Mania Associated with The Use of Bortezomib and Dexamethasone

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SUMMARY

Bortezomib, an antineoplastic agent used in Multiple Myeloma, is a modified dipeptidyl boronic acid that is selectively and reversibly attached to the 26S proteasome. Bortezomib may be combined with corticosteroids in treatment-resistant multiple myeloma patients. Corticosteroids can cause many psychiatric disorders including mania, depression, psychosis, delirium, suicide and aggression. To date only one case of mania associated with the use of bortezomib was reported in which the patient responded to the treatment with olanzapine and valproic acid. In this article, we present a 57-year-old female with multiple myeloma in whom mania developed after the use of bortezomib combined with dexamethasone.Psychiatric symptoms such as sleep deprivation, increased self-esteem and excessive speech appeared within the first week of bortezomib and dexamethasone treatment. Quetiapine was administered for the treatment of psychiatric symptoms. A gradual improvement was noted in manic symptoms after treatment. Bortezomib is a relatively new drug and there are only a few reports with respect to its psychiatric side effects. While using antineoplastic drugs such as bortezomib, caution should be exercised with regards to the psychiatric symptoms.

Keywords: Bortezomib, steroid, corticosteroid, mania, multiple myeloma

INTRODUCTION

Multiple myeloma is a refractory neoplastic disease caused by clonal proliferation of malignant plasma cells (Curran and McKeage 2009). Bortezomib, an antineoplastic agent, is a modified dipeptidyl boronic acid analogue that selectively and reversibly binds to the 26S proteasome (Curran and McKeage 2009). It has been reported that dexamethasone has been added to strengthen the bortezomib treatment in refractory multiple myeloma patients and effective results have been obtained (Palumbo et al. 2008). Corticosteroids are widely used for alleviating or treating symptoms due to many diseases such as autoimmune diseases, organ transplantation, hematological diseases, myopathy and chronic neuropathy (Jick et al. 1972, Kenna et al. 2011, Stiefel et al. 1989). Combined treatment with bortezomib and cyclophosphamide appears to be highly effective in recurrent / resistant multiple myeloma patients (Reece et al. 2008).

The reported psychiatric conditions associated with bortezomib in the literature are limited by only one manic case presentation (Jiang et al. 2014). In a 61-year-old female patient followed-up with multiple myeloma diagnosis, manic symptoms such as insomnia, hyperactivity, euphoric and irritable mood appeared after bortezomib (1.3 mg/m2,intravenous [IV]) and dexamethasone (15 mg, IV).It has been reported that olanzapine 10 mg / day and valproic acid 1000 mg / day for treatment of the mania period is started and mania symptoms disappear.

It is known that various psychiatric symptoms or disorders, including mood disorders (such as mania, hypomania, depression), anxiety disorders, delirium, suicide, aggression,

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homicidal behavior, depersonalisation, isolated cognitive disorders (attention and memory disorders) are associated with corticosteroid therapy (Bhangle et al. 2013, Kenna et al. 2011).

Studies show that the most important risk factor for developing psychiatric symptoms after corticosteroid use is the corticosteroid dose used (Jick et al. 1972, Stiefel et al. 1989). Other risk factors are hypoalbuminemia (Appenzeller et al. 2008), cytochrome P450 enzyme (CYP) 3A4 activity, which has an important role in corticosteroid metabolism (Finkenbine and Frye 1998), low BOS / serum albumin ratio (Nishimura et al. 2008) and female sex (Lewis and Smith 1983, Wada et al. 2001).

While hypomania and mania are the most common psychiatric disorders associated with corticosteroid use (Lewis and Smith 1983, Naber et al. 1996, Nishimura et al. 2008, Wada et al. 2001), depression is more common in long-term corticosteroid treatment (Bolanos et al. 2004, Sirois 2003). If possible, corticosteroid therapy should be discontinued in cases of induced mania or hypomania and, if not possible, dose reduction should be performed (Appenzeller et al. 2008, Lewis and Smith 1983).Informing patients and their relatives about corticosteroid therapy and side effects is considered a preventive treatment for such psychiatric disorders (Brown and Chandler 2001, Patten and Neutel 2000, Warrington and Bostwick 2006).

