Central neurotoxicity of immunomodulatory drugs in multiple myeloma

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Abstract

Immunomodulatory drugs (IMiDs) currently used in the treatment of multiple myeloma, are thalidomide, lenalidomide and pomalidomide. One of the most common side effects of thalidomide is neurotoxicity, predominantly in the form of peripheral neuropathy. We report 6 cases of significant central neurotoxicity associated with IMiD therapy. Treatment with thalidomide (1 patient), lenalidomide (4 patients), and pomalidomide (1 patient) was associated with various clinical manifestations of central neurotoxicity, including reversible coma, amnesia, expressive aphasia, and dysarthria. Central neurotoxicity should be recognized as an important side effect of IMiD therapy.

Introduction

Immunomodulatory drugs (IMiDs) are a class of antineoplastic compounds which include thalidomide and its derivatives lenalidomide and pomalidomide. The first drug of the class, thalidomide, was initially introduced in Germany in 1957 as a sedative, but it was withdrawn from the market in 1961, when it was linked to severe fetal malformations. The use of thalidomide resurfaced when it was found to be active against cancer and leprosy.[1] In multiple myeloma (MM), IMiDs can produce clinical remission and improve patient outcomes, both in newly diagnosed and relapsed/refractory disease.[2] The antineoplastic activity of these agents in MM and other hematologic malignancies is attributed to their immunomodulatory, anti-inflammatory, and antiangiogenic properties. IMiDs target tumor cells directly by inducing cytotoxicity and indirectly by interfering with components of the bone marrow microenvironment that promote MM progression.[3] They induce apoptosis of MM cells and down-regulate the expression of several cytokines involved in cell proliferation and survival, such as TNFα, IL-6, and VEGF. Although their precise mechanism of action has not been fully elucidated,[4] it has recently been discovered that the molecular target of thalidomide is cereblon (CRBN), a protein encoded by a candidate gene for mental retardation.[5]

Neurotoxic adverse effects of thalidomide include peripheral neuropathy and central neurotoxicity (usually sedation and somnolence), and they are known to occur in more than 10% of patients. The most common toxicity is a predominantly sensory axonal neuropathy, clinically manifested by numbness and paresthesia in the extremities.[6,7] The severity of the neuropathy has been related to the duration of the treatment and to the cumulative drug dosage.[8,9] Central nervous system (CNS) toxicity is usually mild, and mainly consists of somnolence. However, at high doses (400 mg/day and above), patients can experience severe lethargy.[10] For lenalidomide and pomalidomide, CNS toxicity (with exception of confusion) has not been established as a known adverse effect. In this study, we report 6 MM patients who developed significant CNS toxicity during treatment with IMiD agents.

Materials and Methods

We screened a clinical database of 508 MM patients directly treated and followed at our institution between January 2007 and December 2013. We identified 6 patients who developed significant symptoms of central neurotoxicity, attributed by the treating physician to the IMiD therapy. Symptoms were considered significant when they required an urgent evaluation in the emergency department (ED). We retrospectively reviewed all available medical records of these cases. This study was approved by our Institutional Review Board.

Results

The basic clinical characteristics of the 6 patients are summarized in Table 1. The following is a brief description of each case.

Case Report #1

A 75-year-old Caucasian female was diagnosed with MM in 2006, after routine laboratory tests with her primary care physician. Bone marrow biopsy revealed 55% plasma cells. She was asymptomatic with normal calcium and creatinine, and skeletal survey was negative for lytic lesions. In view of her anemia (Hb 9.8 g/dL), she was initiated on thalidomide 200 mg daily and dexamethasone. After 16 days of thalidomide she required emergent hospitalization due to altered mental status progressing to unresponsiveness and coma. Laboratory tests, lumbar puncture, and neuroimaging studies were unremarkable, and her mental status changes were attributed to thalidomide. She gradually improved, became alert, and fully recovered within 48 hours after discontinuation of thalidomide.

Case Report #2

A 59-year-old Caucasian male was diagnosed with MM in November 2013. He was started on bortezomib and dexamethasone. Two months later, in view of a suboptimal response, we added lenalidomide 15 mg on days 1-21 every 28 days. Five days after initiating lenalidomide, the patient presented to the ED due to cognitive decline (slow thinking) and expressive aphasia (impaired word finding). No other explanation for his symptoms was found, and these manifestations slowly resolved about 3 days after the discontinuation of lenalidomide. Treatment was changed to thalidomide 50 mg daily, but he could not tolerate it because of significant fatigue. Lenalidomide was reintroduced at a reduced dose of 5 mg daily, and his symptoms did not recur at a follow-up of 16 months.

