Case Report

Bortezomib-Induced Pulmonary Toxicity: A Case Report and Review of Literature

Prakash Kharel,1 Deekchha Uprety,2 Abhinav B. Chandra,3 Yirui Hu,4 Anuradha Avinash Belur,5 and Ajay Dhakal6

1Department of Hospital Medicine, Geisinger Medical Center, 100 N Academy Ave., Danville, PA 17821, USA
2Renal Division, Brigham and Women’s Hospital, Boston, MA, USA
3Yuma Regional Medical Center, Yuma, AZ, USA
4Center for Health Research, Geisinger Medical Center, 100 N Academy Ave., Danville, PA 17821, USA
5Multi Care Regional Cancer Center, Auburn, WA, USA
6Department of Medicine, Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA

Correspondence should be addressed to Prakash Kharel; pkharel@geisinger.edu

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Bortezomib, a proteasome inhibitor, is an established therapy against multiple myeloma. Bortezomib-induced lung injury, although not appreciated during the introductory time of the medication, has now been highlighted in multiple case reports [1–21].

The underlying mechanism of BLI is unclear but a proposed hypothesis is that BTZ withdrawal leads to rebound activation of (NF)-κB causing inflammatory changes in the lungs. This explains the rapid improvement of BLI with steroid therapy reported in several cases. But, there are a number of cases reported, which did not improve with steroid. Alternate hypothesis is that BTZ metabolites accumulate in the lung tissue causing direct lung injury.

Some anecdotes claim that genetic predisposition (especially Japanese population) and history of prior stem cell transplant (SCT) might be risk factors for BLI [1, 9, 21]. The objective of this study is to report a case of BLI, review current literature, and determine the predictors of mortality in BLI based on the analysis of the data from the cases reported.

2. Case Report

A 64-year-old male with chronic low back pain presented to the emergency department with a new onset, severe mid back pain radiating to bilateral shoulders. CT scan, performed to rule out aortic dissection, demonstrated multiple lytic lesions throughout the bony skeleton and a compression fracture at T7 vertebral body with epidural extension of the soft tissue. A bone survey confirmed CT scan findings, and subsequent bone marrow biopsy confirmed the diagnosis of MM. He received radiation therapy to the thoracic spine and completed 2 cycles of CyBorD regimen (cyclophosphamide 300 mg/m² by mouth, BTZ 1.5 mg/m²
subcutaneous, and dexamethasone 40 mg by mouth each on
days 1, 8, 15, and 22). Three days after the completion of
the second cycle, he was admitted to hospital with respiratory
distress. CT chest (Figure 1) showed new interval appearance
of bilateral perihilar ground-glass opacities and peribronchial
and interstitial thickening predominantly in the upper
lobes not seen in prior scan (Figure 2). There were no other
signs or symptoms of pneumonia such as leukocytosis, fever,
or cough. After some benefit from oral prednisone, he was
discharged with a tapering dose of the same. Unfortunately,
the patient was readmitted with worsening respiratory
distress 4 days later. A repeat CT scan of the chest showed
resolution of previously well-defined areas of perihilar
ground-glass opacities but development of hazy areas of
ground-glass opacification throughout both lungs with more
confluent abnormalities in bilateral lower lobes (Figure 3).
The patient was treated with high-dose methylprednisone
and noninvasive positive pressure ventilation without any
improvement. The family requested do-not-resuscitate and
do-not-intubate status. The patient died on the 10th day of
the admission.

3. Methodology
We have reported a case and performed a review of current
literature on BLI and statistical analysis of available data.
Extensive PubMed search was performed to screen the
literature using the search words “bortezomib” and “pul-
monary injury,” “pulmonary toxicity,” “lung injury,” “lung
toxicity,” “pneumonitis,” “pulmonary side effects,” “lung
side effects,” “shortness of breath,” “breathlessness,”
“dyspnea,” “ARDS,” or “respiratory failure.” BLI was de-
defined as new onset of respiratory symptoms with new ra-
diological finding without evidence of infection and other
causes of respiratory symptoms including cardiac causes
and other drug-related adverse effects. Respiratory symp-
toms included fever, dyspnea, cough, breathlessness, or
respiratory failure. Radiological findings included any
pulmonary infiltrate, pleural effusion, pulmonary edema,
ground-glass opacity, diffuse alveolar hemorrhage, reticular
shadowing, or features of pulmonary hypertension and
interstitial pneumonitis. Eligible cases from the literature
were included in the review.

4. Results
An extensive PubMed search yielded 35 events of BLI, 5 of
which occurred with readministration of BTZ after reso-
lution of initial BLI. The mean (standard deviation SD,
minimum, maximum) age is 61.14 years (9.93, 31, 78) and
65.71% were male. 14.29% had current or past smoking
history, 17.24% had history of lung disease, and 31.43% had
prior SCT for MM. 14.29% received steroid just prior to or
along with bortezomib. 14.29% were receiving concurrent
chemotherapy. The mean total BTZ dose was 4.41 mg (2.75,
1, 9), mean duration from the first dose to the onset of BLI
was 20.59 days (16.59, 0.5, 60), and the mean duration from
the last dose to onset of BLI was 3.08 days (2.77, 0, 10).
37.14% of BLIs were fatal.