In this article, we present a case of mania observed during bortezomib, dexamethasone and cyclophosphamide chemotherapy in a female patient followed-up with the diagnosis of multiple myeloma.

CASE

The 57-year-old married female patient living with her family and not working applied to our polyclinic with complaints of insomnia, nervousness and hyperactivity despite physical illness. Chemotherapy was started one month after the patient was diagnosed with multiple myeloma. After treatment with cyclophosphamide (1 mg, IV) and dexamethasone (20 mg, po) on the first day of the week, only dexamethasone (20 mg, po)was used on the second, third and fourth day of the week, and similar drug therapy was repeated a month later (Table 1).

Since the patient did not respond to this drug treatment, the new drug treatment was regulated as cyclophosphamide (450 mg, po), bortezomib (2.2 mg, sc), and dexamethasone (40mg, po). This treatment was used on days 1, 8, 15 and 22 of the month. In the first week of combination therapy with bortezomib, cyclophosphamide and dexamethasone, psychiatric symptoms began in the patient. According to the patient, there were only sleep disturbance and nervousness complaints. Patient relatives stated that the patient's motor activity, speech volume and self-esteem increased and these symptoms became increasingly severe. Signs such as a reduction in sleep duration (1-2 hours), keeping busy cleaning up continuously at night and an increase in religious activities have been observed. There were signs of personality changes and disinhibition in the patient.

She had no history of psychiatric illness, psychiatric drug use, or family history of psychiatric illness. The resume and developmental story of the patient without alcohol, substance, and smoking was natural. Mental examination of the patient revealed complete place, time and person orientation, increased psychomotor activity, increased voluntary and spontaneous attention, accelerated and tangential flow of thought, pressure of speech, irritable mood, increased and labile affection interval and decreased frustration threshold .Patient without the insight had no perception pathology or delusion. Place, time and person orientation were normal. After consultation with the hematology unit, it was decided that dose discontinuation or reduction of corticosteroid was not appropriate. Quetiapine, one of the first-line monotherapy drugs for treating manic episodes of bipolar affective disorder (Yatham et al. 2013), was initiated at a dose of 25 mg / day and increased to 100 mg / day. One week after discharge from the hematology service, the patient was re-examined at the psychiatry outpatient clinic. Despite a partial reduction in symptoms after the treatment, it was determined that the patient still had not slept more than four to five hours a day, and the amount of efficacy directed towards the purpose increased. Printed speech and irritable mood persisted in the interview. Drug dose was increased to 200 mg / day quetiapine with long-term release. After this dose, there was a marked improvement in the patient's complaints. The patient was followed up once a month for six months. She took six courses of chemotherapy. Patient relatives stated that the psychiatric symptoms were increased during the period when the patient received each chemotherapy, and therefore he used 200 mg / day quetiapine. However, on days when chemotherapy was not given, they said she used quetiapine 100 mg / day because of sedation. From the onset of the psychiatric symptoms of the patient complete blood count, renal function tests, liver function tests, and serum electrolyte levels were normal (Table 1). The patient was followed up together in the hematology and psychiatric departments. Sedimentation value was observed to be between 37-88 mm / h during the follow-up. Serum total protein concentration was relatively elevated before the onset of psychiatric symptoms (9.5-10.6 g / dL), but after the onset of the psychiatric symptoms, the tests were observed in the normal range (6.1-6.8 g / dL). Serum albumin concentration was measured to be normal (3.5-4.3 g / dL) before the onset of psychiatric symptoms, while in the period of intensive psychiatric symptoms, it was found to be lower than normal level (3.0 g / dl). Serum albumin level, estimated

Table 1. Before, during, and after treatment; course of drug treatment, laboratory values and scale scores

