

Case Report

Fatal pulmonary toxicity following Carfilzomib administration

A Marschall, JC de la Flor Merino & T Linares Gravalos

Abstract

Carfilzomib has shown excellent outcomes for relapsed Multiple Myeloma. There have been increasing reports on cardiovascular adverse events. However, reports on severe pulmonary adverse events are rare. Our patient was a 79-year-old female, undergoing fourth-line therapy with Carfilzomib. At 24h after first administration, the patient was admitted to the emergency room complaining of dyspnoea. After a full recovery, the patient was re-evaluated. Since echocardiography showed normal cardiac function, Carfilzomib was re-initiated. At 24h after administration, the patient was re-admitted to the emergency room with severe dyspnoea, meeting criteria for ARDS. Despite mechanical ventilation, the patient developed cardiac arrest. Resuscitation was unsuccessful. Although patients might fully recover from a first episode of Carfilzomib-induced pulmonary toxicity, re-initiation of Carfilzomib is not recommended.

Keywords

Carfilzomib, pulmonary toxicity

Teaching point

- This case report emphasizes the importance of recognizing Carfilzomib related pulmonary toxicity and the significance of its distinction from other, more frequent adverse events, such as acute heart failure. Although patients might fully recover from a first episode, Carfilzomib should not be re-initiated.

Introduction

Treatment strategies for multiple myeloma (MM) have undergone a significant change in the past decade. With new drugs becoming clinically applicable, median overall survival in MM patients increased progressively.¹ Carfilzomib (CFZ), a second generation proteasome inhibitor, showed excellent outcomes for relapsed and refractory MM. In the ASPIRE study, overall survival was significantly longer in patients that received combination therapy with CFZ, compared to Lenalomide (LEN) and dexamethasone (DEX) alone.^{2,3} In addition, the ENDEAVOR study showed prolonged progression-free survival for CFZ + DEX combination therapy, compared to Bortezomib (BOR) + DEX.⁴ Despite the promising results on overall survival in MM patients, there have been growing safety concerns ever since its approval by the Food and Drug Administration (FDA) in 2012. There have been increasing reports on cardiovascular and pulmonary adverse events. Previous reports primarily include heart failure, severe hypertension, ischaemic events, cardiac arrest and non-life-threatening pulmonary adverse events.^{5–7} However, reports on severe, or even fatal, pulmonary adverse events are rare.⁶ We present the case of a patient who developed fatal acute respiratory distress syndrome (ARDS) after administration of CFZ.

Case presentation

Our patient was a 79-year-old female, who was diagnosed with MM stage IIB in June 2014. Fourth line therapy with CFZ in combination with DEX

was initiated in November 2019. At 24h after first administration, the patient, who had a history of advanced chronic renal failure secondary to myeloma kidney disease (Grade 4, A3), was admitted to the emergency room complaining of dyspnoea. Blood pressure and pulse rate were normal, oxygen saturation was 92%. Chest radiography revealed bilateral alveolar infiltrates, compatible with pulmonary oedema (Figure 1, A). Laboratory findings did not suggest acute infection. Based on these initial findings the patient was admitted to an internal medicine ward with the working diagnosis of acute congestive heart failure. A subsequent echocardiography revealed normal left ventricular ejection fraction, no dilatation of the left ventricle and normal wall thickness. Within 5 days the respiratory symptoms disappeared completely and chest radiography showed great improvement (Figure 1, B). The patient was discharged and re-evaluated by the department of haematology in December 2019.

Thorough assessment, which included a new echocardiography and chest radiography (Figure 2, A), was completed. Since these tests showed normal cardiac function and no pulmonary infiltrates, CFZ was re-initiated in January 2020. At 24h after administration of CFZ, the patient was re-admitted to the emergency room with severe dyspnoea. Physical examination revealed bilateral crackles and chest radiography showed bilateral alveolar infiltrates (Figure 2, B). Blood pressure was 124/85 mmHg,

