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Case Report Open Access

Successful Treatment of Follicular Non-Hodgkin's Lymphoma with an off-label Use of Lenalidomide: A Case Report

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Abstract

Lenalidomide is an immunomodulatory agent, with anti-angiogenic and anti-neoplastic properties, which has been approved for multiple myeloma and for deletion 5q myelodysplastic syndromes. Lenalidomide is also effective in and tolerated well by patients with follicular lymphoma (FL), diffuse large B-cell lymphoma and transformed large cell lymphoma. This report describes a patient with relapsed/refractoryadvanced-stage follicular non-Hodgkin's lymphoma (fNHL) treated with lenalidomide oral monotherapy. The patient refractory to 2 lines of chemotherapy was treated subsequently with an off-label use oflenalidomide 25 mg tablets. After 6 months follow-up, the patient has no detectable disease. The treatment was well tolerated and led to the complete regression of an aggressive variant of the disease.

Keywords: Lenalidomide; Follicular non-Hodgkin'lymphoma; Immunomodulatory, Refractory

Introduction

Lenalidomide, an analogue of thalidomide, is an orally administered second generation immunomodulator with anti-angiogenic, antineoplastic, anti-inflammatory and pro-erythropoietic properties. Currently, lenalidomide is indicated: i) in combination with dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy and ii) for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1–risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.The precise mechanism of action of lenalidomide is not known [1]. It inhibits tumor growth, induces apoptosis, and directly kills tumor cells in B-cell non-Hodgkin's lymphoma (NHL) cell lines [2,3]. Use of lenalidomide in proliferative neoplasms has recently intensified due to the agent's success in multiple myeloma and myelodysplastic syndrome where it acts to alter immune homeostasis and modulate inflammation within the bone marrow microenvironment. Studies in relapsed and refractory B-cell chronic lymphocytic leukemia (B-CLL) as well as NHL solid malignancies such as central nervous system, ovarian, and renal cell carcinoma demonstrate the potential of this drug in diverse neoplastic processes [4,5]. fNHL is one of a group of diseases known collectively as NHLs, cancers arising from the lymphoid cells of the immune system. These cells normally have a key role in protecting the body from pathogenic microorganisms. Malignant transformation of lymphocytes results in their uncontrolled replication usually starting within the lymph nodes, mainly those of the neck, armpits and groin.The incidence of NHL is similar in men and women and increases with age: rates increase sharply in people over 50 and around two-thirds of all cases are diagnosed in people over 60 years of age [6]. The majority of cases of fNHL are diagnosed at an advanced stage (III/IV) [7]. We report the case of a patient affected by follicular non-Hodgkin's lymphoma successful treated with an off-label use of lenalodomide.

Case Report

A 62-year-old male patient was diagnosed with advanced-stage (IIIA) follicular non-Hodgkin's lymphoma (fNHL) in April 2011. Briefly, treatment schedule was the following: 40 mg/m^2 oral fludarabine (F) on days 1–3, 10 mg/m^{2}i.v.mitoxantrone (N) on day 1 every 28 days for six cycles (FN regimen), followed by one course of infusions of 250 mg/m^2 rituximab. Unfortunately, 45 minutes into infusion of rituximab, patient developed a severe allergic reaction with i) breathing problems and ii) a serious fall in blood pressure. Infusion of rituximab was stopped immediately. In everyday practice, the indication for second-line chemotherapy after immediate or delayed failure of first-line chemotherapy is considered. In our case, the patients was treatedwith a three-drug combination of ifosfamide, epirubicin and etoposide (IEV regimen) [8] as second-line chemotherapy. The IEV schedule was as follows: ifosfamide 2,500 mg/m^2/day i.v. over 4 hours followed by mesna (3 g/m^2) and hydration over 10 h. daily to protect against urothelial toxicity on day 1 to 3, epirubicin 100 mg/m^2 i.v. on day 1; etoposide 150 mg/m^2 i.v. on days 1 to 3. Courses were repeated every 21 days, with a target total of three courses; chemotherapy was given in an outpatient setting. The patient was restaged after completion of IEV chemotherapy. Unfortunately, our patient was considered as having no response to the treatment. In September 2012, for disease progression, the patient was treated with bendamustine, a bifunctional purine analog/alkylating agent, approved by the US Food and Drug Administration (FDA) for treatment of patients with rituximab refractory indolent non-Hodgkin's B-cell lymphomas [9]. Bendamustine was administered as monotherapy at a dose of 120 mg/m^2, as an intravenous infusion (over approximately 1 hour) on days 1 and 2 of a 21- to 28-day cycle. After

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2 cycles of therapy, treatment with bendamustine was interrupted for treatment-resistant. At this point, considered i) the young age and general conditions of the patient ii) progression of the pluriresistant disease and iii) the presence in literature of non-Hodgkin lymphoma response to the treatment with lenalidomide, [10-12] in November 2012 it was decided to treat the patient with an off-label use of lenalidomide. Sadly, in our Local Sanitary Agency (LSA) Naples 3 South Italy (i.e. LSA, NA 3 South, Campania Region), prescriptive pathway of the off-label drug use is really complicated. In fact, all the necessary approvals arrived after 2 months (approval of the director of the sanitary district, favorable opinion of the ethics committee, approval of the director of the pharmaceutical department). Finally, in January 2013 the patient was treated with oral lenalidomide 25 mg once daily on days 1 to 21, every 28 days, for 24 weeks (six cycles). Patient was staged and restaged with computed tomography (CT) of the initially involved sites; the use of PET was optional. Response was evaluated after two cycles and every other cycle thereafter. The patient achieved partial remission after two cycles, and complete remission after four cycles of lenalidomide. The duration of response is ongoing.

Discussion

In conclusion, lenalidomide was very well tolerated in our patient with relapsed and multiple refractory follicular non-Hodgkin's lymphoma. The result was truly amazing. Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma in the western hemisphere accounting for 22% of all cases [13]. Being an indolent lymphoma, the disease course of FL is one of remissions and relapses with conventional chemoimmunotherapies followed not infrequently by development of resistance and/or transformation into a more aggressive histology. The sore point was the complicated prescriptive pathway of the off-label drug usethat delayed treatment. While slow accrual has led to premature closure of several key clinical trials [14], continued cooperative efforts are necessary.Undoubtedly the healthcare professionals should carefully consider the balance of risks and benefits of any off-label use, but in the face of scientific evidence, in some cases, the approvals should be facilitated.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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