Case Report
Considerable response of thalidomide in plasmablastic lymphoma: a case report and literature review

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Received March 3, 2016; Accepted June 5, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Plasmablastic lymphoma (PBL) is a relatively rare and high grade B cell lymphoma. It often occurs in oral cavity of patients with human immunodeficiency virus (HIV) infection, but it can also be seen in HIV-negative patients. PBL presents a therapeutic challenge to clinicians due to its aggressive clinical feature and high relapse rates. No standard treatment guidelines are formulated. Conventional chemotherapy are widely used similar to other aggressive lymphomas and novel drugs are tried. The new options for PBL include bortezomib, lenalidomide and thalidomide. Here we report a case of non-HIV-associated intestinal PBL, who had failed to respond to several other lines of chemotherapy and autologous hematopoietic stem cell transplantation, achieved complete response after thalidomide monotherapy with no obvious side effect observed. We conclude that thalidomide could induce considerable response even when other regimens fail. Thalidomide is a safe and efficacious therapeutic choice for PBL that should be explored in further studies.

Keywords: Plasmablastic lymphoma, therapy, bortezomib, thalidomide

Introduction

Plasmablastic lymphoma (PBL) is a rare entity of B cell lymphoid proliferative disease, which was first described by Delecluse in 1997, as a distinct subtype of diffuse large B cell lymphoma (DLBCL) [1]. It is characterized by a monomorphic proliferation of neoplastic cells which resemble B immunoblasts but have the immunophenotype of plasma cells. PBL is commonly associated with human immunodeficiency virus (HIV) [2]. Given its aggressive and heterogeneous nature and rarity, the prognosis of PBL is still very poor. There are no standard treatment regimens and PBL still presents a therapeutic challenge to clinicians [3]. PBL is widely treated with cytotoxic chemotherapy similar to other aggressive B cell lymphomas, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and more intensive regimens, but the effects are limited [4]. In view of the poor outcomes of PBL, novel agents are needed. Antimyeloma agents, proteasome inhibitor bortezomib and immunomodulator (such as lenalidomide and thalidomide) have been tried based on the similarity between PBL and multiple myeloma and have been reported effective in some patients, but most with limited experience and temporary effects [3]. Here we report a refractory case of non-HIV-associated PBL, who was resistant to several lines of chemotherapy and finally achieved complete response (CR) with thalidomide monotherapy. We review the relevant literatures, too.

Materials and methods

Anamnesis

A 37-year-old woman with a 8-month history of intermittent hypogastric pain, diarrhea and anorexia was admitted to our institution in May 2013. She also complained fever and weight loss (4 kg). The patient's past medical history was unremarkable. During physical examination, only mild tenderness without rebound or muscle tension in the hypogastrium was found, with no peripheral lymphadenecatis or hepa-tosplenomegaly. Abdominal CT demonstrated diffuse wall thickening and enhancement of ileocecum, distal ileum and lower section of ascending colon, associated with peripheral...
lymph node enlargement and capillary increase, as well as mild wall thickening of colon transversum, lower segment of descending colon, sigmoid and appendix (Figure 1A). Gastroscopy revealed chronic inflammation. Enteroscopy showed multiple mucosal depressions in ileocecal valves, distal ileum and ascending colon, with irregular peripheral mucosa nodules. Biopsy of the depression identified the proliferation of heterotypical lymphoid cells. Neoplastic cells were positive for Ki-67 (>80%), CD138, CD38, MUM1, and partly CD30, while negative for CD20, CD79a, CD56, CD10, CD3, CD117, ALK and TIA-1 (Figure 2). Bone marrow aspiration and biopsy were free of lymphoma. The routine blood test showed moderate anemia (hemoglobin 81 g/L). The hepatic and renal functions, electrolyte, lactate dehydrogenase (LDH), serum globulin and immunoglobulin levels were within normal range. Serum protein immunofixation study revealed multiclonal immunoglobulin. Serology was negative for HIV, hepatitis B virus, hepatitis C virus, Epstein-Barr virus (EBV). The ultrasonography didn’t show any enlarged lymph nodes.

Diagnosis and treatments

Based on the clinical and pathologic results, the diagnosis of PBL at stage IVB was made, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1, an International Prognostic Index (IPI) of 2. Then low-intermediate risk group was indicated. The patient started treatment with standard CHOP (E) (cyclophosphamide, epirubicin, vincristine, prednisone, etoposide) chemotherapy. After four cycles, her abdominal pain relieved, but the CT scan demonstrated stable disease. Then the patient received treatment with CHOP-E regimen, in which epirubicin was replaced by liposomal doxorubicin. CT scan performed after the 2nd cycle still demonstrated that the disease was stable. Thereafter we gave the patient PAD (bortezomib, epirubicin, dexamethasone) chemotherapy. After 3 cycles, the degree of enteral wall thickening decreased, but less than 50%, also defining a stable disease. We initiated ESHAP chemotherapy and peripheral stem cell mobilization in April 2014. PET-CT performed in June 2014 presented wall...
thickening and hypermetabolism in ascending colon and colon transversum (Figure 3A). The autologous hematopoietic stem cell transplantation (auto-HSCT) was given to the patient subsequently, with BEAM (carmustine, etoposide, ara-C, melphalan) used as the preconditioning regimen. But sadly, the intestinal wall thickening was not improved, either (Figure 1B). Finally, we introduced TD (thalidomide 200 mg/d d1-28, dexamethasone 40 mg/d d1-4) chemotherapy to the patient in August 2014. Surprisingly, CT scan demonstrated partial response (PR) with more than 50% reduction of enteral wall thickening after 1 cycle (Figure 1C). Then the patient continued maintenance therapy with thalidomide 200 mg daily orally, without obvious side effect.

