Efficacy of Bortezomib in Systemic Extramedullary Localizations of Multiple Myeloma

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Introduction

Extramedullary (EM) localizations are rarely found at the initial diagnosis of a patient with multiple myeloma. Few studies have systematically evaluated the incidence, presenting features, and prognosis of EM lesions. Overall, 13% of multiple myeloma (MM) patients have EM involvement: 7% at diagnosis and 6% during follow-up. EMs are unusual and typically occur as a solitary plasmacytoma, most commonly in the upper respiratory tract, including the nasal cavities, paranasal sinuses, and nasopharynx. Approximately 15% of patients with EM progress to full disease. We describe here an unusual case of a patient with aggressive MM who presented with multiple organ localizations.

Case Report

A 42-year-old woman was referred to our hematologic emergency department in February 2009, with severe respiratory failure. At hospitalization, a computed tomography (CT) scan showed a bulky mass in the mediastinum (8 cm in diameter) that was poorly dissociable from the epiaortic vessels. The mass also modestly reduced the size of the ipsilateral bronchi and was associated with bilateral pleural effusion, with consolidation of the right lung and a thin flap of pericardial effusion. An abdominal CT scan demonstrated a subserosal polypoid solid mass in the right kidney and another mass medial to the left psoas muscle with a longitudinal diameter of 3.2 cm. In the pelvic site, a CT scan showed a large localization, 15 cm in diameter, which expanded from the ovary. In the breast, a hyperdense nodule of 2.5 cm was also revealed. A CT scan of the bone showed osteolytic lesions in the left clavicle and the left humerus, and a hypertrophic mass of 7.5 cm in the left hemisacrum (Figure 1). A CT-guided biopsy of the mediastinal mass was performed, and histopathology examination revealed atypical plasma cells that had an eosinophilic cytoplasm with eccentric nuclei. Immunohistochemical staining was positive for κ chains expression, CD79α, and PC1; it was negative for CD20. Thoracentesis was performed, and cytology examination of the pleural fluid showed many immature large plasma cells with an atypical morphology. Laboratory tests performed at the time of patient hospitalization showed the following levels: hemoglobin at 6 g/dL, white blood cells at 10.8 × 109/L, platelets at 407 × 109/L, creatinine at 0.9 mg/dL, lactate dehydrogenase at 600 U/L, and an increased ß2 microglobulin at 3.6 mg/L. Serum protein electrophoresis detected a rare profile with 3 M protein spikes in the β band. Serum immunofixation demonstrated a 3-monoclonal immunoglobulin (Ig) A-κ. Urine immunofixation and protein electrophoresis revealed the presence of Bence-Jones κ-chains. Bone marrow aspiration showed an infiltration by 40% plasma cells.

Due to lung disease localizations and severe respiratory failure, the patient was initially treated with intermediate-dose chemotherapy (cyclophosphamide 2 g, for 2 doses on days 1 and 4) and high-dose dexamethasone. She obtained only a partial reduction of the EM, and during the neutropenic phase she developed a pulmonary aspergillosis. At 30 days after the start of chemotherapy, and with prompt antibiotic and antifungal therapy, the patient experienced an improvement of the pulmonary infection and of respiratory function.

Considering the rare presenting features and the clinical conditions of the patient, bortezomib (Velcade, Millennium Pharmaceuticals) was started at a dose of 1.3 mg/m² on days 1, 4, 8, and 11, according to the classic schedule, together with dexamethasone, 20 mg for 2 consecutive days after each bortezomib administration, every 21 days. After 3 cycles of treatment, disease re-evaluation was performed in accordance with the International Uniform Response Criteria for MM. The patient achieved a near complete response, with less than 5% plasma cells in the bone marrow and reduction by 50% of the EM. After 6 cycles of therapy, a CT scan showed EM reduction of 75%. Four months after the start of bortezomib therapy, the patient experienced EM progression, with development of new EM masses in the left adrenal gland of 5.5 cm in diameter, and a polypoid mass of 7 cm in the soft tissues of the left gluteus. The patient was thus treated with salvage chemotherapy (dacarbazine, nimustine, and vincristine [DAV]) and underwent collection of peripheral blood stem cells, followed by infusion of melphalan (190 mg total
reported to be at high risk of developing EM. Two recent patients younger than 40 years, another subset of patients explain this finding. Interestingly, Varettoni and coworkers as CT and magnetic resonance imaging, may partially widespread use of more sensitive imaging techniques, such at diagnosis and during follow-up, in recent years. The a statistically significant increase of EM involvement, both MM population. Furthermore, the latter study reported EM MM is significantly lower as compared with the entire series of patients with MM in EM disease have shown that

In conclusion, several single case reports and small dose). An autologous peripheral stem cell transplant was performed in January 2010. Four months after the procedure, the patient developed a mass in the cervical spine, which was treated with radiotherapy. At the time of this report, the patient was receiving treatment for progression of disease with a combination chemotherapy regimen of lenalidomide (Revlimid, Celgene), adriamycin, and dexamethasone.3

