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CASE REPORT

Fatal pneumonitis after treatment with docetaxel and trastuzumab

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ABSTRACT

Pneumonitis is a rare but serious complication of docetaxel treatment. We report a 63-year-old woman with locally advanced breast cancer who was treated with docetaxel and trastuzumab. After the first course she was admitted with febrile neutropenia that resolved rapidly. After the second course she was admitted again with fever and dyspnoea. Despite intensive treatment she died of respiratory failure three weeks later. Autopsy showed diffuse interstitial inflammation of both lungs consistent with drug-induced inflammation. Docetaxel treatment was the most likely cause. It is important to be aware of this toxicity, because the subtle warning signs can easily be mistaken for an opportunistic infection, and, if not recognised in time, the mortality rate is high.

KEYWORDS

Docetaxel, pneumonitis, pulmonary toxicity.

INTRODUCTION

Docetaxel is a chemotherapeutic agent that is increasingly used in the treatment of multiple types of cancer. Currently it is registered for breast cancer, non-small-cell lung cancer, head and neck cancer, gastric/lower oesophageal cancer and prostate cancer. The main side effects of docetaxel are neutropenia, hypersensitivity reaction, stomatitis, peripheral neuropathy and fluid retention. Pneumonitis is a rare side effect, but awareness of this toxicity is important, since the mortality rate is high. Because of expanding indications for docetaxel treatment, we expect an increase in the incidence of pneumonitis.

Trastuzumab is used in adjuvant and palliative treatment of breast cancer and has also been associated with interstitial pneumonitis, but in even fewer patients and less convincingly, despite large-scale use.

CASE REPORT

A 63-year-old female patient was diagnosed with inflammatory breast cancer of the right breast with extensive axillary and supraclavicular lymph node involvement, staged cT4N3M0. Her2/neu was overexpressed in the primary tumour. Oestrogen and progesterone receptors were negative. Neoadjuvant treatment with docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg) once every three weeks was started. One week after the first course, she presented at the emergency department with fever (39.4°C), chills and minimal dyspnoea. Physical examination was otherwise unremarkable. A chest X-ray was normal. Laboratory examination showed transient leucocytopenia (1.1 x 10^9/l). She received intravenous ceftazidime and recovered rapidly. Blood and urine cultures remained negative. After five days she was discharged from the hospital.

During the second course, the patient received ciprofloxacin as antibiotic prophylaxis. On the sixth day she returned to the emergency room with fever, chills and dyspnoea. She had not experienced any chest pain, productive cough, dysuria or other localised symptoms in the previous days. Physical examination showed tachycardia and minimal basal lung crackles. A reduction in breast inflammation and in the size of loco regional lymph node involvement was noted. Her leucocyte count was 0.9 x 10^9/l and C-reactive protein (CRP) was 32 mg/l. Again, the chest X-ray showed no abnormalities. We suspected an upper respiratory tract infection and started broad-spectrum antibiotics. The fever and dyspnoea improved and the patient was discharged on the fourth day with oral antibiotics.

Four days later she was readmitted with fever (40.1°C), dyspnoea and a dry cough. Physical examination revealed fine crackles over both lungs, especially on the left side. A chest X-ray showed a consolidation in the lower lobe of the left lung. Leucocyte count was 6.1 x 10^9/l and CRP 51 mg/l. Amoxicillin/clavulanic acid and erythromycin were given, being the standard regimen in our institution for severe

community acquired pneumonia. Blood and urine cultures remained negative. The fever and dyspnoea persisted. Pulmonary embolism was excluded. Two days later she became tachypnoeic and oxygen saturation dropped to 65%. She was transferred to the intensive care unit and artificial ventilation was necessary. A thoracic computed tomography (CT) scan showed multiple consolidations in the peripheral parts of both lungs and ground glass aspect of lung lobuli indicating inflammation and/or oedema. A blood culture showed coagulase negative staphylococci and the antibiotic regimen was changed to vancomycin and ceftazidime. Broncho-alveolar lavage showed no microbiological pathogens in direct staining and cultures remained negative. Prednisone treatment was started, after which the fever disappeared, but her pulmonary situation worsened steadily. After nine days, adequate oxygenation became impossible. Treatment was stopped and the patient died instantly.

