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PONATINIB-INDUCED PNEUMONITIS WITH SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME

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ABSTRACT

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) that can effectively treat patients with acute lymphoblastic leukaemia (ALL), particularly those with Philadelphia chromosome-positive (Ph+ALL) subtype, who are resistant or have previously received other TKIs.

We report a case of a 42-year-old female with Ph+ALL who was admitted to the intensive care unit with respiratory failure and severe acute respiratory distress syndrome (ARDS), while on treatment with ponatinib. Despite being treated with multiple antibiotics and antivirals, the patient's condition continued to worsen, and pulmonary complications secondary to TKI were suspected. After starting a steroid regimen, the patient's condition improved drastically with resolution of the pulmonary complications.

While many adverse events (AEs) happen in the beginning stages of TKI treatment, certain toxicities may not arise until months after therapy initiation. Cardiovascular complications are the most common AE of ponatinib, including heart failure and arterial hypertension. Pulmonary complications may occur, and management includes drug cessation and individualised steroid therapy.

In case of respiratory failure without signs of infection and no improvement with antimicrobial treatment, clinicians should consider the possibility of pulmonary toxicity associated with ponatinib.

KEYWORDS

Ponatinib, acute lymphoblastic leukaemia, Philadelphia chromosome-positive, ARDS, pneumonitis

LEARNING POINTS

- Although rarely reported, ponatinib may have pulmonary toxicity presenting as new onset of respiratory insufficiency.
- Management of pulmonary complications includes adjusting or discontinuation of ponatinib and simultaneous treatment with steroids.

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INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the second most common acute leukaemia in adults consisting of chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells in the bone-marrow, blood and extramedullary sites[1]. Philadelphia chromosome-positive ALL (Ph+ALL) is a subtype of ALL which has a worse prognosis, with 5-year survival of 5–20% and an allogeneic stem cell transplantation is the only chance for a cure[1]. Tyrosine kinase inhibitors (TKIs) play a crucial role in the treatment of Ph+ALL by blocking the mutated BCR-ABL1 domain[1].

Ponatinib is a potent oral third-generation TKI that inhibits most BCR-ABL mutation domains, including the gatekeeper mutation T315I, and it is currently indicated for the treatment of resistant or intolerant chronic myeloid leukaemia (CML) and Ph+ALL[2]. Cardiovascular complications are an important issue for patients treated with this drug; however, fewer data exist regarding other complications, particularly respiratory manifestations[3].

We present a report regarding a Ph+ALL patient treated with ponatinib who presented in the intensive care unit (ICU) with respiratory failure and severe acute respiratory distress syndrome (ARDS).

CASE DESCRIPTION

A 42-year-old female patient with Ph+ALL was admitted in the ICU due to respiratory distress and need of non-invasive ventilation (NIV). She was initially diagnosed in March 2021 and started treatment with hyper-CVAD and dasatinib protocol with clinical response after the first cycle. In the beginning of November 2021, she was hospitalised to undergo the eighth cycle; however, a relapse was documented. She started second-line treatment with CALGB 10403 protocol with a 28th-day induction treatment in association with ponatinib 45 mg, reduced to 30 mg due to arterial hypertension.

She had two prior admissions in the ICU, one in May 2021 due to citomegalovirus (CMV) pneumonia and one in August 2021 due to septic shock with *Pseudomonas aeruginosa* bacteraemia. In December 2021 she was admitted to the Neutropenic Unit with fever and respiratory distress; ponatinib was suspended at admission. CMV testing and blood cultures were performed and piperacillin-tazobactam was started. The next day, due to respiratory aggravation and increased need for oxygen, amikacin, linezolid, cotrimoxazole and valganciclovir were introduced. On the third day of hospitalisation, she was admitted to the ICU and started non-invasive ventilation with continuous positive airway pressure. Chest radiography showed bilateral infiltrate in both lungs; analytically: pancytopenia with leukopenia (2100/µl with 1800/µl neutrophils), Hg 8.4 g/dl, platelets 44 000/µl, C-reactive protein 312 mg/dl, and procalcitonin was 0.21 ng/ml. No renal or hepatic dysfunction was present.

