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Original Article

Efficacy and safety of lenalidomide in the treatment of a refractory multicentric Castleman disease patient

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Abstract: Castleman's disease (CD) is a lymphoproliferative disorder of unknown etiology characterized by enlarged hyperplastic lymph nodes with marked vascular proliferation. Three histological variants (hyaline vascular, plasma cell, and mixed) and two clinical types (localized and multicentric) have been described. Patients with multicentric Castleman's disease (MCD) have less favorable prognoses and require systemic treatments. The incidence of MCD is low but it has a very high percentage of recurrence despite treatment. Lenalidomide is an oral immunomodulatory drug (IMiD) approved in the United States for patients with multiple myeloma (MM). In recent clinical trials, lenalidomide has shown promising activity in other hematologic malignancies. Herein, we shared our experience on the safety and effectiveness of lenalidomide in the treatment of a 20-year old male patient with refractory plasma cell type MCD. This is a very rare case. As far as we know, the reports related to the use of lenalidomide on CD were limited to Prof Szturz P from Czech. In the report, we alsodo a critical and extensive of the published literature review.

Keywords: Castleman's disease, lenalidomide, multicentric Castleman's disease, refractory

Introduction

A 20-year-old male patient referred to the hospital with progressively increased mass in bilateralneck and repeated epistaxis more than one month on 3 Apr, 2012. Blood examination showed: WBC11 × 10E9/L, neutrophils account for 66.9%, hemoglobin 124 g/L, platelet 289 × 10E9/L. B-ultrasound (BUS) showed multiple sites of lymphadenopathy, including lymph nodes under bilateral chin, neck and supraclavicular. The cervical lymph node biopsy was done and the result indicated plasma-cell-type Castleman's disease at the muticentric clinical type (**Figure 1**). His previous medical history was unremarkable, with neither history of diabetes, smoking nor alcohol. Tests for HIV and human herpesvirus 8 (HHV-8) were negative. The physicians suggested the patient to do systemic chemotherapy. At that moment, the patient had not any of the typical B symptoms, fever, night sweats or loss of weight so he refused the advice coming from the doctor and preferred in the out patient follow-up. One year later, the patient came back to the hospital for follow-up with antibiotic-uncontrolled fever, sore throat, nausea and vomiting on 24 Mar, 2013. This time, the blood routine examination showed: WBC 10 × 10E9/L, hemoglobin 73 g/L, platelet 18 × 10E9/L. Bone marrow showed: the proportion of plasma cells significantly increased together with abnormal lymphocytes. Immunohistochemical staining showed: CD3 (-) CD5 (-) CD15 myeloid (-) CD20 scattered (+) CD34 (-) CD38 (+) CD56 (-) CD61 megakaryocytes (+) CD79 ascattered (+) CD-138 (+++) CD235 aerythroid (+) Tdt (-), MPO myeloid (+). After reviewed the lymph node slides by several experts from different institutions, diagnosiswas still the plasma-cell-type MCD. Physicians considered bone marrow was infiltrated by MCD. R-COP chemotherapy treatment was initiated with combination of Rituximab, Cyclophosphamide, Vindesine and Dexamethasone. After one course the superficial lymph node was significantly reduced through BUS-examination. So the same regimen was continued. However, in the second cycle during

