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Helmet Continuous Positive Airways Pressure (CPAP) treatment in a Non-Small Cell Lung Cancer (NSCLC) patient with severe hypoxemic respiratory failure due to gemcitabine therapy

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Summary. Gemcitabine is a pyrimidine analogue used worldwide for many solid tumours such as pancreatic cancer, ovarian cancer, non small cell lung cancer (NSCLC) and breast cancer. In this case report, we describe a patient who was treated with gemcitabine for NSCLC (poor differentiated squamous cell carcinoma) and who subsequently developed a severe respiratory failure with a radiological pattern of interstitial pneumoniae. Discontinuation of the drug, administration of corticosteroids and respiratory support are the mainstays of the treatment. Helmet Continuous Positive Airways Pressure (CPAP) allowed a prolonged, comfortable and safe treatment of the patient until the resolution of the acute respiratory failure. We think that helmet-CPAP could be a useful tool, even outside of intensive care unit, for the treatment of patients with severe interstitial pneumoniae due to gemcitabine therapy.

Key words: gemcitabine toxicity, helmet cpap, respiratory failure

Introduction

Gemcitabine (2',2'-difluorodeoxycytidine,dFdC; Gemzar®) is a pyrimidine analogue used worldwide for many solid tumours such as pancreatic cancer, ovarian cancer, non small cell lung cancer (NSCLC) and breast cancer (1). The treatment is generally well tolerated with myelosuppression being the most common dose-limiting side effect. Up to 25% of treated patients exhibit dyspnoea. Severe pulmonary toxicity is rare but is quick in onset and rapidly fatal with a mortality rate of 20% (2). Discontinuation of the drug, administration of corticosteroids and respiratory support are the mainstays of such treatment. In this report, we describe a case of a NSCLC patient with gemcitabine-induced lung toxicity and severe hypoxemic respiratory failure treated with a Helmet Continuous Positive Airways Pressure (CPAP).

Case report

An 82-year-old woman with NSCLC (stage cT3N2M0) was admitted to our hospital with severe shortness of breath. She smoked 60 packs/year until five months before the admission, when she presented with fever, haemoptysis and cough. In addition to baseline emphysematous changes, a thoracic CT scan demonstrated a pulmonary mass of 7 cm in diameter in the upper left lobe adhering to the pleura with enlarged mediastinal lymph nodes. A histological examination of the lesion revealed a poor differentiated squamous cell carcinoma.

The patient was considered inoperable and was started on Gemcitabine 1000 mg/m^2 (1500 mg) on days 1, 8 and 15 every four weeks. After her third cycle, she had progressive shortness of breath and became dyspnoeic at rest; grade 4 based on NCI Common

Terminology Criteria for Adverse Events (CTCAE) (3). Upon admission to the hospital she was afebrile. On physical exam, she had diffuse bilateral crackles involving both lower lung fields, with a pulse rate of 130/minute, respiratory rate of 26/minute with oxygen saturation of 80% on room air (improved to 91% with 4 L/min of oxygen by face mask) and a blood pressure of 135/70 mmHg. Laboratory studies revealed a Reactive C Protein (RCP) elevation (223 mg/l), normal liver enzymes (Aspartate Aminotransferase, Bilirubin, Alkaline Phosphatase), renal function and CBC (WBC 8,020 10^3/l, Haematocrit 27,8%, Platelet 191,000 10^3/l). Radiography of the patient's chest showed diffuse bilateral interstitial pulmonary opacities and the upper left lobe mass (Figure 1). Electrocardiogram (ECG) revealed new onset Atrial Fibrillation (AF) with a ventricular rate of 130 bpm.

