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Case Report

# Tolvaptan Treatment for Severe Hyponatremia Secondary to the VRd Protocol (Bortezomib/Lenalidomide/Dexamethasone) for Multiple Myeloma, with A Well-Regulated Sodium Level Achieved During that Treatment

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## Abstract

This medical case report describes the treatment of a 59-year-old male patient with Multiple Myeloma (MM), who was admitted to the hospital with a fractured vertebra caused by an accidental fall. The patient was undergoing the VRd protocol, which consists of bortezomib, lenalidomide, and dexamethasone. Before the start of the third cycle, the patient had evidence of hyponatremia due to SIADH, a complication of bortezomib treatment. The patient was treated with hydric restriction and fluid therapy with 3% hypertonic saline, followed by the administration of tolvaptan to prevent excessively rapid correction of the natremia. The tolvaptan dose was increased gradually, resulting in stable sodium levels, allowing the cycle to be continued as scheduled. However, on the same day that bortezomib was administered, the patient showed pronounced, sustained hypotension, and the VRd protocol was suspended. The case report highlights the importance of early detection and management of hyponatremia in patients with MM undergoing the VRd protocol, as well as the potential use of tolvaptan for its treatment.

**Keywords: Hyponatremia; SIADH; Bortezomib; Tolvaptan**

## Introduction

Multiple Myeloma (MM) is a neoplastic disorder characterised by clonal proliferation of plasma cells, which secrete monoclonal immunoglobulins and cytokines responsible for the associated bone lesions. A MM diagnosis was made by detecting the monoclonal component, plasmacytoma, in blood serum and/or urine; infiltration of plasma cells into bone marrow; tissue damage with the symptoms referred to as CRAB (hypercalcaemia, renal dysfunction, anaemia, and bone lesions); and other predictive biomarkers [1].

In patients who are candidates for autologous transplant, one of the protocols recommended for induction is the VRd protocol, which combines a proteasome inhibitor (bortezomib), an immunomodulator (lenalidomide), and a glucocorticoid (dexamethasone) [2]. This protocol consists of 28-day cycles, with administration during each cycle of subcutaneous bortezomib (1.3 mg/m$^2$ on days 1, 4, 8, and 11); oral lenalidomide (25 mg/day on days 1-21); and dexamethasone (40 mg/day on days 1, 2, 4, 5, 8, 9, 11, and 12) [3].

One of the complications seen when using bortezomib to treat MM is episodes of hyponatremia secondary to that treatment [4]. The signs and symptoms present depend upon the promptness of implementation and the duration and severity of the hyponatremia. The primary symptoms are neurological, ranging from weakness and confusion to convulsions and coma. Treatment is based on the aetiology. One of the causes is SIADH, which may be suspected in patients who present mild to moderate euvolemic hyponatremia. The diagnosis is established in patients with urine osmolality >100 mOsm/kg and plasma osmolality <275 mOsm/kg, and urine sodium concentration >30 mEq/L. Treatment of SIADH consists of hydric restriction and saline replacement with hypertonic serum, as well as pharmacological management with urea and/or vaptans [5].

## Case Presentation

### Basic symptoms

A male patient, 59 years old, with a recently diagnosed onset of IgG kappa MM, DS III (Durie-Salmon staging system), ISS-2 (International Staging System), presented with pancytopenia, plasmacytosis, and cranial, intracranial, pulmonary, and spinal lesions. Prior to the current event, he had received two treatment cycles of the VRd protocol.

### Reason for hospital admission

The patient was admitted to the Trauma Service because of a fractured L1 vertebra caused by an accidental fall on a stairway at his home. Surgery was rejected and the decision was made to use a Jewett corset to treat the fracture.

### Evolution of hyponatremia and therapeutic management

The hospital admission coincided with initiation of the third

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VRd cycle. Before that cycle began, the control blood work showed evidence of progression in the hyponatremia by comparison with the blood work performed by the Trauma Service, with a plasma sodium level of 122 mEq/L and a calculated plasma osmolality of 255.8 mOsm/kg.

Hyperthyroidism was ruled out by previous TSH levels of 1.92 mIU/mL. Analysis of ions in the urine revealed a urine sodium level of 140 mEq/L, urine osmolality of 613 mOsm/kg, and a calculated First index of 1.46. Although cortisol levels were not analysed, adrenal insufficiency was ruled out because the patient was being treated with corticoids. Based on these results, and taking into account the time when the hyponatremia appeared (natremia in normal range prior to initiation of the VRd), the diagnosis was focused on hyponatremia by iatrogenic SIADH.