Discussion

In the literature, several different studies have described the initial features and the outcome of MM with EM. In 2 different analyses by Bladè and colleagues, EM involvement was observed in 15–20% of patients at diagnosis and in an additional 15% of patients during follow-up. The first of these studies focused on 53 patients with IgD MM, a subtype known to be associated with a high frequency of EM lesions.4 The second study described a series of 72 MM patients younger than 40 years, another subset of patients reported to be at high risk of developing EM.5 Two recent studies—a survey of 3,600 MM patients in the Taiwan National Cancer Registry and a longitudinal study on 1,003 consecutive MM patients reported by the University of Pavia—confirmed that the median age of patients with EM MM is significantly lower as compared with the entire MM population.6,7 Furthermore, the latter study reported a statistically significant increase of EM involvement, both at diagnosis and during follow-up, in recent years. The widespread use of more sensitive imaging techniques, such as CT and magnetic resonance imaging, may partially explain this finding. Interestingly, Varettoni and coworkers reported that the presenting features of patients with EM were significantly different from those of the whole cohort of MM patients without EM in regard to age, sex, MM subtype, disease stage, and prior history of monoclonal gammapathy of undetermined significance (MGUS).1 EM MM was associated with younger age and was more common in men. A prior history of MGUS was less frequent in patients with EM MM. Nonsecretory subtype, λ chain expression, advanced stage, and extensive bone disease were significantly more common in EM MM.1

Some authors reported a high incidence of EM at the time of relapse after autologous or allogeneic stem cell transplant.7 In a study of 280 cases from the Spanish Registry, the reported incidence of EM relapse after autologous hematopoietic stem cell transplant was 14%, whereas in a study of 70 MM patients receiving reduced-intensity allogeneic stem cell transplant, one-third had EM relapse in the absence of marrow progression.9

We found no published reports describing the association of EM MM with multiorgan involvement consisting of the mediastinum, breast, kidney, adrenal gland, ovary, skin, and bone. The prognosis of these patients with EM is very poor, and currently, the optimal therapeutic strategy of this subset of patients is still a matter of debate. In particular, recent reports found that single-agent thalidomide had low efficacy for the treatment of EM disease.10,11 In contrast, bortezomib-based regimens seem to be more promising in these patients. A few other anecdotal cases have been reported (Table 1). De Giglio and associates described a patient with MM who developed several hepatic plasmacytomas during treatment with thalidomide; the patient received bortezomib and had a transient response.12 Patriarca and colleagues described a patient with paraspinal and rib plasmacytomas with cranial nerve palsies, who responded to bortezomib with radiologic resolution of cerebral and thoracic EM.13 Another patient with end-stage MM with EM who failed to respond to chemotherapy and thalidomide was reported to have a complete response to bortezomib.14 Rosinol and coworkers described the effects of bortezomib in 4 patients with EM MM.15 The first patient, who had skull EM, experienced a disappearance of the mass after the fourth cycle of bortezomib. The second patient showed a rapid M-protein response and a reduction in the size of the retrosternal EM of up to 25% after a third bortezomib cycle; complete remission was achieved after the sixth cycle. A third patient on bortezomib therapy showed clinical progression, with a solitary plasmacytoma that increased in size. A fourth patient experienced a complete resolution of skull EM after a third cycle of bortezomib.15 Radiotherapy is the best option for solitary plasmacytoma. In MM with EM disease, however, its role is less defined, and it is usually associated with systemic treatment (chemotherapy or novel agents) to complete treatment.

In conclusion, several single case reports and small series of patients with MM in EM disease have shown that
bortezomib is associated with substantial benefits. Large, controlled studies are needed to examine this approach.

References


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Review

Extramedullary Involvement: An Emerging Problem in Multiple Myeloma

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Federico and colleagues describe an interesting case of a 42-year-old woman diagnosed with multiple myeloma (MM), who had extramedullary (EM) multiorgan involve-

Table 1. Response to Bortezomib in Patients With Extramedullary Localizations of Multiple Myeloma