	Reference Ranges	Before treatment	Unresponsive period to cyclophosphamide and dexamethasone treatment (First treatment period)				Bortezomib, Dexamethasone and Cyclophosphamide drug treatment period (Second treatment period)						Second month after treatment
Treatment duration			**1st month**		**2nd month**		**1st month**	**2nd month**	**3rd month**	**4th month**	**5th month**	**6th month**	
Treatment time			**1st day**	**2nd, 3rd and 4th day**	**1st day**	**2nd, 3rd and 4th day**	**1st, 8th*, 15th and 22nd day**	**1st, 8th, 15th and 22nd day**	**1st, 8th, 15th and 22nd day**	**1st, 8th, 15th and 22nd day**	**1st, 8th, 15th and 22nd day**	**1st, 8th, 15th and 22nd day**	
Cyclophosphamide			**1000 mg (IV)**	**-**	**1000 mg (IV)**	**-**	**450 mg (oral)**	**450 mg (oral)**	**450 mg (oral)**	**450 mg (oral)**	**450 mg (oral)**	**450 mg (oral)**	
Dexamethasone			**20 mg (oral)**	**20 mg (oral)**	**20 mg (oral)**	**20 mg (oral)**	**40 mg (oral)**	**40 mg (oral)**	**40 mg (oral)**	**40 mg (oral)**	**40 mg (oral)**	**40 mg (oral)**	
Bortezomib			**-**	**-**	**-**	**-**	**2.2 mg (sc)**	**2.2 mg (sc)**	**2.2 mg (sc)**	**2.2 mg (sc)**	**2.2 mg (sc)**	**2.2 mg (sc)**	
Wbc (x10.e3/uL)	4.5-11	4.5	3.4 ↓		5.2		8.66	10.6	7.15	3.99 ↓	9.28	9.28	4.5
Rbc (x10.e6/uL)	4–5.2	4.12	3.91 ↓		3.99 ↓		4.58	4.56	4.36	3.73 ↓	4.33	4.70	4.7
Plt (x10.e3/uL)	130-400	210	185		260		278	323	225	287	287	226	219
Hb (g/dL)	13-17	12.3 ↓	11.6 ↓		12.1 ↓		12.4 ↓	11.8 ↓	12.1 ↓	9.8 ↓	11.21 ↓	12.56↓	12.1 ↓
BUN (mg/dL)	5-25	8	9		14		12	21	15	11	15	20	14
Cre (mg/dL)	0.44-1	0.75	0.76		0.53		0.72	0.67	0.66	0.64	0.62	0.65	0.73
Na (mmol/L)	135-146	136	134 ↓		-		137	136	136	141	141	144	144
K (mmol/L)	3.5-5.1	4.5	4.4		-		3.9	4.7	4.1	3.8	4.3	4.0	4.0
Ca (mg/dL)	8.6-10.2	9.7	9.1		9.4		-	9.5	-	9.2	9.4	8.8	10.0
AST (U/L)	5-32	14	13		-		27	13	17	14	19	13	18
ALT (U/L)	5-33	13	19		-		38 ↑	28	35 ↑	32	31	33	22
Albumin (g/dL)	3.5-5.2	4.3	3.5		4.2		3.0 ↓	4.3	-	4.0	4.6	4.1	4.4
Protein (g/dL)	6.4-8.5	10.6 ↑	10.0 ↑		9.5 ↑		-	6.8	-	6.1 ↓	6.8	6.1↓	7.4
ESR (mm/h)	0-15	77 ↑	88 ↑		-		37 ↑	42 ↑	40 ↑	-	-	-	13
Albumin (%) (protein electrophoresis)	55.8-65	-	-		-		44.1 ↓	-	-	-	52.5 ↓	-	52.2 ↓
Quetiapine dose							**100 mg/ day**	**200 mg/ day**	**200 mg/ day**	**200 mg/ day**	**200 mg/ day**	**200 mg/ day**	
BPRS							17	13	9	4	4	-	-
YMRS							23	19	12	5	4	-	-