The patient's initial differential diagnosis included a drug-induced process, possible infection, cardiogenic pulmonary oedema and pulmonary embolism. The patient was ruled out for pulmonary embolism based on a negative Pulmonary Scintigraphy; a Doppler Ultrasound of the legs that did not demonstrate deep venous thrombosis. She was treated with antibiotics (ampicillin/sulbactam plus levofloxacin), diuretics (furosemide), systemic steroids (prednisone 80 mg daily), carvedilol and Low Molecular Weight Heparin (enoxaparin). On the second day of hospitalisation, her respiratory conditions deteriorated and the Arterial Blood Gas (ABGs) displayed a severe respiratory failure; PH 7,52, PCO_2 32 mmHg, PO_2 48 mmHg (FiO_2 0,45; P/F ratio 96). A second radiography of the chest revealed a worsening of the interstitial pulmonary opacities (Figure 2).

On the basis of the overall clinical condition, along with the intensivist we decided not to refer the patient for an invasive respiratory treatment. For this reason and due to the need of continuous respiratory support, we applied the Helmet CPAP (pressure 7,5 cm H20, FiO_2 35%). This system consists of a transparent hood that is able to hold the entire head of the patient. The hood is joined by means of a rigid ring to a Latex-free collar that provides a soft seal around the patient's neck. There are no pressure points on the face, avoiding skin necrosis and pain and improving patients' tolerance. After the first hours of treatment, the respiratory rate, the heart rate, the arterial pressure and ABGs improved. Bronchoscopy with Bronco Alveolar Lavage (BAL) showed a cytological prevalence of pulmonary macrophage. Blood cultures were negative for aerobic and anaerobic bacteria. Serology and nasal swabs for bacterial and respiratory viruses (Pneumocystis jiroveci, Legionella, adenovirus, influenza, parainfluenza, and respiratory syncytial virus, CMV) failed to identify an infectious aetiology for the pulmonary condition.

On the basis of these results, the diagnosis was believed to be drug induced interstitial pneumonitis due to gemcitabine. By hospital day 11, the patient progressively alternated between Helmet CPAP with

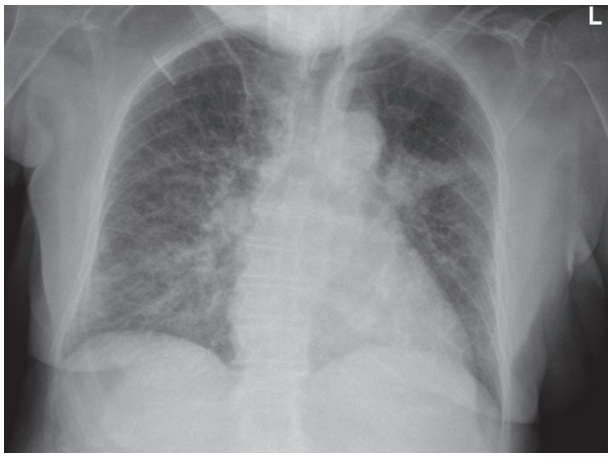

Figure 1.

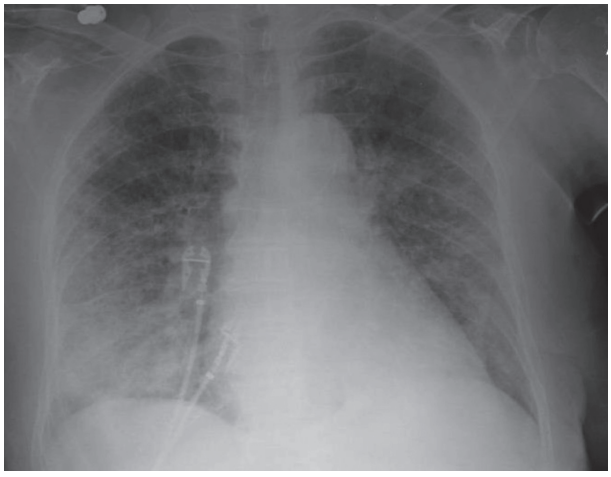

Figure 2.