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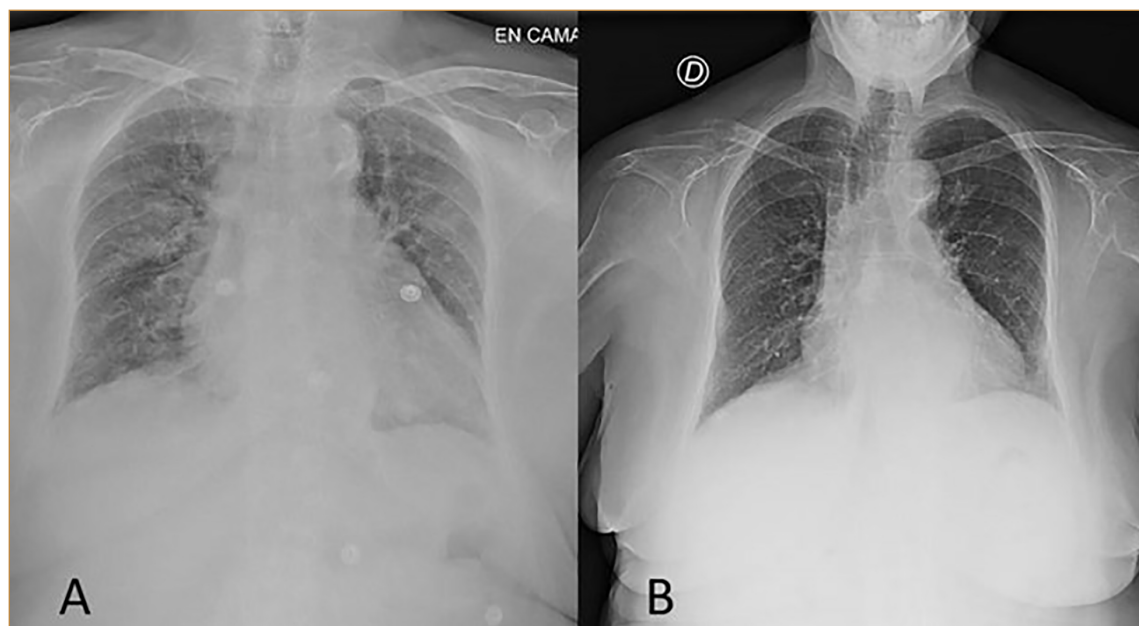


Figure 1. A: Chest radiography revealed bilateral alveolar infiltrates, compatible with pulmonary edema; **B:** Chest radiography 5 days after admission, showing great improvement

pulse rate was 69 bpm and oxygen saturation was 89%. Arterial blood gas analysis showed a pH of 7.36, paCO_2 of 30.2 mmHg and a paO_2 of 59.9 mmHg. Pro-BNP was 2,740 pg/mL and echocardiography showed no changes with respect to the previous studies. Furthermore, the patient presented with acute anuric renal failure. The patient was admitted to the intensive care unit (ICU) where haemodialysis was initiated immediately. Despite all therapeutic measures, the patient developed progressive respiratory deterioration and decline of paO_2 ($\text{PaO}_2/\text{FiO}_2$ 120 mmHg) and therefore, considering the normal echocardiography and

blood pressure, meeting criteria for acute respiratory distress syndrome (ARDS). Respiratory status further declined and the patient required mechanical ventilation. Despite mechanical ventilation and high FiO_2 , the patient remained profoundly hypoxic and developed cardiac arrest. Unfortunately, cardiac resuscitation was unsuccessful and the patient died on first day in ICU.

Discussion

CFZ is a second generation selective proteasome inhibitor and was approved by the FDA for the treatment of relapsed or progressive MM in 2012.³