On the third day after ICU admission there was progression to respiratory failure and hypoxemia needing intubation and invasive ventilation, with the implementation of a sedoanalgesia regimen with propofol and fentanyl. Further testing with microbiology of tracheal aspirate and molecular biology study of respiratory virus, for *Pneumocystis jiroveci*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were requested. Development of severe ARDS was noted and after persistent hypoxemia and a PaO_2/FiO_2 ratio <150 she underwent a prone position with no clinical improvement. Mechanical ventilation was optimised using neuromuscular blockade boluses with rocuronium to ensure plateau pressure <30 cm H_20. Despite that, on the fifth day after admission, she maintained a P/F ratio <100 with FiO_2 1.0 and PEEP 12 cmH_20, sustained respiratory acidosis (pH 7.3, pCO_2 52 mmHg) without improvement with a prone position, for which she was referred to extracorporeal membrane oxygenation (ECMO) centre for venous-venous ECMO; however, admission was denied after multidisciplinary discussion. Given the severity of the disease, piperacillin/tazobactam was switched to meropenem, maintaining the remaining antibiotic therapy, and a negative balance strategy was adopted. On the seventh day after admission, a thoracic and abdominal computerised tomography (CT) scan was performed after no respiratory improvement and evidence of abdominal distension with absence of gastrointestinal transit. It showed a ground-glass consolidation involving both lungs diffusely *(Fig. 1)*, a pericardial effusion and an increase in the calibre of the ileum, transverse and ascending, leading to toxic megacolon suspicion.

An echocardiogram confirmed a moderate pericardial effusion, with partial collapse of the right ventricular free wall without tamponade physiology and good biventricular function. The patient underwent emergency surgery with decompressive cecostomy, without major complications. All microbiologic examinations and molecular biology studies were negative, including influenza virus, SARS-CoV-2, CMV and *P. Jirovecii*. On the ninth day of admission, despite 10 days of broad-spectrum antibiotic and antiviral therapy, there was no significant recovery regarding the hypoxemia despite all

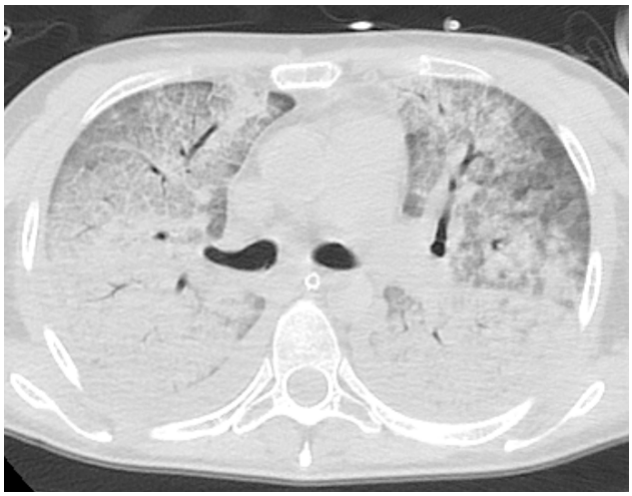

Figure 1. Pulmonary CT performed on the seventh day after ICU admission – ground-glass consolidation evolving in both lungs diffusely throughout its extension, reflecting diffuse alveolar injury.

measures previously mentioned. After carefully reviewing literature, pulmonary complications secondary to TKI were suspected and methylprednisolone was started, initially with a 24-hour regime of 120 mg every 6 hours, followed by three days of 40 mg every 6 hours. Marked improvement clinically was noted with significant decrease in oxygen requirements, from FiO_2 100% to 25% within 3 days with sustained PaO_2/FiO_2 ratios >200 and radiographic clearing of the bilateral infiltrate *(Fig. 2)*. Methylprednisolone doses were gradually reduced every 3 days and then switched to dexamethasone 8 mg per day. Weaning from sedoanalgesia was possible but due to an ineffective cough and ventilator weaning failure, a percutaneous tracheostomy was performed. After that, progressive mechanical ventilation weaning was possible and the patient was transferred to the Neutropenic Unit after 32 days of ICU admission without need of oxygen.