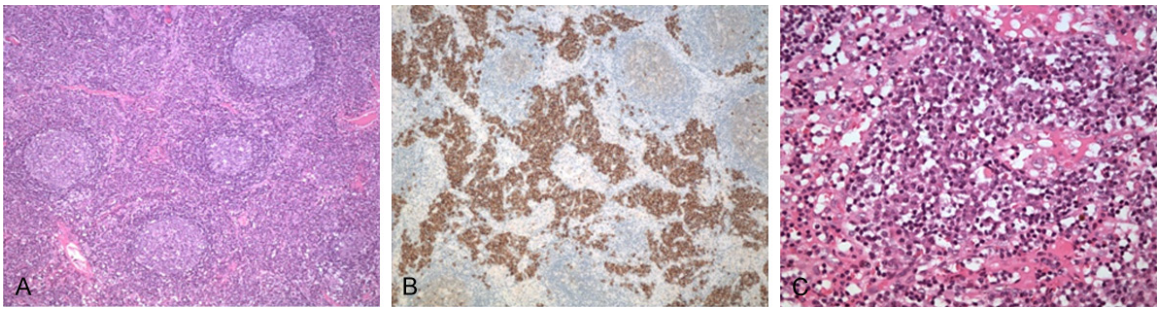

Figure 1. The cervical lymph node biopsy from our patient at the first onset of MCD: A. Diffuse plasma cell proliferation in the interfollicular region. (Original magnification × 100). B. Anti-CD38 antibody staining. (Original magnification × 100). C. Cluster of mature plasma cells is filling the sinusoids. (Original magnification × 400).

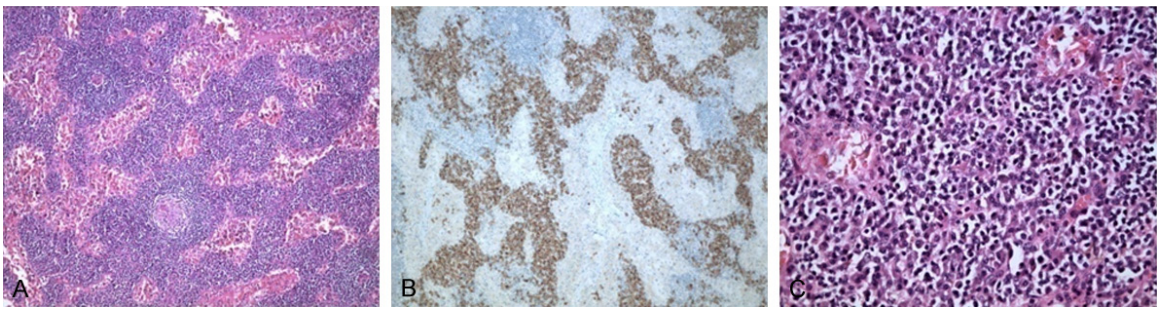

Figure 2. The leftarmpit lymph node biopsy from our patient when he experienced PD for the third time: A. Lymph node lymphoid hyperplasia with a large number of plasma cells lymphatic, sinus expansion, almost all of the inner medulla proliferation of plasma cells. (Original magnification × 100). B. Anti-CD38 antibody staining. (Original magnification × 100). C. Numerous plasma cells in the interfollicular region. (Original magnification × 400).

the injection of Rituximab the patient complained chest tightness, shortness of breath, dizziness, and the blood pressure reduced to 78/43 mmHg from 112/78 mmHg before the administration of Rituximab, the drip was stopped immediately at a consideration of a severe allergy to Rituximab. Three cycles of COP regimen were given in the following days. Before the fifth chemotherapy, examination results suggested that platelet reduced again, with increased neck lymph node. The patient was at a state of progressive disease (PD). So the chemotherapy was changed to CHOP regimen. The response after 2 months therapy was not satisfied, therefore, this treatment was terminated and ECHOP (etoposide, cyclophosphamide, adriamycin, vincristine, and prednisone) was selected as a third-line therapy. The mobilization and collection of peripheral blood stem cells was started on 12 Aug, 2013 and the patient received autologous stem cell infusion on 9 Sep, 2013. The total input of stem cells and maintainagents was up to 182 mL, MNC 3.62 × 10E8/Kg, CD34 + 1.88 × 10e6/L. After that, the cervical lymph nodes shrinked and platelet was up to normal. The patient got partial response and took 100 mg/d thalidomide for maintenance-therapy. Unfortunately, the examination showed the patient was at a state of PD on Feb, 2014 and one cycle of CHOP and two cycles of ECOP chemotherapy showed limited efficacy. The assessment of the disease was stable disease (SD) and maintained 4 months; the patient fell into PD for the third time and came to our hospital on 15 Sep, 2014. PET-CT documented regional body scan multiple nodes of different sizes with elevated metabolic FDG (SUV maximum of about 9.28) and spleen elevated metabolic FDG (SUV maximum of about 7.81), which indicated the presence of tumor tissue activity after considering chemotherapy. And second lymph node biopsy was done from the leftarmpit, the result showed: lymph node lymphoid hyperplasia with a large number of plasma cells lymphatic, sinus expansions, almost all of the inner medulla prolif-

