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Case Report

Bortezomib Induced Mania: An Unrivalled Case Report

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Abstract

The second most common haematological malignancy, Multiple Myeloma (MM), is caused by the clonal proliferation of malignant plasma cells. With little side effects, Bortezomib, first proteasome inhibitor, increased response rates and overall survival in newly diagnosed and recurring patients of MM. While corticosteroids are known to result in several psychiatric manifestations, there are only a few reported cases of mental illnesses caused by Bortezomib accounted for in the literature. This article describes a 68-year-old man who has multiple myeloma. He has been stated as experiencing manic symptoms and is currently undergoing regular treatment with Bortezomib, Dexamethasone, and Cyclophosphamide. After the second cycle, there was a noticeable increase in irritation, which subsequently escalated to reflect symptoms of decreased sleep, aggressive conduct, spending spree, and increased energy. He was diagnosed as a case of Drug induced (Bortezomib) Mania. Chemotherapy was abruptly discontinued and treated with Tab Olanzapine 10 mg/day. The symptoms were seen to gradually improve, and alternative chemotherapy was intended to resume soon after. The case report highlights high index of suspicion of psychiatric complications, timely detection and immediately stopping related drug (Bortezomib) are key steps in management.

Keywords: Mania; Bortezomib; Multiple Myeloma

Introduction

10% of all hematologic malignancies and 1% of all cancers are caused by Multiple Myeloma [1]. In the past two decades, introduction of novel agents like immunomodulators, proteasome inhibitors (Bortezomib, carfilzomib) has led to higher response rates (75-95%) and overall survival (OS: 3-3.5 years) [2]. In a research comparing the efficacy of Thalidomide with Bortezomib, the Bortezomib group had a higher incidence of depression [3].

Case Report

In September 2022, a 68-year-old male, resident of Pune, presented with complaints of neck pain and swelling along the right side of the neck since last 2-3 months. His general and systemic examination were unremarkable except a palpable swelling (2 X 2 cms) in cervical region. MRI Cervical spine revealed presence of an ill-defined lesion affecting the right side of atlas and axis vertebrae, with lytic destruction of soft tissue, suggestive of Plasmacytoma or metastatic lesion. PET CT scan was suggestive of Musculoskeletal FDG avid an expansile lytic lesion involving the right C1 and C2 ver-

tebra. Metabolically active and inactive extensive skeletal lesions described to be likely neoplastic (Multiple myeloma). Bone marrow aspiration and biopsy were consistent with Plasma cell myeloma. Serum protein electrophoresis and immunofixation demonstrated the diagnostic M band and the diagnosis of Multiple myeloma was hence confirmed.

Patient was advised 06 cycles of chemotherapy with parenteral Bortezomib (2mg in 100ml NS over 30mins), Dexamethasone (40mg in 100ml NS over 30mins) and Cyclophosphamide (300mg in 500ml NS over 2hours) administered every fortnightly. After the first cycle in Oct 2022, the family noticed slight irritability and reduced need for sleep in the patient, but it was thought to be attributed to the apprehension of the illness and old age. He received his second cycle in Nov 2022.

During his follow up in Nov 2022, the Oncologist perceived the patients' abnormal behaviour, in the form of being loud, overtalkative being overfamiliar with him and the hospital staff, with an elevated mood. At times he barged in the room without permission and continued to speak uninterruptedly. He was subsequently referred to Psychiatry OPD for consultation. However, his family refrained from consulting then, until over the next month, when his agitated behaviour increased, and he tried to aggressively hurt his son for no apparent reason.

aDuring evaluation, he had increased irritability whenever interrupted, reduced need for sleep, increased talkativeness, increased energy, and violent behaviour. History also revealed an excessive spending spree, like on furniture and seeking money to purchase a new car which he needed for his own independent use. He was also suspicious of his villagers who were trying to harm his status. Past history of COVID -19 infection in 2021 treated with steroid (Dexamethasone). He was diagnosed as a case of Mania as per ICD-10. Young Mania Rating Scale (YMRS) score was 26, suggestive of moderate severity of Mania. In view of the clinical presentation of mania with the temporal relationship with a usage of Bortezomib and Dexamethasone as chemotherapeutic agents and no past history of steroid induced psychiatric symptoms, drug induced (Bortezomib) mania was diagnosed. Chemotherapy was advised to be discontinued and Tab Olanzapine 5mg at night was started. The patient and the family noticed significant improvement in patients' behaviour and symptoms. The alternative chemotherapy medication shall be reinstituted subsequently.

Discussion

The therapy choices for myeloma patients have significantly increased in recent years with the discovery of targeted medications such the immunomodulatory agents thalidomide, lenalidomide and proteasome inhibitors, of which Bortezomib was the first commercially accessible [4]. A phase II trial of patients with relapsed and refractory multiple myeloma cases who were treated with single agent Bortezomib resulted in an overall response rate (ORR) of 35% and a median time to progression (TTP) of seven months [5]. Corticosteroids have been widely used in malignancies and found to be effective in combination with Bortezomib for significant treatment response in cases of Multiple myeloma. It is estimated that about 20% patients on high dose corticosteroids (>40mg/day prednisolone or equivalent) can manifest with psychiatric complications. The varied presentation with use of corticosteroids can span mood disorders like-mania, hypomania, depression, anxiety disorders, delirium, or isolated cognitive disorders. There is no systematic study evaluating the frequency and associations of corticosteroid-induced mania, but only a few case reports available [6]. But, in the index case, patient had previously tolerated high doses of *corticosteroids* without experiencing neuropsychiatric symptoms.

On the contrary, Bortezomib is rarely identified to cause mania or psychiatric complications, highlighted in only two case reports [2,7]. Bortezomib can induce apoptosis, decrease cytokines such as IL-1 and TNF, decrease cell adhesion molecules and reduce inflammation [8]. It is known that intracellular sodium level decreases during the manic episode and returns to normal during the recovery period. The anticonvulsant drugs act by inhibiting these sodium channels. It is proven that corticosteroids disrupt the sodium channel functions in the cell membrane. It can be hence postulated that Bortezomib and corticosteroids act through these mechanisms in the development of mania. In a case of Bortezomib-induced mania, a response was obtained to Olanzapine 10 mg/day and Divalproex Sodium 1000 mg/day drug treatment [2].

Conclusion

Drug combination of Bortezomib and dexamethasone is FDA approved in 2003 and efficacious in patients of Multiple myeloma. The manifestation of mania due to the usage of this combination has been reported in two case reports. Recognition of corticosteroid and Bortezomib-related symptoms at an early stage will help prevent serious psychiatric side effects and psychopathology. This

warrants further studies on the neuropsychiatric complications of the drug Bortezomib and direct rationale on the usage in patients of Multiple myeloma.

Consent to Publish

Written consent obtained from the patient.

Authors' Contributions

SP, AC, and BG were involved in the patient's case, which included monitoring the patient's psychopathology and providing (pharmaco-)therapeutic care. MS conducted the necessary literature research and contributed significantly to the drafting and editing of the article.

Declaration of Competing Interest

Nil.

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