

Bortezomib-Induced Bilateral Eye Swelling and Cutaneous Adverse Reaction in a Patient with Plasma Cell Leukemia—A Case Report

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Abstract

Bortezomib, a proteasome inhibitor, is an established therapy against plasma cell leukemia—a variant of plasma cell dyscrasias. Its most frequent side effects have been listed as peripheral neuropathy, neuropathic pain, thrombocytopenia, and gastrointestinal problems. Allergic skin reaction is a rarely documented side effect in patients receiving bortezomib-based chemotherapy. A combination therapy consisting of intravenous bortezomib, oral Revlimid tablets, and oral dexamethasone tablets has been prescribed for the patient after his recent diagnosis of plasma cell leukemia. While receiving his third treatment cycle, he developed an allergic reaction (skin rash) involving the neck, and wrists, and mild bilateral eye swelling. The infusion was stopped immediately and then ciprofloxacin ophthalmic solution and oral diphenhydramine 25 mg were prescribed to the patient with significant improvement in his clinical condition. He was temporarily taken off bortezomib. At a follow-up visit a week later, a significant improvement was noticed in his condition. Rash had reduced on neck and wrists, and eye swelling had reduced as well. As of the time of writing this case report, he has been temporarily taken off bortezomib, but other medications in the treatment regimen were continued as prescribed.

Keywords

Plasma Cell Leukemia, Hematology, Bortezomib, Chemotherapy

1. Introduction

Bortezomib, a proteasome inhibitor, inhibits the activity of nuclear factor kappa B (NF- κ B), which is a key mediator of inflammation that downregulates several paraneoplastic pathways. The overexpression of phorbol-12-myristate-13-acetate-induced protein 1 (NOXA), a proapoptotic protein, is another way by which bortezomib exerts its anticancer action. NOXA may interact with the antiapoptotic proteins of the Bcl-2 subfamily, Bcl-X(L), and Bcl-2 to cause apoptotic cell death in malignant cells [1]. Bortezomib is a well-established treatment for multiple myeloma and its variants, including plasma cell leukemias [2]. Most of the bortezomib's side effects are mild to moderate and generally tolerable. Among the most common side effects are peripheral neuropathy reported in about 30% - 40% of cases, and thrombocytopenia in 30% of cases [2]. About 10% of cases have cutaneous adverse reactions documented [3]. However, most of them have been mild cases. There have also been a few reports of severe cutaneous adverse reactions (SCARs) caused by bortezomib, such as Stevens-Johnson syndrome (SJS) [4]. The cases of allergic skin reactions that occur in patients receiving bortezomib-based chemotherapy are not frequently documented. Here, we describe a case of bilateral eye swelling and rash induced by bortezomib in a 58-year-old man undergoing chemotherapy for plasma cell leukemia.

2. Case Presentation

A 58-year-old man being managed at the clinic for plasma cell leukemia was noticed to develop bilateral eye swelling and rash involving the wrists and neck while receiving bortezomib infusion. There is no known history of drug or environmental allergies. There is no known family history of allergies.

The patient was prescribed a treatment regimen consisting of intravenous bortezomib, oral lenalidomide (Revlimid), and oral dexamethasone after his diagnosis of plasma cell leukemia. He commenced the treatment as follows. Bortezomib is administered as an intravenous bolus injection of 1.3 mg per square meter of body surface area once weekly for three weeks, then the same regimen is continued after a week of rest (bortezomib is administered on days 1, 8, and 15 of every 28 days). Additionally, he was receiving 12 mg of dexamethasone pills every week for three weeks, with the continuation of the regimen after a week of rest. Revlimid is taken at the dose of 25 mg orally once a day for 21 days followed by a seven-day break.