* Time to start of psychiatric symptoms, IV: Intravenous, sc: Subcutaneous , BPRS: Brief Psychiatric Rating Scale, YMRS: Young mania rating scale

electrophoresis, was also found to be below normal (44.13% [normal range, 55.8-65.0%]) during this period. After recovery of the psychiatric symptoms, albumin level (4.0-4.6 g / dL) were normal. PET scan revealed that there were lytic lesions on only costal bones but no other organ involvement. The treatment response of the patient during the follow-up was assessed by the Young Mania Rating Scale (YMRS) that assessed mania symptoms in the last two days and rated 12 points or more in favor of mania / hypomania, and the 18-item Brief Psychiatric Rating Scale (BPRS), which assessed the general psychiatric symptoms of last three days. In the first psychiatric evaluation, the BPRS score was 23 while the BPRS score was 17. When the patient used quetiapine 100 mg / day drug therapy, the score of BPRS was 13, while the BPRS score was 19. After long-term 200 mg / day quetiapine treatment, the patient's YMRS scores were reduced to 12, 5 and 4 at 3 months, respectively, and BPRS scores decreased to 9, 4 and 4, respectively.

DISCUSSION

Corticosteroids used in the treatment of many diseases can cause many systemic side effects. Some of these systemic side effects are also psychiatric side effects. The most common psychiatric disorders due to steroids are mania and hypomania (Lewis and Smith 1983, Naber et al. 1996, Nishimura et al. 2008, Wada et al. 2001).

Bortezomib is an antineoplastic agent which is also used in multiple myeloma patients and has effects such as induction of apoptosis, reducing the expression of inflammatory cytokines such as IL-1 and TNF by suppressing NF-κB activity, inhibiting neutrophil microcirculation outflow by reducing neutrophil aggregation in cerebral micro vessels, increasing hypoxia in the central nervous system, preventing angiogenesis and reducing cell adhesion molecules (Kelly et al. 2008, Wojcik et al. 2004, Roccaro et al. 2006).

Psychiatric conditions related to bortezomib are emphasized in only two publications. In the first of these, a woman with a diagnosis of multiple myeloma similar to ours is a mania that occurs in a patient (Jiang et al. 2014, Mancano 2015). The second study compared the efficacy of bortezomib with thalidomide and reported that the frequency of depression was higher in the group using bortezomib (Hjorth et al. 2012).

Cyclophosphamide was also used in addition to the combination of dexamethasone and bortezomib when the manifestation of mania was detected. Psychiatric symptoms occurred in the patient on cyclophosphamide (450 mg /day,po)in the second chemotherapy period, while no mania was reported despite cyclophosphamide (1 gram, IV)in the first chemotherapy treatment course. This reduces the likelihood of cyclophosphamide-induced occurrence of mania. Two mania cases have been reported in the literature following the use of cyclophosphamide. However, in both cases, cyclophosphamide is involved in combined drug therapy (Pacchiarotti et al. 2007, Tutkunkardas and Mukaddes, 2010). In another case, in a combination chemotherapy treatment with ifosfamide, it was observed that when the ifosfamide treatment was replaced with cyclophosphamide, mania symptoms improved (Kerdudo et al. 2006).

Our patient did not show psychiatric symptoms during the initial treatment period (Table 1) when she received dexamethasone (20 mg/day, po) for four consecutive days totaling 80 mg; and psychiatric symptoms appeared during the second treatment period (Table 1) when she received a single oral dose of dexamethasone (once 40 m/week). Although these indicate that the probability of drug interaction is relatively low, higher daily doses may support mania formation. In a study by Nishimura et al. (2008) in 135 patients followed-up with systemic lupus erythematosus (SLE) diagnosis and using corticosteroid therapy reported that mania was detected in 9 (64%) of 14 patients with psychopathology.

