Synergistic Effect and Tolerance of Concurrent Radiotherapy and Lenalidomide Use in Relapsing Mantle Cell Lymphoma: A Case Report

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E-pub: 11/20/2020 https://doi.org/10.7812/TPP/19.156

ABSTRACT

Introduction: Mantle cell lymphoma is an aggressive disease. Limited treatment options are available for refractory or relapsing presentation. We report the first case, to the best of our knowledge, of concurrent radiotherapy and lenalidomide use in this setting, focusing on its possible synergy and tolerance.

Case Presentation: A 76-year-old man with a history of mantle cell lymphoma presented with ptosis of the left eyelid, eyelid swelling, and nasal obstruction. Results of positron emission tomography-computed tomography revealed a pathologic fluordeoxyglucose uptake at the pharynx and left eyelid. He received treatment with ibrutinib, which was stopped 3 months later because of digestive toxic effects. Radiotherapy for the eyelid and pharynx was performed at a dose of 18 Gy, with concurrent lenalidomide administration. Evaluation 3 months later revealed complete disappearance of the 2 relapse sites.

Discussion: This case highlights the role of concomitant lenalidomide treatment and low-dose radiotherapy in patients with relapsing mantle cell lymphoma. Use of this combination treatment has achieved a complete local control with a safe toxicity profile. The case also illustrates the possible lenalidomide-induced radio sensitization.

INTRODUCTION

Mantle cell lymphoma (MCL) is a subtype of B-cell lymphoma that accounts for 3% to 6% of non-Hodgkin lymphoma.1 It is commonly considered to have aggressive behavior with poor prognosis. Refractory or relapsing presentation that involves the eyelid and pharynx is observed in only 10% of cases.2 There is no standard therapy for patients with relapsing MCL. We report a case of relapsing MCL of the eyelid and pharynx treated with concurrent low-dose radiotherapy and lenalidomide with complete response and safe toxicity profile.

CASE PRESENTATION

Presenting Concerns

A 76-year-old man with a history of coronary bypass was diagnosed with stage IV MCL disease (bone marrow infiltration) in 2008. He received 8 courses of R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone). Complete remission was achieved. Maintenance rituximab was administered for 2 years. In 2017, after 7 years of clinical, biological, and radiologic remission, the patient presented with a pathology-proven nasopharyngeal relapse. He underwent chemotherapy with rituximab, dexamethasone, and bortezomib, and his condition improved. One year later, he presented with ptosis of the left eyelid, eyelid swelling, nasal obstruction with dyspnea, and snoring. The patient had systemic B symptoms (fever and night sweats). Results of positron emission tomography-computed tomography revealed pathologic fluordeoxyglucose uptake at the pharynx (maximum standardized uptake value = 3.8) and the left eyelid (maximum standardized uptake value = 3.4) (Figures 1 and 2). According to the Mantle Cell Lymphoma International Prognostic Index scoring system,3 the patient was considered high risk. Pharyngeal biopsy confirmed the diagnosis of MCL. Immunohistochemical studies showed overexpression of CD20, CDS, and cyclin D1. His Ki-67 level was 30%.

Therapeutic Intervention and Treatment

The patient started receiving treatment with ibrutinib in September 2018. Treatment was stopped 3 months later because of gastrointestinal intolerance. Subsequently, the patient was treated with 3-dimensional conformal radiotherapy for the eyelid and pharynx at a dose of 18 Gy per 10 fractions with concurrent lenalidomide (25 mg/d for 3 weeks per month). Clinical improvement was observed after 3 fractions (5.4 Gy), with a complete disappearance of swelling and nasal obstruction at the end of treatment. Grade II dysphagia occurred early during treatment but was well manageable and resolved within 2 weeks.

Follow-Up and Outcomes

Three months later (in May 2019), a complete clinical and radiologic response in the 2 relapsing sites was observed with no sequelae (Figures 3 and 4). A timeline of the case appears in Table 1.

DISCUSSION

MCL is a distinct subtype of non-Hodgkin lymphoma with specific clinical, biological, and molecular characteristics.

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Keywords: radiotherapy and lenalidomide, relapsing mantle cell lymphoma
Figure 1. Positron emission tomography-computed tomography with the full-color images showing pathologic fluorodeoxyglucose uptake in the pharynx.

CASE REPORT
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Figure 1. Positron emission tomography-computed tomography with the full-color images showing pathologic fluorodeoxyglucose uptake in the pharynx.
Figure 2. Positron emission tomography-computed tomography with the full-color images showing pathologic fluorodeoxyglucose uptake in the eyelid.
MCL demonstrates heterogeneity in its histopathologic and molecular genotypes, which relate to different clinical presentations. Thus, MCL management varies greatly among different subtypes.

