Adv Ther (2011) 28(Suppl.1):11-16.
DOI 10.1007/s12325-010-0102-x

CLINICAL CASES

Lenalidomide Treatment for Patients with Multiple Myeloma: Diagnosis and Management of Most Frequent Adverse Events

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Received: September 21, 2010 / Published online: March 9, 2011

ABSTRACT

The introduction of novel antimyeloma therapies, including thalidomide, lenalidomide, and bortezomib, has expanded treatment options for patients with this disease. These compounds have altered the natural history of multiple myeloma, resulting in substantial improvements in patient outcomes. However, like with any other drug, their use is associated with a specific toxicity profile. The major adverse events (AEs) associated with lenalidomide include: hematological toxicities (myelosuppression), mainly neutropenia, venous thromboembolism, gastrointestinal disturbance, skin toxicity, atrial fibrillation, asthenia, and decreased peripheral blood stem cell yield during stem cell collection when lenalidomide is used after a long period of time. These AEs are predictable, consistent, and manageable with patient monitoring, supportive care, and dose adjustment. In this article, using three clinical cases as examples, we discuss the diagnoses and management of the most frequent AEs associated with lenalidomide treatment in patients with multiple myeloma.

Keywords: adverse events; lenalidomide; multiple myeloma

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INTRODUCTION

The prognosis of patients with multiple myeloma (MM) has changed dramatically over the last decade, with the introduction of novel agents such as bortezomib, thalidomide, and lenalidomide.[1] The sequential administration of these agents, in conjunction with other classic treatments such as dexamethasone and bone marrow transplantation, has doubled the median survival of patients with MM and has resulted in a significant increase in global objective responses.[2] Lenalidomide, in combination with dexamethasone, is indicated in the treatment of patients with

MM after failure of first-line treatment. There are 34 ongoing studies to evaluate the role of lenalidomide in the first-line setting, including: patients undergoing a bone marrow transplant, in which the agent results in better responses and improvement in event-free survival compared with conventional chemotherapy; in combination with melphalan and prednisone as well as other agents in patients not suitable for high-dose chemotherapy and bone marrow transplantation; and as maintenance treatment to prolong response duration.[3]

When selecting the most appropriate treatment for a given patient it is necessary to consider not only expected efficacy, but also the toxicity profile of the agent. In addition to the results of randomized trials, it is necessary to consider the specific characteristics of the patients, such as: age; comorbidities; organs and systems affected; concomitant treatments; the biological characteristics of the patient; and the expected toxicity profile with each agent.[4,5]

A key aspect in the care of patients with MM is the prevention, diagnoses, and proper management of treatment-related complications. This approach not only improves patient quality of life, but also results in better outcomes, as it avoids dose reductions and treatment interruptions. Thus, in elderly patients it may be appropriate to start with a reduced dose.

In this paper, using three clinical cases as real-life examples, we discuss the main adverse events (AEs) and management recommendations of lenalidomide in patients with advanced MM. Despite being an immunomodulatory agent similar to thalidomide, the toxicity profile is quite different and does not result in polyneuropathy, constipation, or somnolence. The most frequent grade 3-4 AEs observed with lenalidomide in combination with dexamethasone include myelosuppression (neutropenia, thrombocytopenia, and, less often, anemia) and deep venous thrombosis (DVT) (particularly in combination with high-dose dexamethasone in the absence of thrombotic prophylaxis).[6-8] The incidence of grade 3-4 AEs is not related to the number of prior treatments, but the efficacy is higher in patients in whom the treatment is administered in the first-line setting.[9] In addition, the risk to develop a serious AE decreases after 3 months of treatment.[10] It is important to recognize that many of the AEs observed with lenalidomide and high-dose dexamethasone (480 mg/cycle) are due to the high doses of dexamethasone. The incidence and severity of AEs decreases substantially when in combination with low-dose dexamethasone (160 mg/cycle) to the point that, despite having a lower response rate, the low-dose regimen results in better overall survival.[11] Finally, lenalidomide is currently being investigated in combination with a number of other agents and regimens demonstrating the expected AEs profile.[12-15]