In a similar study (Kenna et al. (2011), it was reported that more than half of the 55 patients (n=30, [54.5%]) who had used steroid treatment with different diagnoses and emerged a psychiatric disorder were predominantly diagnosed with mania or hypomania, and mean duration of onset of psychiatric symptoms was 5 days for mania 12 days for depression and 7 days for delirium. Steroid-induced manifestations of mania / hypomania were found to present earlier than symptoms of depression (Bolanos et al. 2004, Herbert 1998, Kenna et al. 2011).

In our patient psychiatric symptoms did not occur during the period when she was on 20 mg of oral dexamethasone (equivalent to133 mg / day prednisone). However, when the dose was increased to 40 mg, the mania symptoms appeared within the first week. This can be attributed to higher daily dose, despite lower weekly dose in the second treatment period.

The onset of symptoms soon after a high dose is compatible with the emergence of acute symptoms in the literature with high doses (Jick et al. 1972). The patient received the full dose of quetiapine (200 mg / day) on the day and the day after taking the chemotherapeutic drug combination (bortezomib, dexamethasone and cyclophosphamide) , but she was on100 mg/day quetiapine on the other days when she did not receive chemotherapy. This supports the emergence of symptoms with post-dose acute effects. The steroid dose is the most important risk factor for psychiatric disorders due to steroids. The average daily dose of prednisone that increases the risk for depression is 73.2 ± 48.4 mg. For mania it is reported to be 44.8 ± 45.6 mg (Kenna et al. 2011).

In our patient mania symptoms appeared when a dose of 40 mg /day dexamethasone (equivalent to 266 mg / day

prednisone dose) was used. Psychiatric symptoms in patients are also reported to be a cumulative effect of previous doses after the last dose is given (Ferris and Eisele 2003, Galen et al. 1997).

Chau and Mok (2003) followed 126 treatment cycles in 92 SLE patients using corticosteroids.

It has been found that 5% of patients develop corticosteroid-induced psychosis or mania. Mean albumin level of these cases was significantly lower than that of the patients who did not develop psychiatric disorders.

Low serum albumin level, another risk factor other than dose, was also observed in our patient (Table 1). Albumin level was normal before the psychiatric illness and when the symptoms improved. However, the level of albumin is low when the symptoms are active. This suggests that there is a relationship between psychiatric symptoms and albumin level. However, the causality of this relationship is unclear. In addition to routine biochemical tests, protein electrophoresis and albumin percentage were measured in our patient. Albumin value was below the normal limit at each measurement, but the lowest value was observed during the period when the patient's symptoms were severe.Although albumin is shown as a risk factor for mania development (Chau and Mok 2003), albumin is known to be a negative acute phase reactant (Sonoda et al. 2015). Thus, the level of albumin may decrease in response to increased inflammation during the period when the underlying disease is exacerbated.

Female gender shown in other study (Kenna et al. 2011) to be a risk factor may also have affected the outcomes of corticosteroid treatment in our case.

In the literature there is only one case of mania reported with bortezomib treatment.

At the ninth day (after taking chemotherapy on days 1 and 8) of chemotherapy in a 61-year-old female patient with multiple myeloma diagnosis, mania symptoms were reported. It was reported that the patient received bortezomib (1,3 mg/m2, iv), dexamethasone (15 mg, iv) and thalidomide (75 mg, po). Although the symptoms were partially reduced after haemodialysis due to creatine elevation, on the 16th day of chemotherapy (after taking the third dose on day 15) symptoms increased again. Treatment with olanzapine (10 mg/day, po) and valproic acid (1000 mg/day, po) was started in the patient diagnosed with mania. The mania symptoms was improved after this drug treatment and the patient's chemotherapy was regulated as vincristine, adriamycin and dexamethasone.