eration of plasma cells. Immunohistochemical showed: CD3 (+), CD20 (+), CD21 (follicular dendritic cells +), CD79a (+), CD38 (+), IGg4 (+, less), Kappa (K) (+), Lambda (λ) (+), Ki-67 (+), EBER (-), (**Figure 2**). The patient demonstrated refractory disease, making him potential candidate for experimental treatment. Based on literature review and our experience, we chose lenalidomide with a dosage of 10 mg per-orally on days 1-21 in a 28-day cycle. PET/CT showed complete disease remission after 2 cycles. The monotherapy with lenalidomide was very well tolerated by the patient. Until now, the patient stillinsists on takinglenalidomide, andmonthlyfollow-uptoour clinic. The current assessment of the disease with non-PET-CT is CR.

Discussion

Castleman's disease (CD) is a rare disorder involving lymphoid tissue proliferation with undetermined etiology that was first described by Castleman in 1956 [1]. It comes in two forms (unicentric and multicentric) and three types of variants (hyaline vascular, plasma cell, and mixed). Unicentric Castleman's disease (UCD) is confined to a single lymph node; it is usually asymptomatic though sometimes has local manifestations related to mass effects. In contrast, multicentric Castleman's disease (MCD) typically presents with lymphoid hyperplasia at multiple sites; it is associated with systemic symptoms and abnormal laboratory findings, with a less favorable prognosis. Relatively speaking, the type of hyaline vascular proliferation is more common, more benign and has a good prognosis post-excision. Most of the patients diagnosed with the hyaline vascular type are asymptomatic. On the contrary, the plasma cell variant is less common but more aggressive. It can involve any organ and usually associated with multiple lymphadenopathies. Patients with plasma cell variant are usually symptomatic and may need chemo or radiotherapy [2, 3].

Patients with MCD have less favorable prognoses and require systemic treatment. Currently, the effective therapeutic alternatives in MCD include treatment with monotherapy of rituximab or in combination therapy with cytotoxic chemotherapeutic agents (such as etoposide, cyclophosphamide, adriamycin, vincristine, and prednisone), immunomodulatory drugs (thalidomide), anti-IL-6 (siltuximab) or against its receptor (tocilizumab). However, several approved therapies for MCD cannot be uniformly applied due to the intolerable side effects. The cytotoxic chemotherapy has been widely used to treat MCD with varying degrees of response because of the toxicity risk of the treatment. MCD with plasma cell type is very rare. The percentage of recurrence of this disease is especially high despite treatment. There are often no standard therapy recommendations in case of ineffectiveness. For those patients with relapsed/refractory disease novel experimental approaches may be a good opportunity.

Lenalidomide is an immunomodulatory drug (IMiD), which is well established and approved in the treatment of multiple myeloma (MM) and 5q-myelodysplastic syndrome (MDS) [4-7]. The mode of action includes immune modulation, anti-angiogenetic, anti-inflammatory, and anti-proliferative effects. In recent clinical trials, lenalidomide has shown promising activity in hematologic malignancies, including chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) [8-14].

We described here our experience of lenalidomide in the treatment of a refractory plasma cell type of MCD. This is a very rare case. As far as we know, the report of use of lenalidomide on CD was limited to Prof Stutz P et al. from Czech [15-19]. Our patient is a very young male with a long and complicated clinical story. He received several chemotherapy regimens and autologous stem cell transplantation, but he still experienced PD two and half a year later since the onset of disease. After a long communication with the patient and his parents we selected lenalidomide mono-therapy for him. Fortunately, we observed an excellent effect on this patient with manageable toxicity. So far the patient insisted on lenalidomide maintenance therapy. Grade III thrombocytopenia and pneumonia occurred once again, which were controlled and cured by supportive care. The current assessment of the disease with non-PET-CT is CR 7 and a half months passed sincestart taking lenalidomide. Taking into consideration the good effect and acceptable toxicity profile, the authors believe lenalidomide maybe represent an attractive alternative agent for pati-

ents who carry on the relapsed/refractory CD although confirmation in a larger series of similar patients is required. Nevertheless, efforts in this area may ultimately affect treatment choices for these individual patients.

Disclosure of conflict of interest

None.

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