatment, including peripheral neuropathy, elevated aminotransferases, hair loss, and dry cough, and these adverse effects were controlled with symptomatic treatments. At the time this paper was submitted, the patient had never suffered from infection.

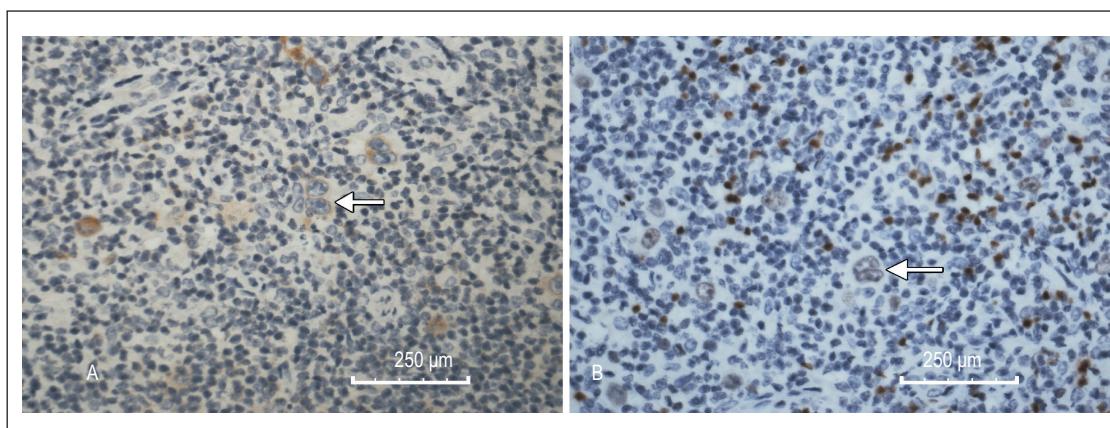


Figure 1. Pathologic examination shows that the Hodgkin lymphoma (HL) cells are positive for CD30 and PAX5. Tissue specimens were collected after lymph node biopsy, sectioned, and stained to detect CD30 and PAX5. Nuclei were counterstained with hematoxylin and eosin. A, Reed-Sternberg (RS) cells show CD30-positive membrane (white arrow). B, RS cells show PAX5-positive nuclei (white arrow).

