Central neurotoxicity of immunomodulatory drugs in multiple myeloma

Urmeel H. Patel, Muhammad A. Mir, Jeffrey K. Sivik, Divisha Raheja, Manoj K. Pandey, Giampaolo Talamo
Penn State Hershey Cancer Institute, Hershey, PA, USA

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 The first drug of the class, thalidomide, was initially introduced in Germany in 1957 as a sedative, but it was withdrawn from the market in 1961, when it was linked to severe fetal malformations.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 was resurrected when it was found to be active against cancer and leprosy. In multiple myeloma (MM), IMiDs can produce clinical remission and improve patient outcomes, both in newly diagnosed and relapsed/refractory disease. 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. 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, it has recently been discovered that the molecular target of thalidomide is cereblon (CRBN), a protein encoded by a candidate gene for mental retardation.

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. The severity of the neuropathy has been related to the duration of the treatment and to the cumulative drug dosage. 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. 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 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.

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

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.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright U.H. Patel et al., 2015. Licensee PAGEPress, Italy. 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.

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     |

Discussion

Chemotherapy-induced neurotoxicity can affect the peripheral, the autonomic, or the central nervous system. 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. 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

[Hematology Reports 2015; 7:5740]
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 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.

References

1. Zhou S, Wang F, Hsieh TC, et al. Thalidomide-a notorious sedative drug. Curr Med Chem 2013;20:4102-8.
2. Andhavarapu S, Roy V. Immunomodulatory drugs in multiple myeloma. Expert Rev Hematol 2013;6:69-82.
3. Knight R. IMiDs: a novel class of immunomodulators. Semin Oncol 2005;32: S24-30.
4. Paravar T, Lee DJ. Thalidomide: mechanisms of action. Int Rev Immunol 2008;27: 111-35.
5. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. Science 2010;327:1345-50.
6. Plasmati R, Pastorelli F, Cavo M, et al. Neuropathy in multiple myeloma treated with thalidomide: a prospective study. Neurology 2007;69:573-81.
7. Isordo G, Bergui M, Durelli L, et al. Thalidomide neuropathy: clinical, electrophysiological and neuroradiological features. Acta Neurol Scand 2004;109:188-93.
8. Cavalletti G, Beronia A, Reni L, et al. Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. Neurology 2004;62:2291-3.
9. Tosi P, Zamagni E, Cellini C, et al. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. Eur J Haematol 2005;74:212-6.
10. Dimopoulos MA, Eleutherakis-Papaikovou V. Adverse effects of thalidomide administration in patients with neoplastic diseases. Am J Med 2004;117:508-15.
11. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. Cancer Chemother Pharmacol 2009;63:761-7.
12. Richardson PG, Delforge M, Bekssac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia 2012;26:595-608.
13. Abdallah AO, Atrash S, Shahid Z, et al. Patterns of central nervous system involvement in relapsed and refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2014;14:211-4.
14. Muscal JA, Sun Y, Nuchtern JG, et al. Plasma and cerebrospinal fluid pharmacokinetics of thalidomide and lenalidomide in nonhuman primates. Cancer Chemother Pharmacol 2012;69:943-7.
15. Yutaka H, Maliko Y, Shinichiro O, et al. Thalidomide for the treatment of leptomeningeal multiple myeloma. Eur J Haematol 2006;76:358-9.
16. Li Z, Qiu Y, Personett D, et al. Pomalidomide shows significant therapeutic activity against CNS lymphoma with a major impact on the tumor microenvironment in murine models. PLoS One 2013:8:e71754.
17. Berg SL, Cairo MS, Russell H, et al. Safety, pharmacokinetics, and immunomodulatory effects of lenalidomide in children and adolescents with relapsed/refractory solid tumors or myelodysplastic syndrome: a Children’s Oncology Group Phase I Consortium report. J Clin Oncol 2011;29: 316-23.
18. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-71.
19. Weber DM, Chen C, Nievizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357:2133-42.
20. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.
21. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-66.