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Key words: multiple myeloma, central neurotoxicity, immunomodulatory drugs, thalidomide, lenalidomide, pomalidomide.

Contributions: GT, conception and manuscript writing; UHP, collection of data and manuscript writing; JKS, analysis of data; DR and MKP, interpretation of data and final approval of the manuscript.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 7 November 2014.
Revision received: 9 February 2015.
Accepted for publication: 17 February 2015.

Hematology Reports 2015; 7:5704
doi:10.4081/hr.2015.5704

Case Report #3

A 64 year-old Caucasian male was diagnosed with MM in May 2012. He was started on lenalidomide 15 mg on days 1-21 every 28 days, and dexamethasone 20 mg once a week. He noticed impairment of short-term memory immediately after starting treatment. He preferred to continue the treatment, since his symptoms did not impair his activities of daily living (ADL). He reached partial remission, and underwent an autologous stem cell transplant (ASCT) 5 months after his initial diagnosis. He resumed lenalidomide as maintenance therapy, and his MM remained in complete remission as of April 2014. Of note, he reported that his amnesia had resolved during the 2 months in which he held the lenalidomide for the ASCT, and it recurred during the maintenance period.

Case Report #4

A 79-year-old African-American female was diagnosed with MM in February 2014. She was not a good candidate for aggressive chemotherapy, due to her comorbidities and poor performance status. She was initiated on low-dose lenalidomide 2.5 mg on days 1-28. After 4 weeks of therapy, she developed progressive somnolence, until she was found to be unresponsive. Clinical and laboratory work-up did not reveal any cause of lethargy. Her symptoms resolved a few days after discontinuing lenalidomide, but they recurred again 2 weeks after reintroduction of the agent. Lenalidomide was finally discontinued. Her current mental status is unknown, as she was lost to follow-up.

Case Report #5

A 68-year-old white male was diagnosed with MM in April 2013. He initiated treatment with lenalidomide 25 mg on days 1-21 every 28 days and dexamethasone 40 mg once a week. MM remained stable 13 months after the diagnosis. While on treatment, the patient complained of amnesia, with impairment of short-term memory and recollection of names. Although a consultation with Neurology raised the possibility of early Alzheimer's disease, the patient was convinced that his symptoms were related to the lenalidomide therapy, as they temporarily improved every month, during the week off lenalidomide. He preferred to continue lenalidomide, because his symptoms were mild and did not affect his ADL.

Case Report #6

A 75-year-old Caucasian male was diagnosed with IgG-λ MM in November 2009. He was enrolled in the ECOG trial E1806, and he was randomized to melphalan, prednisone, and lenalidomide. He reached partial remission after 12 cycles of therapy, and continued with lenalidomide maintenance. MM relapsed in 2012, and treatment was changed to bortezomib and dexamethasone, followed by ASCT. MM relapsed 8 months after the ASCT, and he began therapy with pomalidomide 4 mg on days 1-21 every 28 days. In the following months, MM reached partial remission. Patient complained of being unable to find words and properly express them. Neurological examination revealed dysarthria. Due to his advanced age, these symptoms were initially attributed to the onset of senile dementia, and therapy with pomalidomide was continued. However, when the MM progressed 7 months later, and his treatment was switched to carfilzomib, his cognitive symptoms resolved. The patient died of progressive disease 54 months after the initial diagnosis of MM.

All 6 cases underwent a neurologic work-up with history (directed specifically at alcohol, toxins, and concomitant drugs), physical examination, laboratory tests (including metabolic profile, liver function tests, and plasma viscosity), and neuroimaging with either CT or MRI of the brain. In all cases, the results of the work-up did not find any evident cause for the central neurotoxicity, other than the exposure to the chemotherapy agent. Creatinine clearance was normal (*i.e.,* >60 mL/min/1.73 m^2) in all patients. Due to the age of these patients (the youngest was 59 year-old), their CNS symptoms could not be unequivocally attributed to the IMiD treatment. However, after the negative results of the initial neurologic diagnostic work-up, chemotherapy-induced central neurotoxicity remained the presumptive diagnosis according to the judgment of the treating physicians. Concomitant drugs were of particular concern, especially because many patients with MM take opioids for pain control, and corticosteroids as adjunctive therapy to the IMiDs. None of our patients were receiving opioids at the time of their symptoms, and 3 of them received corticosteroids. However, the nature of their neurologic symptoms was believed to be different from that expected with steroid therapy (*i.e.*, insomnia, agitation, and psychosis).