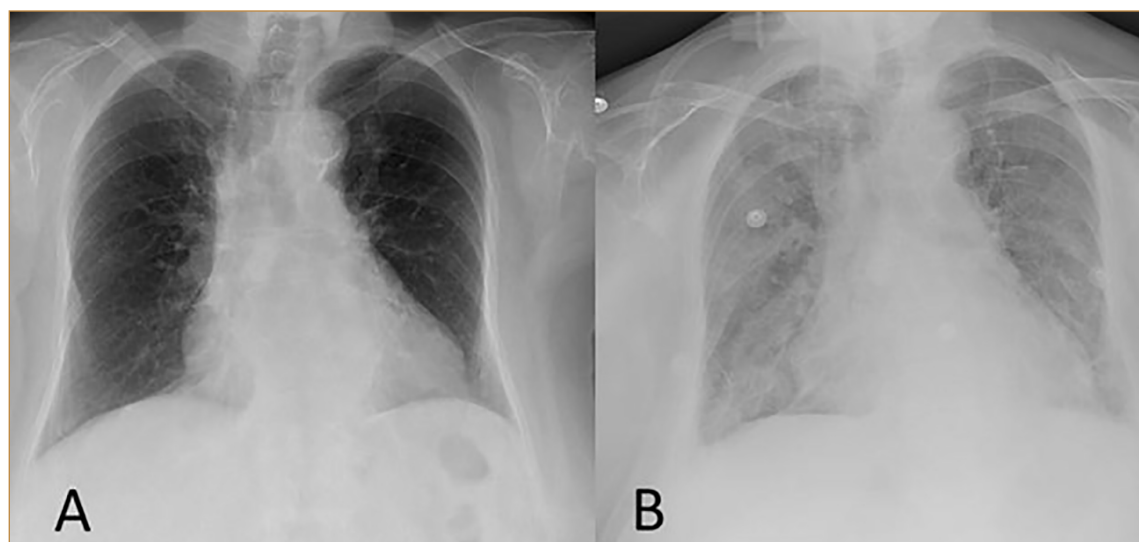


Figure 2. A: Chest radiography at re-evaluation; **B:** Chest radiography at re-admission to emergency room, showing bilateral alveolar infiltrates

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Ever since, there have been rising safety concerns. Based on two phase II studies, the most common cause of death was progression of MM, followed by cardiac toxicity.^{8,9} In a recent meta-analysis on cardiovascular adverse events of CFZ, heart failure (4.1%) and hypertension (12.2%) were the most common types of cardiovascular adverse events. Arrhythmias (2.4%) and ischaemic events (1.8%) were less common.⁷

Regarding pulmonary adverse events, in phase 2 studies dyspnoea and pneumonia were the most common pulmonary complications that led to discontinuation of treatment.^{8–10} In a review of four phase II studies, including 526 patients, Siegel et al found that the majority of dyspnoea events were grade 1 or two. Only 25 patients (4.8%) presented grade 3 dyspnoea and no grade 4 dyspnoea was reported. Other pulmonary adverse events were relatively rare, in comparison to the previous mentioned cardiac and pulmonary adverse events (pleural effusion: 4%, pulmonary hypertension: 2%, pulmonary artery embolism: 1%, haemoptysis 0.6%, pneumonitis: 0.4%). No case of ARDS was reported in phase II studies.¹¹

Our patient presented with acute respiratory deterioration on two occasions, both within 24–48h after administration of CFZ. In consideration of the findings in echocardiography (which showed no signs of heart failure), chest radiography (which showed bilateral alveolar infiltrates) and arterial blood gas analysis ($\text{PaO}_2/\text{FiO}_2 < 200$ mmHg), our patient meets criteria for ARDS. Given the clear temporal relationship between the administration of CFZ and the onset of symptoms, we believe that our patient suffered from CFZ related pulmonary toxicity. The recurrence of symptoms after a second administration of CFZ supports this hypothesis.

Carfilzomib-induced anaphylaxis is a major differential diagnosis in this case, which needed to be ruled out. However, considering that our patient did not present anaphylaxis-typical respiratory (wheezing, high airway peak pressure), haemodynamic (tachycardia, low blood pressure, cardiac output and systemic vascular resistance as assessed by volumetric measurement system), nor haematologic (eosinophilia) changes, we consider anaphylaxis an unlikely explanation for the patients deterioration.^{12,13}

There have been various reports on severe cardiac adverse events after CFZ administration.^{5,7} However, to our best knowledge, there is only one case report of fatal pulmonary toxicity caused by ARDS after CFZ administration.⁶ Our case report emphasises the importance of recognising CFZ related pulmonary toxicity. Furthermore, it highlights the significance of its distinction from other adverse events that cause similar clinical presentations, such as acute heart failure. Previous case reports on CFZ-related cardiac adverse events point out the significance of discontinuation of CFZ, once the adverse event has been detected. This case report underlines the fact that this is true for pulmonary toxicity as well.

Conclusion

We report a case of fatal pulmonary toxicity in association with the administration CFZ. When pulmonary toxicity is detected, CFZ should be discontinued. Although patients might fully recover from a first episode, re-initiation of CFZ is not recommended.

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none

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