Unfortunately, the patient presented progression of the disease and, due to her fragile state, treatment for Ph+ALL was not continued, and she was referred to palliative care; she passed away after 69 days of hospitalisation.

DISCUSSION

Several TKIs have been previously approved for the treatment of CML and Ph+ALL such as imatinib, nilotinib and dasatinib[1]. Resistance is a major reason for therapy failure, with primary or secondary resistances ranging from

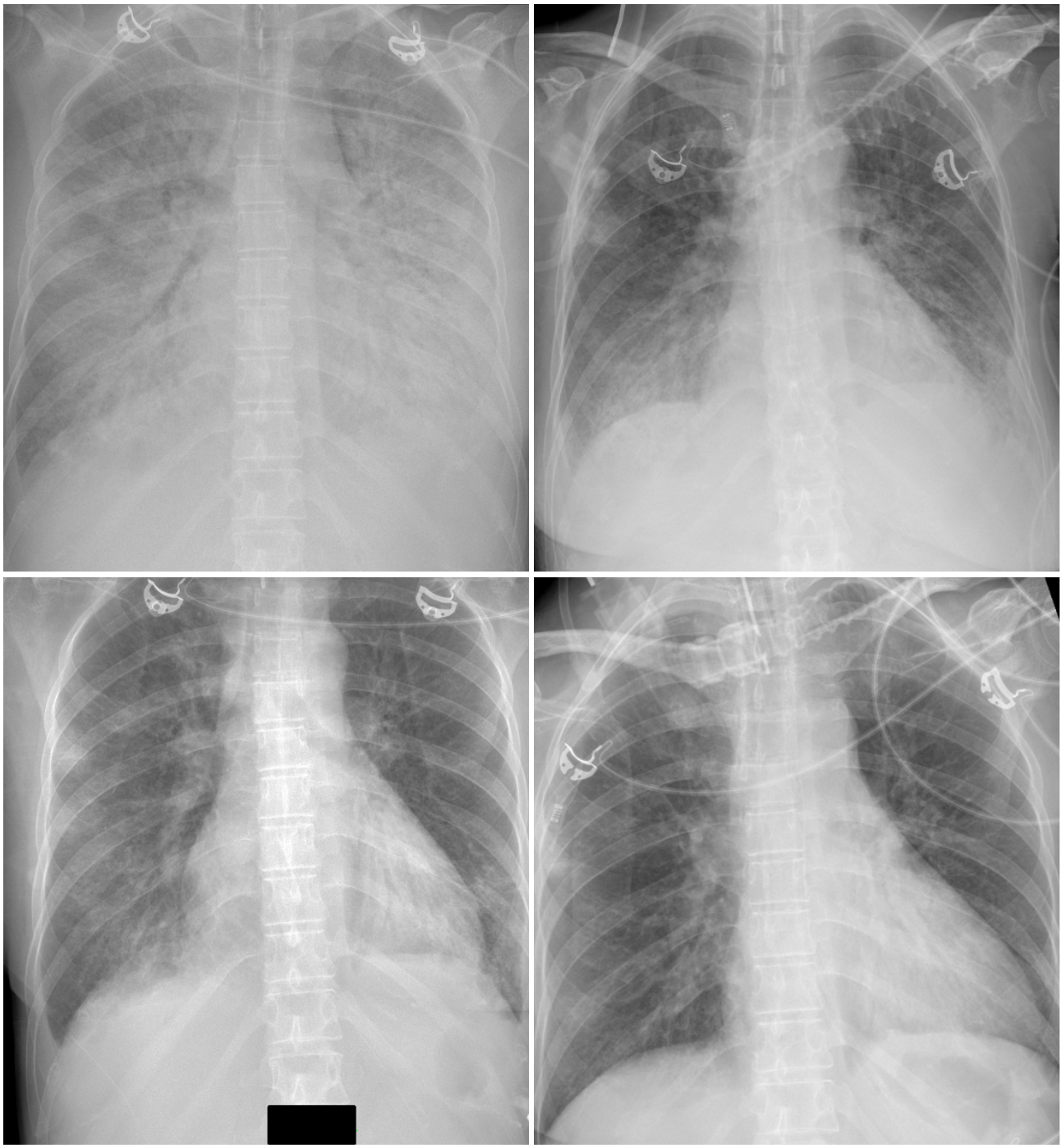

Figure 2. Sequential chest radiography showing marked improvement of the bilateral infiltrates, after starting methylprednisolone – day 0, day 3 (up), day 5, day 8 (down).

20–30%[4]. One of the most common mutations occurs in the BCR-ABL kinase domain at the gatekeeper T315I substitution, which results in resistance to the previously mentioned TKIs[2]. Ponatinib is a third-generation TKI with a potent activity against native and all tested mutant forms of BCR-ABL, including T315I, thus being indicated in the treatment of patients with CML and Ph+ALL who previously received other TKIs, with the ability to generate a cytogenetic response in 45% of Ph+ALL patients after dasatinib failure[5]. Although most adverse events (AEs) occur early during treatment with TKIs, the onset of some toxicities, including clinically significant ones, may be delayed for months after the start of therapy, ranging from chronic problems to potentially life-threatening situations[3].

Among the TKIs, dasatinib has the highest incidence of pulmonary toxicities, including pulmonary hypertension, pleural effusions and clinically significant pneumonitis[3]. Both hypersensitivity pneumonitis and interstitial pneumonitis have been described in a considerable variation in time to onset, ranging from a median of 49 days with imatinib and 229 days with dasatinib[7]. Findings on high-resolution CT include ground-glass