Treatment of the hyponatremia was initiated, with hydric restriction at 500 mL/day. This was ineffective, and the natremia level decreased to 114 mEq/L and the neurological situation worsened, with confusion and generalised weakness. Fluid therapy with 3% hypertonic saline (3% HTS) was initiated, and natremia was monitored after administration of HTS. Intravenous therapy with 3% HTS was continued until the patient's plasma sodium increased to 122 mEq/L. Administration of tolvaptan was initiated only after the plasma sodium level was above 120 mEq/L to prevent excessively rapid correction of the natremia. The initial tolvaptan dose given was 3.5 mg, which led to an increase of 1 mEq/L in 24 hours, so the dose was increased to 7.5 mg, which resulted in a plasma sodium concentration of 125 mEq/L in 24 hours. Following this progressive response, the dose was increased to 15 mg/day, which achieved stable sodium levels, approximately 133 mEq/L on day 8 of the cycle (C3D8), at which point tolvaptan treatment was discontinued (Figure 1). The positive response to tolvaptan allowed the cycle to be continued as scheduled, and so bortezomib was administered on C3D8.

### VRd suspended for hypotension

On that same day, after the bortezomib was administered, the patient showed pronounced, sustained hypotension (64/40 mmHg) and also reported dizziness. The patient had a similar syncopal episode secondary to administration of bortezomib during a previous cycle.

Intravenous therapy was used to manage the hypotension, along with adjustment of the hypertension medication (enalapril, bisoprolol, and furosemide). Despite the treatment, the patient's hypotension proved to be refractory, so the final administration of bortezomib for the cycle was suspended.

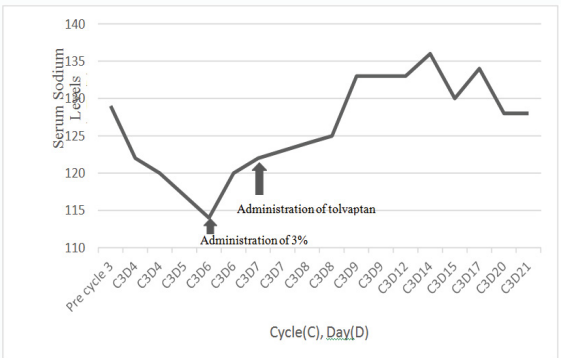


**Figure 1**: Natremia during VRD treatment and response to therapy with tolvaptan. Duplicated days represent natremia monitoring more than once on the same day.

### Concomitant problems during hospital admission

On admission, the patient suffered from other complications. Upon arrival he presented cachexia, weakness, and oliguria. During physical examination, he was experiencing pains that were difficult to treat using the basic analgesic guidelines, and which required treatment with opioids.

His blood work on admission showed a NT-proBNP value of 6007 pg/mL. Physical examination also revealed tachycardia. After performing an electrocardiogram, this was diagnosed as an atrial flutter with uncertain initiation, CHADS2-VASc score=2, and treatment was therefore started with an anticoagulant (apixaban, 5 mg/12 h) and heart rate control (bisoprolol, 2.5 mg/12 h).

### Current status/follow-up

After the acute episode, the patient was finally transferred to a health care centre for his follow-up and pain management. VRd treatment was suspended because of the associated toxicity. The patient again showed mild hyponatremia, which was treated with urea (15 g/day), but without an adequate response. The patient currently requires treatment with tolvaptan to keep his blood sodium concentration within the normal range.

## Discussion

The VRd protocol is one of the most commonly used approaches for treating MM. Hyponatremia frequently occurs secondary to that treatment and can be severe, thereby compromising the treatment's continuation [6,7]. However, there are no clear recommendations regarding the appropriate therapeutic response in such cases. Suspending the treatment can have negative consequences for evolution of the MM, and it is therefore necessary to establish strategies that can allow the treatment to continue. It is also important to avoid excessively rapid correction of the natremia, to prevent osmotic demyelination syndrome [8].

This lack of recommendations regarding how to manage hyponatremia secondary to VRd can cause discontinuation of the treatment for that reason. In our case, although in the end administration of bortezomib was suspended because of arterial hypotension, progressive correction of the natremia was achieved, and this allowed administration of the next dose from the VRd cycle. A similar case has been reported, in which it was possible to continue VRd therapy thanks to treatment with tolvaptan [9]. In our patient, dose escalation with monitoring of plasma sodium was used to prevent osmotic demyelination syndrome. During the patient's follow-up, after administration of tolvaptan was suspended, chronic low levels of plasma sodium were observed. These were initially treated with urea without an adequate response, but those levels finally responded to tolvaptan. Despite the suspension of the treatment, this long-term evolution seems to provide evidence that the SIADH caused by bortezomib is chronic in nature and may require long-term treatment with tolvaptan [9].

The causal mechanism by which bortezomib leads to hyponatremia has not been established, but the good response to tolvaptan suggests a mechanism where sensitivity to Antidiuretic Hormone (ADH) is increased, or else a hypophysary mechanism that increases the level of ADH secretion, which has been proposed as a causal mechanism for hyponatremia with other antineoplastic agents [10,11].

## Conclusion

Tolvaptan appears to be a safe and effective alternative [12] for treating severe hyponatremia that occurs secondary to treatment with bortezomib/lenalidomide. This approach allows continuation of the oncologic treatment, and it may be useful in cases where long-term SIADH develops after being induced by the VRd protocol.

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