Discussion

Chemotherapy-induced neurotoxicity can affect the peripheral, the autonomic, or the central nervous system.[11] The most common form is peripheral neuropathy, which manifests with hypoesthesia (numbness), paresthesia (tingling, pins and needles, or a limb falling asleep), and hyperesthesia (pain), often in a stocking and glove distribution. Physicians treating MM are well aware of peripheral neuropathy as a common complication of chemotherapy agents, especially bortezomib and thalidomide. This consists of an axonal length-dependent sensory neuropathy which often leads to reduction of dosages and cessation of the responsible drugs.[12] On the other hand, except for the somnolence induced by thalidomide, little is known about central neurotoxicity in the treatment of MM. We identified 6 MM patients who experienced clinically significant CNS toxicity during exposure to an IMiD agent. Although the causality of the symptoms could be disputed, the exclusion of other medical causes of CNS symptoms in all cases, along with the rapid reversibility of the symptoms after interruption of the therapy, are highly suggestive of a cause-effect relationship. CNS involvement in MM is

Table 1. Patients' characteristics.

Case	Age	Paraprotein	Drug presumably responsible	Onset of symptoms after drug exposure	Clinical manifestations
1	75	IgA-κ	Thalidomide 200 mg	16 days	Coma
2	59	λ light chain	Lenalidomide 15 mg	5 days	Expressive aphasia
3	64	IgG-κ	Lenalidomide 15 mg	Immediately	Amnesia
4	79	IgG-κ	Lenalidomide 2.5 mg	4 weeks	Lethargy
5	68	IgG-κ	Lenalidomide 25 mg	Immediately	Amnesia
6	75	IgG-λ	Pomalidomide 4 mg	Immediately	Expressive aphasia

extremely rare,[13] and we did not find any evidence of it in our patients. Their CNS symptoms actually occurred while their MM was stable or in partial/complete remission. While the exact mechanism for IMiD-induced central neurotoxicity is unclear, it is known that penetration into the CSF has been reported after oral administration with both thalidomide in humans and primates, lenalidomide in primates, and pomalidomide in rats.[14-16] Unlike thalidomide, lenalidomide does not seem to induce drowsiness and somnolence in the vast majority of patients (in fact, it can be administered in a.m., whereas thalidomide should be administered at bedtime). However, somnolence was reported as the dose-limiting toxicity (DLT) in a phase I study in patients with advanced solid tumors.[17]

Clinically significant CNS toxicity during IMiD therapy is rare. In fact, we found only 6 cases in our database of 508 MM patients treated with 562 lines of IMiDs, *i.e.*, thalidomide (n=149), lenalidomide (n=385), and pomalidomide (n=28). This corresponds to approximately a 1% event rate. The frequency of occurrence seems counterintuitive, because one would expect the highest rate of CNS toxicity with thalidomide: the pivotal trial of thalidomide reported somnolence in 34% of patients at the dose of 200 mg/day,[18] whereas central neurotoxicity was not observed with lenalidomide,[19,20] nor with pomalidomide.[21] In our opinion, we did not find thalidomide as the most common drug responsible for central neurotoxicity probably because of the way we collected our data. In fact, our study is limited by its retrospective nature, and it included only the most significant cases, *i.e.*, those requiring an urgent evaluation in the ED. It is likely that the true frequency of central neurotoxicity with IMiD therapy is higher and underrepresented, due to the subtle presentation of the symptoms and the fact that they can easily be attributed to other causes, such as comorbidities and concomitant drug therapy that may affect the CNS.

The clinical manifestations of central neurotoxicity varied among our patients: we found impairment of short-term memory, dementia-like amnesia, expressive aphasia, dysarthria, lethargy, and reversible coma. After review of the literature, we found a single case report of a patient with severe tremors due to thalidomide-induced central neurotoxicity,[22] which was not observed in our series. In our patients, all symptoms were reversible, as they resolved after discontinuation of the offending agent. In one case, they did not recur after reintroducing the drug at a lower dose.

Conclusions

Our report encourages an increased awareness of central neurotoxicity as a possible side effect of IMiD therapy, along with early recognition and regular neurological evaluation during the treatment period.

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