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrophoretic Profile</th>
<th>Stage</th>
<th>BM Infiltration</th>
<th>β2-Microglobulin (mg/dL)</th>
<th>LDH (UI/L)</th>
<th>EM Localization</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiñol et al13</td>
<td>IgG-λ</td>
<td>IIA</td>
<td>3%</td>
<td>2.5</td>
<td>191</td>
<td>Central nervous system, vertebra, ribs</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>IgG-λ</td>
<td>IIA</td>
<td>100%</td>
<td>3.4</td>
<td>119</td>
<td>Retrosental</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>IgG-λ</td>
<td>IIA</td>
<td>100%</td>
<td>5.9</td>
<td>240</td>
<td>Sacral</td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>IgG-λ</td>
<td>IIA</td>
<td>100%</td>
<td>3.2</td>
<td>409</td>
<td>Occipitoparietal</td>
<td>CR</td>
</tr>
<tr>
<td>Patriarca et al13</td>
<td>IgG-λ</td>
<td>IIA</td>
<td>1%</td>
<td>Not done</td>
<td>Not done</td>
<td>Thoracic, paravertebral, lateropericardic, retroperitoneal, periduodenal</td>
<td>CR</td>
</tr>
<tr>
<td>Paubelle et al14</td>
<td>IgG-κ</td>
<td>IIA</td>
<td>NR</td>
<td>1.5</td>
<td>Not done</td>
<td>Not done</td>
<td>CR</td>
</tr>
<tr>
<td>De Giglio et al12</td>
<td>IgA-κ</td>
<td>IIA</td>
<td>NR</td>
<td>Not done</td>
<td>Not done</td>
<td>Hepatic</td>
<td>PR</td>
</tr>
</tbody>
</table>
with therapy with innovative drugs.\textsuperscript{9} However, improved control of medullary disease in the era of novel drugs translates into a survival prolongation that increases the potential risk of developing EM progression.\textsuperscript{9}

EM manifestations of MM may differ in terms of growth patterns and localization. Bladé and colleagues recently identified 3 different mechanisms involved in the development of EM disease: local growth, hematogenous diffusion, and dissemination caused by invasive surgical procedures.\textsuperscript{9} Adhesion molecules such as VLA-4, CD56, and CD44, which enhance the interaction between myeloma cells and extracellular matrix protein or bone marrow stromal cells, play an important role in the pathogenesis of extramedullary spread.\textsuperscript{10} Also, the role of chemokines, such as CCR1, CCR2, and CXCR4, in the circulation and adhesion of myeloma cells has been described. In fact, CCR1, CCR2, and CXCR4 are expressed at lower levels in patients with active disease in comparison to patients with indolent disease.\textsuperscript{10} The interaction between myeloma and endothelial cells mediated by P-selectin has been considered in EM myeloma progression, and downregulation of P-selectin is found in MM patients with extrasosseous spread.\textsuperscript{11} Finally, a series of genes involved in angiogenesis and adhesion (angiopeptin-1, Notch3, and fibronectin1) are upregulated in EM myeloma.\textsuperscript{12} These observations lend support to the idea that increased angiogenesis and changes in the pattern of expression of adhesion molecules are critical for the diffusion and growth of myeloma plasma cells outside the bone marrow microenvironment.

In MM patients with EM involvement, prognosis and response to therapy are still a matter of debate.\textsuperscript{6} In 2 independent retrospective series, the presence of EM involvement was associated with significantly shorter progression-free survival and overall survival.\textsuperscript{5,5} However, when the analysis was restricted to patients who received high-dose melphalan and stem-cell support, there were no differences in outcome between patients with and without EM involvement.

The best first-line therapy for newly diagnosed patients with EM disease remains to be defined. Potential benefit has been reported with combinations of chemotherapy used in lymphoma, although a prospective validation of these approaches is needed. According to the results of 2 retrospective series, it seems that conventional treatments provided similar response rates regardless of the presence or absence of EM disease.\textsuperscript{4,5}

Among novel therapeutic agents, thalidomide did not result in improved outcomes in patients with EM myeloma.\textsuperscript{10} This finding was clearly demonstrated by both the Barcelona and Royal Marsden groups.\textsuperscript{4,5} In contrast, several case reports showing the efficacy of bortezomib in EM myeloma have been reported.\textsuperscript{14} The report presented by Federico and colleagues adds information to the subject, although the small number of patients reported thus far and the absence of controlled trials represent a limitation in the assessment of efficacy of bortezomib in EM involvement.\textsuperscript{1} Finally, there is no published experience on the effectiveness of lenalidomide (Revlimid, Celgene) in EM myeloma.\textsuperscript{6}

Another important issue is the use of combinations of novel agents, such as bortezomib and thalidomide, in association with dexamethasone for upfront therapy of EM myeloma. Although this approach is generally considered the gold standard for MM patients eligible for high-dose chemotherapy and peripheral blood stem cell rescue, whether it should become part of the induction regimen for younger patients with EM myeloma who are candidates for intensive regimens must be demonstrated in prospective studies.

In conclusion, the higher incidence of EM disease observed in recent years may reflect both the increasing use of more sensitive imaging techniques and the prolongation of survival with new treatment strategies. The risk of EM spread of myeloma appears unrelated to the use of novel agents; these agents, particularly bortezomib, should be incorporated into induction regimens of therapy. Treatment of patients with EM myeloma continues to be a therapeutic challenge, and therefore experimental studies on the mechanisms of myeloma growth at EM sites and drug sensitivity represent a scientific priority in the translational research on this subject.

References