CLINICAL CASES

Case 1

The first case is a 54-year-old man with a past medical history of type 2 diabetes and incipient neuropathy, who presented in September 2005 with nonirradiated pain in the dorso-lumbar area, with no prior history of trauma. Radiological studies showed a pathologic compression fracture in T7 and L1. The patient was diagnosed with stage II-A, IgA-κ, Bence Jones negative MM. Other relevant data include hypercalcemia; a homogeneous motility gamma component of IgA-κ (4.26 g/dL); a 90% bone marrow infiltration with pathological immunophenotype; and lytic lesions in the skull and the fifth rib. The patient received induction polychemotherapy with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone

alternating with vincristine, carmustine, doxorubicin, and dexamethasone every 35 days (VBCMP/VBAD schema) with zoledronic acid attaining a partial response. In November 2006 he was treated with high-dose melphalan, with bone marrow transplant showing a maintained partial response.

The patient was then treated with maintenance interferon until April 2008, when he presented with back pain. On physical examination there was decreased strength and sensitivity in the lower extremities. Plasma electrophoresis showed a monoclonal peak of IgA-κ of 4.3 g/dL and a 76% infiltration of the bone marrow with plasma cells. A magnetic resonance imaging (MRI) scan of the spine showed an infiltrative lesion in the T6 area, with invasion through the foramen causing serious stenosis of the spinal canal. With the diagnosis of disease progression causing cord compression, the patient was treated with high-dose dexamethasone and radiation therapy to the spinal area. Subsequently, he was treated with lenalidomide 25 mg/day for 21 days, dexamethasone (40 mg/week), and zoledronic acid (4 mg/month). The patient received initial prophylaxis for DVT with low molecular weight heparin (LMWH) during the first four cycles and changed to aspirin after the fourth cycle.

Treatment was, in general, well tolerated, with mild anemia treated with erythropoietin (EPO); a respiratory infection managed with oral antibiotics; and thrombocytopenia that required dose holding occurred in the 10th cycle. The dose of lenalidomide and dexamethasone was reduced to 15 mg/day and 20 mg/week respectively after the 12th cycle because of asthenia, persistent thrombocytopenia, hyperglycemia, and myopathy. The treatment has resulted in a complete response in the bone marrow aspirate, negative proteinuria, and normal MRI of the spine.

Case 2

The second case is a 68-year-old female with a diagnosis of a Bence Jones MM stage II in 2005. The patient was treated with conventional polychemotherapy with VBCMP/VBAD, followed by an autologous bone marrow transplant, which resulted in a complete response that was maintained until January 2008, when a relapse was diagnosed.

The patient was started on lenalidomide 25 mg/day. Two weeks after the first cycle, the patient developed grade 4 neutropenia complicated with fever that required hospital admission and broad-spectrum antibiotics. At that point, the dose was reduced to 15 mg/day, and the patient required support with granulocyte colony-stimulating factor (G-CSF) to maintain a neutrophil count above 1000 cells/uL. After six cycles, and despite treatment with colony-stimulating factors, the neutrophil count was persistently grade 3, leading to a second dose reduction to 10 mg/day. The treatment resulted in a partial response after four cycles, that has been now maintained for 30 cycles. In addition to the hematological toxicity, the patient developed an adrenal insufficiency, that is being treated with corticosteroids.

Case 3

The last case is an 82-year-old female who presented with a monoclonal peak in plasma electrophoresis and hypercalcemia. The patient complained of back pain irradiated to her lower extremities. Blood tests showed anemia with a hemoglobin level of 11.5 g/dL, hypercalcemia (11.5 mg/dL), and a serum paraprotein peak of 5.4 mg/dL corresponding to a IgG-κ. Plain x-ray showed scattered nonspecific lytic lesions in the skull, and MRI of the lumbar spine was consistent with degenerative changes, and disc

protrusion compression the L5 nerve root. The bone marrow aspirate showed a 70% infiltrate by plasma cells.