opacities, septal thickening, unilateral or bilateral pleural effusions, and alveolar condensation[7]. It is hard to determine risk factors for pulmonary toxicities since its occurrence is infrequent and fewer data exist regarding ponatinib[6]. A case of interstitial pneumonitis was described during a phase-one clinical trial and more recently there was a publication regarding a ponatinib-induced pneumonitis[8]. Bronchoalveolar lavage plays an important role in excluding alternative diagnoses; however, severe respiratory failure and refractory hypoxemia contraindicate the performance of this examination, so serial imaging may aid monitoring for resolution[3]. Management of pulmonary complications during TKI therapy is based on case reports and includes discontinuation and concomitant treatment with steroids, with dose and duration of therapy individualised[6,9]. The onset of symptoms a month after starting ponatinib with the absence of clear signs of infection, and the patient's marked improvement after starting corticosteroid therapy, makes ponatinib-induced pneumonitis with severe ARDS a highly likely diagnosis.

Cardiovascular AEs are a particular concern in patients taking ponatinib, particularly heart failure, with an occurrence rate between 1% and 8%[4,5]. Other cardiovascular complications include arterial hypertension, coronary events, cerebrovascular events, peripheral vascular events and significant pericardial effusion, with a cumulative rate of 26%, 10%, 7%, 7% and 1% respectively, at 28 months[4,5].

CONCLUSION

Ponatinib is a third-generation TKI indicated for resistant Ph+ALL. Clinicians must be aware of all potential side effects, particularly cardiovascular ones. Pulmonary toxicity should be suspected in the onset of respiratory insufficiency that is not associated with infection and does not improve with antimicrobial therapy.

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