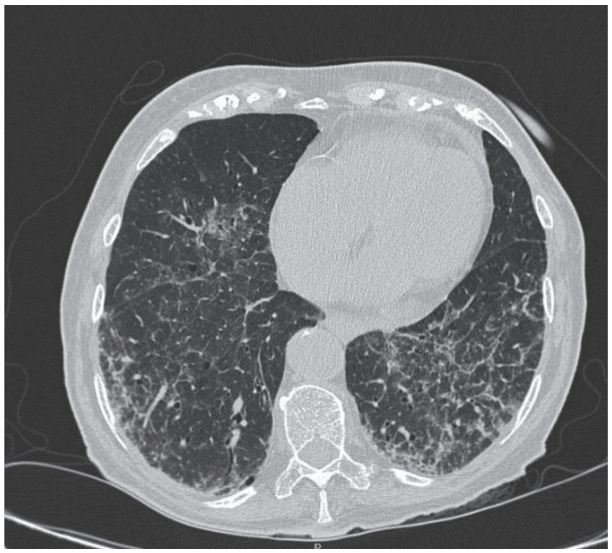

Figure 3.

Oxygen Mask (OM) and by day 15 was able to wean off the Helmet CPAP and use OM only. A thoracic CT displayed an interstitial thickening with ground-glass opacity principally at the pulmonary bases interspersed between changes of emphysema (Figure 3).

Interestingly, a sharp increase in platelets value (PLT) with a nadir in day nine (1.494.000 10^3/l) and with a progressive reduction until normalisation in day 20 (470.000 10^3/l) was observed, along with improved respiratory conditions. Steroid therapy was gradually reduced as the patient's clinical symptoms and the radiological findings improved. Patient was discharged at home without oxygen and with low dose of prednisone (16 mg/die). One month later, a follow-up computed tomography scan of the chest showed complete resolution of pneumonitis.

Discussion

Gemcitabine is a deoxycytidine analogue effective in the treatment of pancreatic, bladder, ovarian, NSCL and breast cancer. It is transported into the cells by membrane nucleoside transporters and inside the cytoplasm is transformed in its active forms diphosphate (dFdCDP) and triphosphate (dFdCTP), which inhibit Ribonucleotide Reductase (RR) and the DNA synthesis (4, 5). Gemcitabine is administered as a single agent or in combination with other anti-neoplastic drugs. It is known that concurrent radiotherapy or anti-neoplastic drugs determine an excessive pulmonary toxicity (6, 7). Data from 4,448 patients treated with gemcitabine reported an incidence of 0.45% for dyspnoea and 0.27% for severe pulmonary toxicity (8).

Among the case reports published on the subject of gemcitabine-induced pneumonitis, three types of pneumonitis have been described; capillary leak syndrome, diffuse alveolar damage, and alveolar haemorrhage (9). Symptoms occur over days or even weeks, but rarely can appear after a prolonged course of gemcitabine use (10). The onset of severe gemcitabine pulmonary toxicity tends to be quick in nature and rapidly fatal, with a mortality rate of 20%. Clinical presentation includes intense dyspnoea, fatigue, fever, dry cough, tachycardia, signs of hypoxemic respiratory failure and pulmonary bilateral basal crackles. Chest X-Ray often shows reticulonodular interstitial infiltrates and CT scan shows ground glass opacities, thick septal lines, reticular opacities, and pleural effusions are the most frequent manifestations. Systemic steroid and respiratory support represent the main therapy (11).

In this case report, we describe a patient who was treated with gemcitabine for NSCLC and who subsequently developed a severe respiratory failure with a radiological pattern of interstitial pneumoniae. On the second day of admission, the patient became severely dyspnoeic and required high-flow oxygen in facial mask to obtain an oxygen saturation of only 82%. Together with the intensivist and considering the patient clinical condition, we decided to apply the helmet-CPAP. This treatment allows a better pulmonary gas exchange recruiting poor ventilated lung areas and improves the arterial oxygenation. Differently from CPAP facial masks, helmet-CPAP can be used continuously for many days without skin damage because there are no pressure points on the face (12). By day 15, the patient was able to wean off the helmet-CPAP and use only OM. Helmet-CPAP enabled us to overcome the acute phase avoiding the orotracheal intubation and the complication related to the invasive mechanical ventilation. We think that helmet-CPAP could be a useful tool, even outside of intensive care unit, for the treatment of patients with severe interstitial pneumoniae due to gemcitabine therapy.

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