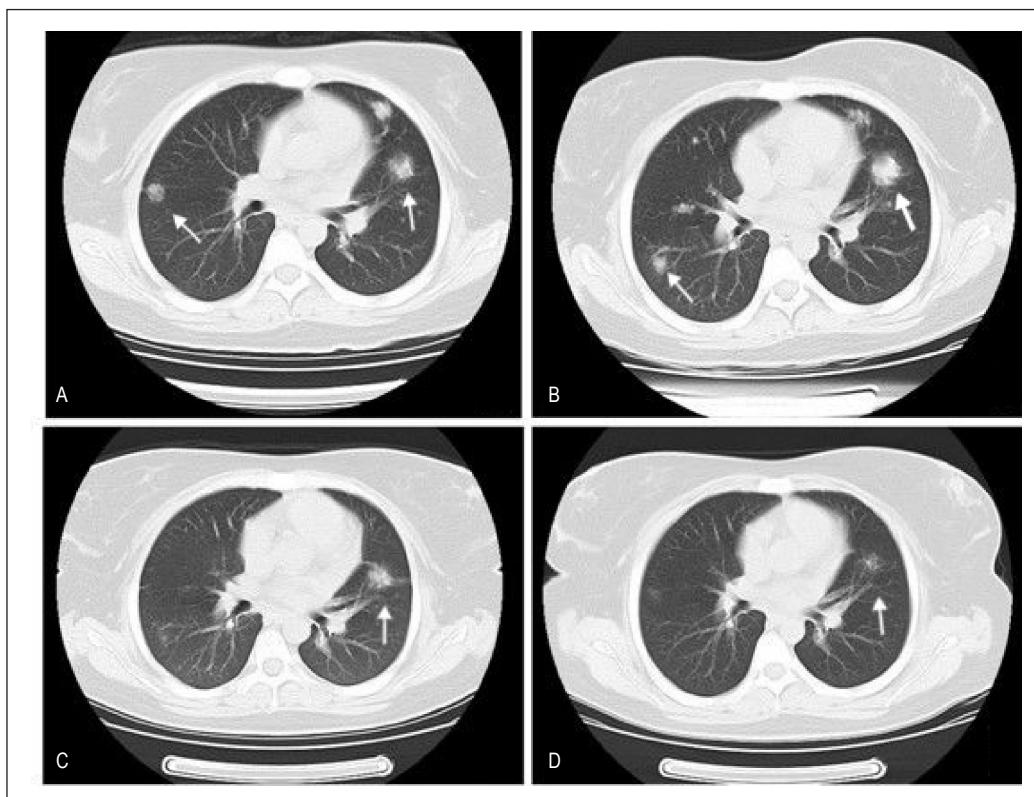


Figure 2. Changes in lung nodules as shown on computed tomography (CT) scan. Nodules are denoted by white arrows. A, nodules before treatment with gemcitabine, dexamethasone, and nedaplatin (GDP) in June 2011. B, nodules before brentuximab treatment in October 2011. C, in November 2011, after the first course of brentuximab, significant shrinkage of lung nodules was noted. D, in February 2012, after the fourth course of brentuximab, the nodules had nearly disappeared.

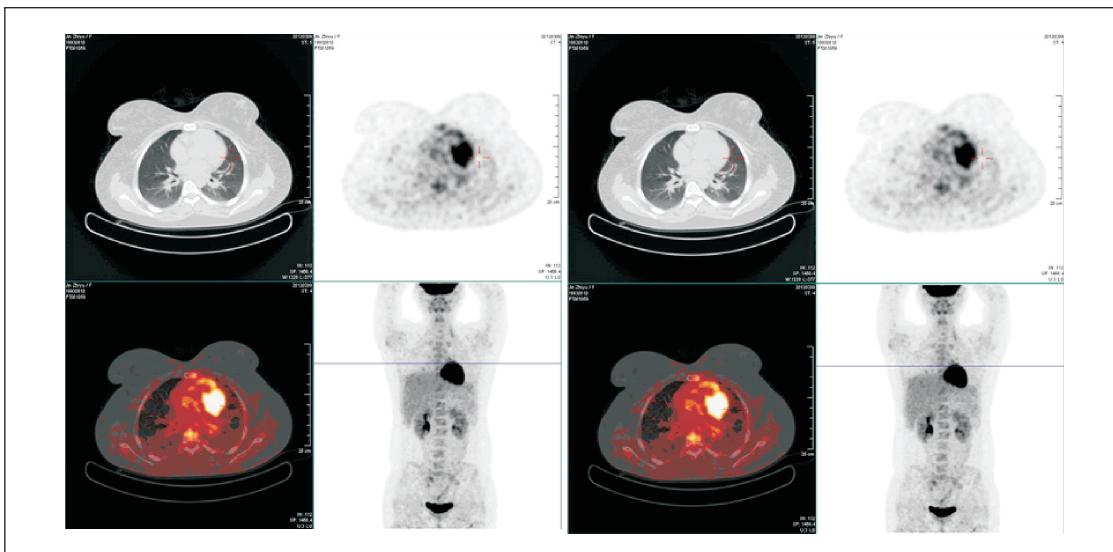


Figure 3. Positron emission tomography (PET)/CT scan after treatment with 6 courses of brentuximab in March 2012. The patient achieved complete remission.

Discussion

We introduced brentuximab therapy to a patient with HL refractory to chemotherapy, radiotherapy, and ASCT. The patient's most recent relapse involved several organs, including the liver, lungs, bones, bone marrow, and mediastinal and retroperitoneal lymph nodes. To the best of our knowledge, this is the first patient with HL in the mainland of China who underwent brentuximab treatment.

Brentuximab, a new targeted therapy for lymphoma, is an antibody-drug conjugate which consists of the anti-CD30 monoclonal antibody cAC10 conjugated with the cytotoxic agent monomethyl auristatin E (MMAE). As a monoclonal antibody, cAC10 has a direct toxic effect on CD30-positive lymphoma cells. Moreover, chemotherapeutic drugs can also be coupled to the monoclonal antibody to directly target tumor cells, resulting in more specific and effective anti-tumor action. This new drug has shown dramatic efficacy on a number of relapsed and refractory HL patients^[6].

Our data showed that brentuximab's efficacy on this refractory

and relapsed case appeared quickly. The patient's fever subsided 1 week after beginning treatment. Further, after 6 courses of brentuximab, all lesions disappeared and CR was achieved. Importantly, the treatment was safe for the patient. Adverse effects including peripheral neuropathy, elevated aminotransferases, hair loss, and dry cough appeared but could be controlled with symptomatic treatments. Serious adverse effects, such as lung damage and leukoencephalopathy^[8], did not occur.

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