Results

After 10-month thalidomide monotherapy, CT scan showed the enteral and appendical wall wholly returned to normal in June 2015 (Figure 1D), indicating a CR state. The effect of thalidomide is surprisingly obvious, so the patient continued thalidomide therapy subsequently. PET-CT performed in November 2015 did not show any lesion of the disease (Figure 3B). The patient survives with no disease up to now.

Discussion

PBL was considered as a new disease entity in 2008 WHO classification. It is often associated with HIV infection and commonly occurs in oral cavity, but may occur in other extranodal organs [2]. 63% of PBL are HIV-positive [3]. In HIV negative PBL patients, about one third have iatrogenic immunosupression because of tumors, solid organ transplant and autoimmune disorders and the median age at presentation is 58 years, with a slightly male predominance of 1.9:1 [5].

The pathogenesis of PBL is not fully understood. Virus and genetic abnormalities are fre-
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EBV plays an important role in PBL tumorigenesis. EBV-encoded RNA (EBER) is detected in 46% of HIV-negative PBL patients [6]. The main recurrent cytogenetic abnormalities detected in PBL are MYC translocations, which occurs in about 50% of PBL [7]. The present case was a immunocompetent middle-aged woman with no EBV infection. The genetic examination was not conducted as a routine, so we didn’t know whether any genetic abnormalities was responsible for PBL genesis.

PBL is similar to B immunoblasts in morphology and demonstrates immunophenotype resembling plasma cell tumors, with no/weak expression of leukocyte common antigen (CD45) or the mature B cell markers [2]. The tumor cells of this case were positive for Ki67 proliferation index, plasma cell markers CD138, CD38 and MUM1, partly CD30, negative for B cell markers CD20 and CD79a. The immunophenotype was in accordance with the features of PBL.

In HIV-negative patients, although oral cavity is the major site of lesion, PBL can be observed at extra-oral sites. The most commonly involved extraoral site is the gastrointestinal tract. The major presentations of the case were abdominal pain, diarrhea, anorexia, which were similar to the previous report [8].

The treatment strategy of PBL is heterogeneous and standard treatment guidelines for PBL are lacking. Chemotherapy and/or radiotherapy with or without surgical excision have been used depending on the stage of the disease, the presence of systemic symptoms or the association with HIV infection [9]. An important aspect of the initial treatment is chemotherapy. CHOP and CHOP-like regimens are most commonly used. The overall response rate (ORR) to chemotherapy was 77% (CR, 46%; PR, 31%), but the median overall survival (OS) time was 14 months, with 5-year OS rate of 31% [4]. Because of the unsatisfactory survival rates, CHOP regimen is thought inadequate and current NCCN guidelines recommend more intensive regimens [3]. Patients with chemotherapy-sensitive disease might benefit from auto-HSCT in the first remission [10].

The plasma differentiation characteristics of PBL provide a rationale for the treatment of PBL using proteasome inhibitor bortezomib which is highly active in myeloma. Some successful clinical experiences of bortezomib have been reported and it was used single or in combination with other drugs [11-15]. This novel drug may play a promising role for the treatment of PBL. Although the present patient didn’t achieve satisfactory response to bortezomib possibly due to the heterogeneity of PBL, the potential role of bortezomib should be further explored.

Immunomodulators such as lenalidomide and thalidomide were previously reported for treat-
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To our knowledge, we report a case of non-HIV-associated extensive intestinal PBL and show the effectiveness of thalidomide as monotherapy in PBL first.

The immunomodulatory and antiangiogenic properties and the effect of directly inducing cancer cell apoptosis of thalidomide may contribute to its anti-tumor effect [17, 19]. The successful experience in this case suggests that thalidomide alone could have an anti-lymphoma effect in PBL. The advantages of thalidomide also include its slight hematopoiesis suppression, high tolerance and low price [13].

In conclusion, PBL is a type of high grade lymphoma. There is no consensus on the treatment of PBL. Given the anti-tumor activity and special advantages of thalidomide, it may be a promising choice in the treatment of PBL in the future, as monotherapy or in combination with other drugs. Further studies are needed to evaluate the therapeutic role of thalidomide in PBL.

Acknowledgements

The authors thank Dr Hailong Tang for providing help in preparation of the manuscript.

Disclosure of conflict of interest

None.

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