Extranodal involvement is common, especially in the bone marrow, peripheral blood, gastrointestinal tract, and Waldeyer ring. Ocular involvement is rare but most commonly occurs in the orbit (90%), lacrimal gland (50%), and eyelids (50%). Our patient had ocular involvement that was detected on positron emission tomography-computed tomography 8 years after a complete response of primary treatment.

Outcome is poor for patients with relapsing or refractory disease, and there is no standard therapy in such cases. The treatment choice should be primarily made on the basis of the patient’s previous treatment, their comorbidities and performance status, the regimen’s expected toxic effects, and the clinician’s experience with regimens. Several chemoimmunotherapy regimens have been explored, including aggressive combination therapy, such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) for some patients, particularly as a bridge to hematopoietic cell transplantation.

The mainstay of therapy in this setting relies on targeted therapy to disrupt the B-cell receptor signaling pathway with ibrutinib, a Bruton tyrosine kinase inhibitor. In our case, treatment with ibrutinib was associated with severe gastrointestinal toxic effects. Other emerging drugs that have received approval in relapsing and refractory disease are immunomodulators, such as thalidomide and lenalidomide.

To the best of our knowledge, this is the first reported case of relapsing MCL treated with concomitant lenalidomide administration and radiotherapy to a total dose of 18 Gy with complete local control. Use of this combination treatment has achieved an excellent local control in a patient with myeloma. Considering the high efficacy of radiotherapy, this case could point to possible lenalidomide-induced radio sensitization; however, further studies are needed to support this hypothesis.

Several phase 2 studies tested lenalidomide as monotherapy for relapsing MCL and revealed encouraging outcomes and a safe toxicity profile. Overall response ranged from 28% to 53%. Grade 3 to 4 hematologic adverse events occurred in at least 5% of patients, including neutropenia, thrombocytopenia, leukopenia, anemia, and febrile neutropenia. Nonhematologic adverse events,
including neuropathy, thrombosis, and teratogenicity, were also reported.6

The role of radiotherapy for MCL is still unknown, although radiosensitivity has been demonstrated in vitro.7 Retrospective studies have reported favorable outcomes with the use of involved field radiotherapy for advanced or relapsing MCL. Rosenbluth and Yahalom8 reported results of 21 patients treated with involved field radiotherapy for MCL (mainly stage IV or relapsing disease). The mean radiotherapy dose was 30 Gy (10–45 Gy).8 Encouraging results were reported (overall response rate of 100%, a complete response in 64%, and a median time to progression of 10 months). The authors suggested that a total dose of 24–30 Gy was reasonably effective for MCL. However, Neville et al.9 suggested a dose effect on the risk of local failure. Higher doses increased time to local progression.

This case report suggests that low-dose radiotherapy with lenalidomide use is effective. However, caution must be taken with combination therapies because there can be increased toxic effects. The dysphagia seen in our patient at a dose of 18 Gy was unexpected and can be attributed to a synergistic effect on toxicity. Thus, lower-dose radiotherapy in combination with lenalidomide is encouraged for relapsing disease.

**CONCLUSION**

Low-dose radiation therapy and lenalidomide use may be an effective and safe alternative in the treatment of relapsing or refractory MCL. A possible synergistic effect is suggested, and caution should be applied. This observation should be followed up with further studies to assess efficacy and early and late toxic effects.

**Disclosure Statement**

The author(s) have no conflicts of interest to disclose.

**Acknowledgments**

Kathleen Louden, ELS, of Louden Health Communications performed a primary copy edit.

**How to Cite this Article**


**References**


**Table 1. Timeline of the case**

<table>
<thead>
<tr>
<th>Date</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Results</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Stage IV mantle cell lymphoma (bone marrow infiltration)</td>
<td>8 courses of R-CHOP plus maintenance rituximab</td>
<td>Complete remission</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2017</td>
<td>Nasopharyngeal relapse</td>
<td>Chemotherapy with rituximab, dexamethasone, and bortezomib</td>
<td>Complete remission</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2018</td>
<td>Eyelid and pharyngeal recurrence</td>
<td>Conformal radiotherapy for the eyelid and the pharynx to a dosage of 18 Gy for 10 fractions with concurrent lenalidomide</td>
<td>Complete remission</td>
<td>Complete remission</td>
</tr>
<tr>
<td>May 2019</td>
<td>——</td>
<td>——</td>
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R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone.
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