With the diagnoses of MM IgG-κ in stage III-A, the patient was initially treated with bortezomib in combination with melphalan and prednisone for two cycles with no response. Treatment was then switched to lenalidomide 25 mg/day plus dexamethasone 20 mg orally for 21 days every 28 days. After two cycles, the monoclonal component decreased by 60%. Treatment, however, was not very well tolerated, with grade 3 and 4 neutropenia and anemia that required support with G-CSF and EPO. Because of poor tolerance, the dose was reduced to 15 mg/day. The patient presented with a DVT that was managed with LMWH followed by oral anticoagulation with close control, and continued to develop grade 2 hematological toxicity, leading to a second dose reduction to a 10 mg/day dose.

The treatment resulted in a complete response with normalization of the plasma proteinogram and blood, but the patient persisted with fatigue and somnolence and required hematological support with EPO. Because of these complications, the dose was further reduced to 10 mg every other day. The patient has remained in complete response for over 6 months, with no need for EPO support.

DISCUSSION

Lenalidomide is currently accepted as a distinct therapeutic option in patients with refractory MM in combination with dexamethasone. Like with any other therapeutic agent in oncology, there is a narrow therapeutic window. The drug is more effective when used at the recommended maximum dose for as long as possible; however, the development of AEs often precludes the chronic maintenance of a high dose. Thus, a critical aspect in the clinical use of lenalidomide is the aggressive management of AEs, which includes administration of supportive medication (G-CSF, EPO, antithrombotic prophylaxis) as well as dose reduction.[16-26] This report illustrates practical aspects in the clinical use of lenalidomide, with three clinical cases as examples.

The first clinical case is a very good example of the usefulness of the combination of lenalidomide and dexamethasone as second-line treatment for refractory MM. One of the most important issues in the first clinical case, where asthenia and thrombocytopenia developed as a consequence of the administration of the combined treatment, is the good management of antithrombotic prophylaxis. The case also confirmed that toxicity related to lenalidomide treatment is very manageable, and also highlights that the toxicity can also be related to dexamethasone. Therefore, it is necessary to adjust not only lenalidomide, but also the dexamethasone dose. The most important AEs included asthenia and thrombocytopenia that led to an early dose reduction, but allowed maintenance of combined treatment and, hence, its efficacy.

The second case exemplifies the most common AE associated with the combined treatment of lenalidomide and dexamethasone. Neutropenia leads to dose reduction in most of the cases, and possibly treatment discontinuation. However, the incidence of febrile neutropenia is much lower. In this case, the prior autologous bone marrow transplant increased the risk for neutropenia development. Nevertheless, the prompt management of the toxicity with the administration of G-CSF led to an early reduction of the dose of the drugs, which allowed a longer disease control.

Finally, the third case demonstrates an elderly patient with comorbidities. Lenalidomide and dexamethasone combination led to the development of neutropenia and asthenia, which required administration of G-CSF and EPO, and dose reduction. Subsequently, and related to treatment with EPO, the patient developed DVT that was managed with LMWH, but led again to dose reduction. This case exemplifies the role of comorbidities for the development of AEs associated with the combined treatment. However, and despite reduction of both lenalidomide and dexamethasone, treatment continued and resulted in a complete response.

CONCLUSION

The introduction of new agents with immunomodulatory activity such as lenalidomide has considerably improved the prognosis of MM in both young and elderly patients. When selecting a treatment, it is important to consider not only the effectiveness of the agent, patient characteristics (age, comorbidities), and biological characteristics of the disease, but also the related toxicity. Lenalidomide is accepted as standard treatment for all patients with refractory/relapsed MM, and is particularly suitable for those with pre-existing neuropathy that cannot be treated with thalidomide or bortezomib. In cases of venous thromboembolic disease, the use of bortezomib or lenalidomide combined with antithrombotic therapy is recommended. Finally, in cases of renal insufficiency it is recommended to reduce the dose of lenalidomide accordingly.

Dose reduction should always be considered in older patients (>75 years) or in those with significant comorbidities (lung, heart, liver, kidney). It is important to carefully monitor and manage the treatment-related AEs in order to avoid treatment discontinuation, and therefore increase treatment efficacy.

ACKNOWLEDGMENTS

The authors declare that they have no conflicts of interest. Ana Pilar González Rodríguez is the guarantor for this article, and takes responsibility for the integrity of the work as a whole. This supplement was supported by Celgene.

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