The t-test showed no significant difference in mean age,
mean number of BTZ doses, and mean duration from the 1st
dose of BTZ to the onset of BLI between deceased and
survivors. But, the difference in mean duration (SD, mini-
imum, maximum) from the last dose of BTZ to the onset of
BLI between deceased (1.59 days (SD, 0, 5)) and survivors
(3.95 days (SD, 0, 10)) were found to be statistically sig-
nificant ($p = 0.009$) Table 1. 45.45% deceased had prior SCT
compared to 11.11% deceased who had no stem cell
transplant ($p = 0.0360$). No significant association could be
found between the outcome of BLI and various factors like
sex, previous lung diseases, history of smoking, concurrent/
prior steroids, and treatment of BLI with steroids Table 2.
5. Discussion

Most of the adverse effects associated with bortezomib are mild to moderate and are generally manageable, including gastrointestinal symptoms, peripheral neuropathy, and thrombocytopenia [1]. BLI is a serious yet underappreciated adverse effect of BTZ associated with a high mortality rate of 37.14% as suggested by our analysis of reported cases available. Some initial case reports suggested a mortality rate as high as 50% [1]. In one phase IV clinical study of 666 patients who had received bortezomib published by Narimatsu et al., 3.6% of pulmonary complications and 0.5% of total deaths were attributed to these complications [22]. Some studies have shown that genetic predisposition to BLI, especially with Japanese population, and history of prior SCT might be risk factors for BLI [1, 9, 21]. Some cases responded very well to steroids [11], while others did not. Our patient responded to steroid to some extent and was discharged. He later presented with worsening pulmonary symptoms and died. It is important to establish the dose and duration of steroid for the patients who respond to therapy. For others who do not respond to steroid, there is a need to identify other mechanisms of BLI, so that appropriate treatment may be directed. Clinicians should have a high degree of suspicion for BLI, as it can be misjudged as other more common respiratory conditions. Appropriate supportive management along with steroids and immediate withdrawal of BTZ should be the primary management strategy.

Our study showed that fatal BLIs were associated with early onset after the last dose of BTZ (with mean 1.59 days vs. 3.95 days among nonfatal BLI) and with history of prior SCT. No significant association could be found between the outcome of BLI and various factors like sex, previous lung diseases, history of smoking, concurrent/prior steroid intake, concurrent steroid as part of chemotherapy regimens, and steroid administered to treat BLI. Small sample size, retrospective nature of the study, and analysis of composite data from the reported cases in the PubMed are major limitations of the study.

Carfilzomib (CFZ) is an irreversible, second-generation selective proteasome inhibitor that is used to treat relapsed or refractory MM. In July 2012, the FDA granted approval of carfilzomib for the treatment of patients with multiple myeloma who have received bortezomib published by Narimatsu et al., 3.6% of pulmonary complications and 0.5% of total deaths were attributed to these complications [22]. Some studies have shown that genetic predisposition to BLI, especially with Japanese population, and history of prior SCT might be risk factors for BLI [1, 9, 21]. Some cases responded very well to steroids [11], while others did not. Our patient responded to steroid to some extent and was discharged. He later presented with worsening pulmonary symptoms and died. It is important to establish the dose and duration of steroid for the patients who respond to therapy. For others who do not respond to steroid, there is a need to identify other mechanisms of BLI, so that appropriate treatment may be directed. Clinicians should have a high degree of suspicion for BLI, as it can be misjudged as other more common respiratory conditions. Appropriate supportive management along with steroids and immediate withdrawal of BTZ should be the primary management strategy.
respective controls (29 versus 13 percent) and cough (25 versus 14 percent), but there were no BLI-like noninfectious progressive lung injuries reported [23, 24]. According to FDA-approved manufacturer’s prescribing information, carfilzomib was associated with development of pulmonary hypertension in 2% of patients [25]. Severe pulmonary hypertension (grade ≥ 3) was in less than 1%.

Based on our literature review, only 5 case reports of CFZ-associated noninfectious progressive lung injury have been identified. In one of the reported cases, the patient presented with dyspnea on exertion, fatigue, and a dry cough after the second dose of CFZ which got worse with subsequent dose until CFZ was discontinued. A CT chest revealed diffuse bilateral ground-glass micronodular opacities and increased reticular markings. The pulmonary function test showed a severe restrictive ventilatory defect, with severely reduced diffusion capacity and desaturation to 84% on exertion. Symptoms and CT scan finding improved after oral prednisone [26]. In other case report, the patient developed an acute respiratory distress syndrome requiring mechanical ventilation. After a week, the patient developed diffuse alveolar hemorrhage and despite aggressive supportive care, the patient died after three weeks [27]. The third case report was also about fatal pulmonary hemorrhage after CFZ. The patient had developed acute dyspnea within 2-3 hours of first dose of CFZ, along with infiltrates on chest X-ray. Symptoms resolved after corticosteroid and bronchodilators along with resolution of X-ray finding next day. The patient was subsequently treated five scheduled doses without any problem. After about a month, when second cycle of CFZ was given, the patient again developed acute dyspnea, with no resolution of symptoms. The patient later died of pulmonary hemorrhage despite aggressive therapy [28]. Recent case series reported one case of pulmonary hypertension after CFZ and other case of dyspnea with lung disease with pulmonary function test showing significantly decreased unadjusted diffusion capacity of the lung [29]. With increasing use of CFZ, more information may emerge regarding the CFZ-associated lung injuries in future.

6. Conclusion

BLI is a serious condition with a mortality rate of 37.14%. Early onset of BLI from the last dose of BTZ and prior SCT can be the predictors of mortality. Further studies are needed to confirm these findings. Limited data have emerged on the possible association of CFZ with various lung injuries. Clinicians should be mindful of this potentially fatal adverse effect of proteasome inhibitors like BTZ or CFZ.

Abbreviations

BTZ: Bortezomib
BLI: BTZ-induced lung injury
SCT: Stem cell transplant
SD: Standard deviation.

Disclosure

This case report was accepted as “online only” abstract in ASH Annual Meeting 2014.

Conflicts of Interest

The authors declare no conflicts of interest.

References


