Vinorelbine-induced acute respiratory distress syndrome treated with non-invasive ventilation and immunosuppressive therapy

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Abstract
Severe drug-induced lung disease, resistant to steroids, is a dramatic situation due to the absence of therapeutic alternatives. We describe a case of vinorelbine-induced acute respiratory distress syndrome that did not respond to supportive care plus high-dose steroids. Cyclophosphamide pulse therapy was initiated with subsequent clinical and radiological improvement, allowing the patient to be discharged. We suggest that vinorelbine-induced lung toxicity is driven by a primarily immune-mediated mechanism and that it can respond favourably to immunosuppressive therapy.

Introduction
Vinca alkaloids are complex compounds with anti-neoplastic action derived from cellular mitosis blockade [1]. Vinorelbine (VNR) belongs to this family of drugs and has demonstrated activity in metastatic breast carcinoma [1]. It is usually well tolerated, but pulmonary toxicity, although rare, can be severe [2].

Case Report
We present a 62-year-old female with no significant past medical history until 1992, when she was diagnosed with breast cancer. She was initially treated with surgery plus adjuvant chemo and radiation therapy. Contralateral disease was detected in 2010 with progressive node and pulmonary involvement. The patient proved intolerant to second-line chemotherapy (carboplatin plus paclitaxel) and was started on VNR in August 2014. The first cycle was uneventful, and a second course of treatment was administered in September. Four days later, she began complaining of exercise intolerance and lack of strength in the lower limbs, followed by dyspnoea, and was seen at our emergency department 11 days after the second cycle. She was afebrile and reported no sputum production. Blood gas analysis showed severe hypoxemia (PO₂/FiO₂ ratio ~100) with concomitant respiratory acidosis. A contrast-enhanced chest computed tomography (CT) revealed diffuse ground-glass opacities in both lung fields, with no images suggesting pneumonia or any change in the previously known lung metastasis. Two sets of blood cultures were taken, and she was started on ceftriaxone plus azithromycin. Urinary antigens for Streptococcus pneumoniae and Legionella were negative, as was a nasopharyngeal swab for the influenza virus. On the next day, she presented severe respiratory distress despite administration of high-flow oxygen. Echocardiographic assessment of left ventricular function revealed no abnormalities. Because she maintained a good functional status, she was admitted for a trial of non-invasive bi-level ventilation (NIV), with a positive inspiratory pressure of 18 cm H₂O and expiratory pressure of 10 cm H₂O. She required FiO₂ between 0.7 and 1 to achieve saturations of 89–91%. VNR toxicity was considered, and steroid therapy (prednisolone 1 mg/kg/day) was added. Due to persistent respiratory failure, antibiotic therapy was empirically changed to ceftriaxone plus azithromycin. Urinary antigens for Streptococcus pneumoniae and Legionella were negative, as was a nasopharyngeal swab for the influenza virus.
due to poor risk:benefit ratio. A second chest CT on the 10th day after hospital admission revealed persistent ground-glass opacities. Steroid therapy was intensified to methylprednisolone 1 g/day for three consecutive days. Yet there was no consistent improvement, and she remained fully dependent on NIV. A new chest CT on the 22nd day of hospitalization revealed no significant change in ground-glass opacities (Fig. 1). In this setting, considering the absence of additional organ dysfunction or infection, we decided to start cyclophosphamide (CYC). She received a first dose of 1 g on the 24th day. Progressive improvement was noted, with decreasing respiratory rate and improving gas exchange (PO2/FiO2 ~150). Weaning from NIV was started five days after CYC. Chest CT scanning after 13 days showed improvement of the ground-glass infiltrates (Fig. 2), and 14 days after CYC, she was breathing independently, requiring only oxygen by face mask. She was transferred to the ward 44 days after being admitted to the intermediate care unit with improving respiratory function. A second dose of CYC was administered one week later, and she was discharged home eight days after that with a fraction of inspired oxygen of 31% (PO2/FiO2 ~ 230). Her chest X-ray, on discharge, was clearer. One month later, she was seen in the outpatient clinic and remained well. In early January, 2015, she was admitted with a respiratory infection and aggravated hypoxemia, with no signs of pneumonia in the chest X-ray. Although responding initially to antibiotics, she developed a respiratory nosocomial infection and died after 19 days of inpatient hospital care.

**Discussion**

This case illustrates a severe side effect of VNR that is still poorly understood. Most toxic lung effects of antineoplastic agents result from direct cytotoxic injury caused by the drug and/or products of its metabolism, or bioactivation (oxidant-mediated injury) [3]. A hypersensitivity-like reaction with a drug-specific antibody or T-cell response can also lead to lung injury by a primarily immune-mediated mechanism [3].

VNR-related respiratory toxicity is most often reported when combined with other agents, most notably mitomycin [4]. Two types of respiratory side effects have been reported: an acute reaction with bronchospasm, fever, hypotension, and alveolar infiltrates, which occurs within minutes of drug administration, and a subacute form, occurring hours to days after therapy, with progressive dyspnoea, diffuse interstitial infiltrates, and in some cases acute respiratory distress syndrome (ARDS) [2,5].

We believe VNR-induced toxicity to be the cause of ARDS in our patient given the temporal association, the apparent stability of the neoplastic disease, and the absence of other causes of ARDS, namely, documented infection. The fact that there was no improvement with broad-spectrum antibiotics and no exacerbation after aggressive immunosuppressive therapy argues against an infectious aetiology.

The treatment of antineoplastic agent-induced pulmonary injury is empirical and includes drug discontinuation, glucocorticoid therapy, and supportive care. There are reports of good corticoid response and complete recovery in VNR-related lung injury [4,6,7]. In our patient, the complete lack of improvement after steroid therapy led us to consider the possibility of a rescue immunosuppressive therapy using CYC.

CYC is a powerful immunosuppressive drug that is a therapeutic option in severe interstitial lung diseases (ILD), usually in combination with corticosteroids. However, its usefulness is controversial, with limited evidence of benefit. Systemic sclerosis-associated ILD, idiopathic pulmonary fibrosis exacerbations, and idiopathic inflammatory myopathy-associated ILD are examples where a potential efficacy of CYC was suggested, in terms of
lung function, progression of the disease, and even survival [8–10].

Severe refractory antineoplastic agent-induced pneumonitis generally has a poor prognosis. There are currently no treatment recommendations besides continued steroid therapy. In a literature search for the use of other immunosuppressive agents as salvage therapy, we found one case of carmustine-induced pneumonitis, resistant to steroids, successfully treated with cyclosporine A and one case of steroid-resistant methotrexate pneumonitis, in a rheumatoid arthritis patient, who recovered rapidly after intravenous CYC pulse therapy [11,12]. A T-cell lymphocytic alveolitis is reported in lung toxicity cases of both of these drugs, suggesting an immune-mediated reaction in the pathogenesis of the disease and constituting the rationale for use of additional immunosuppressive therapy [11,13]. A lymphocytic dominance, in bronchoalveolar lavage and biopsy, is reported in pulmonary toxicity associated with VNR-based chemotherapy [14].

In conclusion, the recognition of this severe side effect can have significant therapeutic implications. Although the outcome was ultimately fatal, we saw clear improvement in lung function after immunosuppressive therapy that allowed weaning from mechanical ventilation and hospital discharge.

Disclosure Statement

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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