During the first infusion of his third treatment cycle, he experienced an allergic reaction which is characterized by rashes on the neck and wrists and mild bilateral swelling of the eyes (see **Figure 1**). The patient denied fever, shortness of

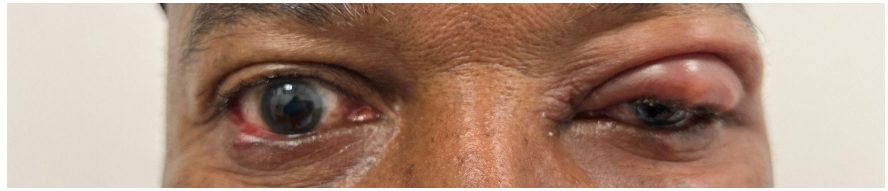


Figure 1. Showing eye swelling, after bortezomib infusion was administered.

breath, dizziness, lightheadedness, and nausea during this period and his vital signs were stable. The infusion was stopped, and oral diphenhydramine 25 mg was prescribed to him. Although he has been on a treatment regimen of dexamethasone, Revlimid, and bortezomib (he had received two cycles prior), no changes in the treatment regimen have been made before the onset of symptoms. He did not report any other toxicity symptoms potentially related to bortezomib. Ciprofloxacin 0.3% ophthalmic solution and diphenhydramine 25 mg oral tablets were prescribed to the patient. At the one-week follow-up visit, his condition had significantly improved as the eye swelling had resolved. He is currently on Revlimid and dexamethasone and has been temporarily off bortezomib.

3. Discussion

Plasma cell leukemia is a rare and aggressive form of leukemia and plasma cell dyscrasia [5]. It is a variant of multiple myeloma that affects plasma cells, making them resistant to cell-programmed apoptosis. Traditional cytostatic chemotherapy has resulted in a poor prognosis for Plasma Cell Leukemia. The introduction of bortezomib (a proteasome inhibitor) and lenalidomide (an immunomodulatory agent that modulates the release of inflammatory mediators) has improved the prognosis to some extent [5].

Bortezomib belongs to a class of chemotherapy that inhibits proteasomes, breaking down proteins tagged by ubiquitin. It is a modified dipeptidyl boronic acid that reduces the NF- κ B translocation/transcription activity and blocks drug-related signaling pathways critical to vital functions of myeloma cells [6]. Its mechanism of action has been described as binding reversibly to the 26S proteasome's chymotrypsin-like subunit, resulting in the degradation of various pro-apoptotic factors [7].

A recent meta-analysis has established that using a combination of bortezomib, lenalidomide, and dexamethasone in treating multiple myeloma had the largest survival benefit compared to other medication combinations [8]. It has been reported that in multiple myeloma treatment, the combination therapy of bortezomib and steroids is more effective than bortezomib monotherapy. Therefore, the first choice for multiple myeloma treatment is the combination of these two drugs [9].

The case described above depicted the development of a maculopapular rash involving the neck and both wrists, with bilateral eye swelling and redness while receiving a bortezomib infusion. According to reports, bortezomib administration causes an increase in the release of proinflammatory cytokines (including

IL-6 and TNF-) as well as the generation of a cell-mediated immune response, which may play a role in bortezomib-induced cutaneous reactions [10] [11].

A prospective observational study was by Wu *et al.* The study was conducted on 47 patients recruited from 3 prospective randomized clinical trials. Cutaneous adverse reactions were observed in 6 (13%) participants, out of 47 patients receiving bortezomib infusion. In patients who developed bortezomib-induced skin toxicity, the time between the first bortezomib dose and the eruption of cutaneous reactions was at least 30 days [10].

In this case, the patient was noticed to have ocular involvement described as bilateral eye swelling and redness—more in keeping with conjunctivitis. Ocular manifestations have been reported in some cases of bortezomib-induced cutaneous reaction, including corneal ulcerations. The most common ocular condition has been reported to be bilateral conjunctivitis, which occurs in about 15% - 75% of patients [12]. At a follow-up visit, about days after the discontinuation of bortezomib, the patient's cutaneous reaction and bilateral eye swelling were found to have resolved.

4. Conclusion

Proteasome inhibitor-based therapy is becoming more common in medicine, particularly for plasma cell leukemia and multiple myeloma. As a result, cutaneous reactions and ocular swelling are likely to occur more frequently, as cases of such have been reported. A major limitation of this article is the absence of a pathological diagnosis of the cutaneous reaction—in terms of a biopsy or patch test with bortezomib and the other medications the patient was on. However, a high index of suspicion was unleashed, as the cutaneous reaction resolved with the discontinuation of bortezomib. Adequate monitoring of patients receiving bortezomib chemotherapy is required to intervene promptly if an adverse reaction occurs.

Consent

The patient's consent was obtained orally.

Authors' Contributions

All authors have participated in the procurement of this document and agree with the submitted case report.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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