In addition to this case, in a study comparing bortezomib and dexamethasone with thalidomide and dexamethasone in melphalan-resistant multiple myeloma patients, depression was observed in 5 of the 64 patients who received bortezomib only (Hjorth et al. 2012). In addition, mania symptoms may also be confused with posterior leukoencephalopathy (PLES), which is reported to develop due to bortezomib (Kager et al. 2009). PLES can characteristically cause headache, nausea and vomiting, altered consciousness, impaired vision, epileptic seizures, and focal neurological deficits (Bakshi et al. 1998). This diagnosis is unlikely in the case we have presented because the patient was clearly conscious, completely oriented and PLES symptoms were absent. In a case series, psychiatric disorders such as delirium and depression, which may develop due to progressive mental impairment, serum electrolyte imbalance, chemotherapy, hypercalcemia, uremia, anemia and others, have been reported to occur in patients with multiple myeloma (Silberfarb and Bates 1983). Psychiatric disorders can occur due to clinical and disease-induced processes caused by multiple myeloma. Psychiatric symptoms may also arise according to the degree of hypercalcemia occurring in multiple myeloma. In the literature, mild-to-moderate hypercalcemia causes depression, apathy, irritability and reduced spontaneity, whereas severe hypercalcemia can lead to delirium, psychosis, catatonia, lethargy and coma (Parks et al. 2017). The normal serum calcium levels measured before, during, and after treatment in our patient suggests that experienced symptoms are independent of hypercalcemia.

In the light of this literature information, it is seen that drugs that may cause symptoms of mania in our case are bortezomib and dexamethasone.

Bortezomib may induce apoptosis, reduce cytokines such as IL-1 and TNF, decrease cell adhesion molecules and reduce inflammation (Kelly et al. 2008, Wojcik and Di Napoli 2004). It has been reported that IL-1β levels decrease, TNF-α and IL-6 levels increase or remain unchanged in patients with manic episodes compared to the control group (Kalelioğlu et al. 2017).

It is known that the level of intracellular sodium decreases during the manic phase, returns to normal in the recovery phase, and anticonvulsant drugs act by inhibiting these sodium channels (Vawter et al. 2000).Corticosteroids have been shown to disrupt sodium channel function in the cell membrane (Wada et al. 2001).In addition, both dexamethasone and bortezomib are primarily metabolized by the cytochrome P450 enzyme (CYP) 3A4. It is known that the activity or level of bortezomib may increase during co-administration. Bortezomib and corticosteroids may be thought to have an effect thought these possible mechanisms in mania formation.

The literature on the treatment of corticosteroid-induced psychiatric symptoms is limited to multiple case presentations and a few small studies. In the treatment of mania or hypomania induced by drugs, it is suggested to first reduce the dosage of the drug and, if possible, discontinue the drugs (Appenzeller et al. 2008, Lewis and Smith, 1983).

Pharmacotherapy should be considered when this is not possible. Our patient responded partially to 100 mg / day quetiapine treatment and completely to 200 mg / day dose. Although quetiapine is often used alone in the treatment of mania, it has been reported that there is regression even at very low doses (25 mg / day) in the presence of corticosteroid-induced mania (Siddiqui et al. 2005). In bortezomib-induced mania, response was observed to olanzapine (10 mg /day) and valproic acid (1000 mg /day) (Jiang et al. 2014).

CONCLUSION

Most of the evidence from previous studies on bortezomib and dexamethasone-related mania is case reports, case series, and studies including small numbers of patients. To understand the psychiatric side effects of these drugs, there is a need for further study, especially with information on patients using bortezomib, which is less data in the literature.

Peripheral neuropathy, thrombocytopenia, neutropenia and ECG abnormalities are common side effects of bortezomib (Lu et al. 2009).However, psychiatric symptoms and illnesses are rarely reported. The fact that the psychiatric cases associated with bortezomib, approved by the FDA in 2003, are also relatively few, may be due to the presence of less information about this drug (Lamers et al. 2013). Recognition of symptoms related to corticosteroids and bortezomib in early stages will help prevent serious psychiatric side effects and psychopathology.

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