Case Report
The Efficacy and Safety of Lenalidomide plus Rituximab in an Orbital Relapse of Diffuse Large B-Cell Lymphoma

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1. Background
Diffuse large B-cell lymphoma (DLBCL), with an annual incidence of 7-8 cases per 100,000 people per year, is the most common subtype of aggressive non-Hodgkin’s lymphoma [1], and notwithstanding recent chemotherapeutic advances, disease relapse occurs in up to half of all patients [2].

The extranodal presentation to the head at the onset of the disease is very uncommon [3]. However, orbital lymphomas represent about 5–15% of extranodal lymphomas and approximately 50% of all primary malignant tumors of the orbit. The incidence of an isolated recurrence at the orbit remains unknown [4]. It usually occurs in elderly patients. It is characterized by a poor prognosis, and until now, it lacks standard therapy [5].

Multiple therapies targeting the biological pathways of B-cell lymphomas are under clinical evaluation. Among them, lenalidomide, an immunomodulatory agent with both tumoricidal and immunomodulatory effects, appears particularly promising. Its tumoricidal effects include inhibition of vascular endothelial growth factor-mediated microvessels formation, leading to cancer cells’ cycle arrest and apoptosis [6]. Immunomodulatory effects of lenalidomide include inhibition of proinflammatory cytokines such as tumor necrosis factor α, increased the cytotoxicity of natural killer (NK) cells, inhibition of regulatory T cells, and increased anti-inflammatory cytokines [7–9]. The association of lenalidomide with the anti-CD20 monoclonal antibody rituximab has been studied in several trials, showing encouraging results [10, 11].

2. Case Presentation
A 74-year-old male presented to our department with a red, ulcerated plaque on the left arm with three months of duration. Recently, the lesion was rapidly increasing in size and started bleeding. Excisional biopsy was performed, and the material was sent for histopathological examination. Microscopic examination revealed diffuse infiltrates of large noncleaved cells, with large nuclei and conspicuous nucleoli. Immunohistochemical evaluation revealed the abnormal cells to be CD20+ Bcl6+ MUM1+ CD10–c-Myc– and CD3–. The proliferative index (Ki 67) was 90%. A diagnosis of
nongerminal center diffuse large B-cell non-Hodgkin’s lymphoma (non-GCB DLBCL) was established. The bone marrow did not reveal any involvement of lymphoma. A fluorodeoxyglucose positron emission tomography (FDG-PET) was performed and it showed a diffuse involvement of mediastinal nodes.

The patient was subsequently started on systemic chemotherapy with rituximab combined with liposomal doxorubicin, cyclophosphamide, vincristine, and prednisone (R-COMP) for six cycles, followed by involved field radiotherapy on the arm. He well tolerated the therapy and obtained a complete remission.

Two years after the completion of therapy, the patient came to our observation with a left eye swelling leading to exophthalmos and blurred vision (Figure 1). A core biopsy was performed, and it revealed a disease with the same immunohistochemical panel of the diagnosis. Magnetic resonance imaging (MRI) showed a high-density process involving the left orbit and the surrounding soft tissues. An FDG-PET/Tc excluded any systemic involvement.

Bone marrow biopsy was not performed due to patient refusal.

At the time of the relapse, the patient was 76 years old and considered ineligible for high-dose second-line chemotherapy. Moreover, radiotherapy was not considered for the large extension of the disease because of the long-term side effects of rays on the patient’s sight. In the absence of standardized therapy for these patients, we chose the combination of rituximab (375 mg/mq D1) plus lenalidomide (15 mg D1–21) every 28 days for 6 courses. At the end of the therapy, complete remission was confirmed by MRI and FDG-PET/CT scan evaluation (Figure 2).

After remission, lenalidomide (15 mg D1–21, every 28 days) monotherapy maintenance was started and planned to be continued until progression or unacceptable toxicity. After 24 months since the start of lenalidomide monotherapy, the patient is still in complete remission with an excellent quality of life.

3. Discussion and Conclusions

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin’s lymphoma, accounting for approximately 30% of new cases. Despite the high rate of response to first-line standard chemotherapy R-CHOP, 30–40% of patients are refractory or relapse. High-dose chemotherapy followed by autologous stem cell transplant is considered a good option in relapsed/refractory young fit patients, with rates of overall survival at 4 years up to 60% [12]. Nevertheless, for patients not eligible for intensive salvage therapy, including...
most >70 years of age, front-line represents almost always the only chance for a cure, especially in non-GCB subtypes [13].

In our case, a 77-year-old patient presented with a relapsed non-GCB DLBCL involving the orbit. Long and even short-term prognosis of this localization in elderly patients is considered unfavorable, and we do not have a recommended therapy yet. Our patient was not eligible for standard high-dose chemotherapy, and radiotherapy was considered palliative. We decided to use the association of lenalidomide and rituximab as a manageable and well-tolerated therapy [14]. The efficacy of lenalidomide monotherapy has been investigated in heavily-pretreated DLBCL, resulting in higher overall response rate and longer progression-free survival as compared to standard intensive chemotherapy [15].

Furthermore, as recently observed in large multicenter randomized trials, a positive trend favoring lenalidomide plus R-CHOP versus R-CHOP alone was observed in previously untreated high-risk DLBCL [16]. Moreover, this drug association has also been tested in refractory/relapsed aggressive NHL involving the central nervous system and the ocular district, recording promising results [17]. Of note, the incidence of grade 3-4 toxicities was found remarkably higher among patients treated with standard chemotherapy as compared to those treated with lenalidomide plus rituximab [18], encouraging the use of this drug association for patients considered unsuitable for intensive treatment.

Finally, lenalidomide as maintenance therapy, meaningfully improved the outcome of patients with DLBCL if compared to placebo. Intriguing, the progression-free survival benefit of lenalidomide maintenance was equally important in patients who achieved complete remission as in those achieving a partial remission [19].

Therefore, our case report shows that the association of lenalidomide plus rituximab could be an option in the treatment of isolated orbital relapse of systemic non-GCB DLBCL. This strategy, improved by the following lenalidomide maintenance treatment, might be an attractive and well-tolerated therapeutic option in relapsed/refractory elderly patients who are unfit for intensive salvage chemotherapy.

Consent
Written informed consent was obtained from each patient for publication of this case report and accompanying images.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

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