At autopsy heavy (2140 g), oedematous and firm lungs were found. Histological examination showed diffuse alveolar damage and interstitial inflammation of both lungs and pneumonic consolidations in the right lung. Small islands of invasive adenocarcinoma were demonstrated microscopically in the right breast and regional lymph nodes. Distant metastases were not found.

DISCUSSION

Pneumonitis is a rare side effect of docetaxel. In the past decade, several case reports and small case series of docetaxel-induced pneumonitis were reported. Almost 50% of reported patients died because of respiratory failure, usually after two to four courses of chemotherapy.[1-6] More recently, clinical trials have been published on the use of docetaxel in the treatment of non-small-cell lung cancer. Several studies showed patients developing grade 3-4 drug-induced pulmonary toxicity when using docetaxel in combination with different chemotherapy schedules or radiotherapy.[10-13] Pneumonitis rates as high as 7 to 10% occurred especially during or after concurrent radiotherapy.

The diagnosis of drug-induced pneumonitis may be obscured, as was probably the case in our patient, by the administration of high-dose dexamethasone (8 mg twice daily for three days) with each course of docetaxel. Corticosteroids in this dose range will suppress early signs of pneumonitis for several days. The subsequent appearance of fever and dyspnoea due to pneumonitis may coincide with the time period of neutropenia, leading to an erroneous diagnosis of neutropenic fever due to an opportunistic infection. The lack of objective thoracic X-ray abnormalities, as in this case, is not uncommon, both in early drug-induced pneumonitis and in neutropenic fever from pulmonary origin. Potential clues in this case were the repetition of fever, dry cough and dyspnoea after both the first and second course of treatment and the presence of fine crackles over both lungs, despite normal thoracic X-ray examination. An increased awareness of possible drug-induced pneumonitis, which is the purpose of this case report, should lead to early consultation with a pulmonologist and evaluation by (high-resolution) CT scan instead of relying on X-ray examination. When docetaxel-induced pneumonitis is part of the differential diagnosis, docetaxel treatment should only be continued after thorough pulmonological examination.

The mechanisms of drug-induced pneumonitis are not well-understood.[7] Various mechanisms have been proposed. One hypothesis is that docetaxel may cause proliferation of cytotoxic T cells directed against a specific pulmonary antigen co-expressed by the tumour,[2] thus leading to a hypersensitivity type of lung damage. Alternatively, docetaxel might cause direct pulmonary damage through reactive oxygen metabolites. Finally, a pharmacogenetic variant or a dosing error might have led to excessive docetaxel exposure in our patient, but the grades of haematological and non-haematological toxicities encountered in our patient being within the normal range argue against this.

Our patient developed symptoms of mild dyspnoea and fever after the first and second course of docetaxel and trastuzumab. Chest X-rays were initially normal. Blood and urine cultures remained negative. She was treated twice for febrile neutropenia, and exhibited a clinical course within the expected range. It is noteworthy, though, that the clinical presentation on the two occasions was very similar. The third admission, however, four

Figure 1. *Lung tissue with broad interalveolar septa and influx of neutrophilic granulcytes with haemorrhage*

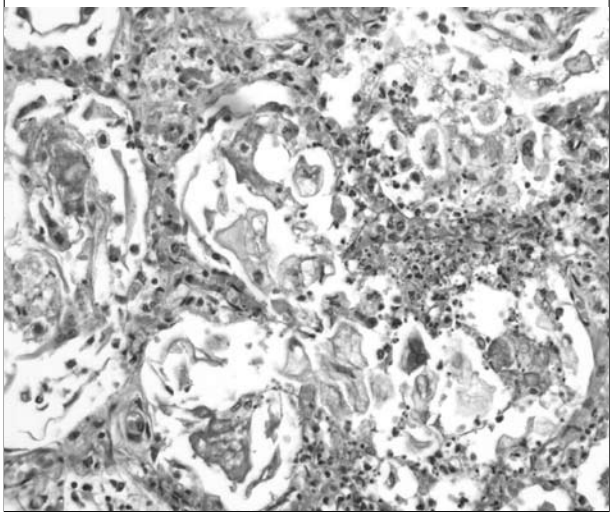
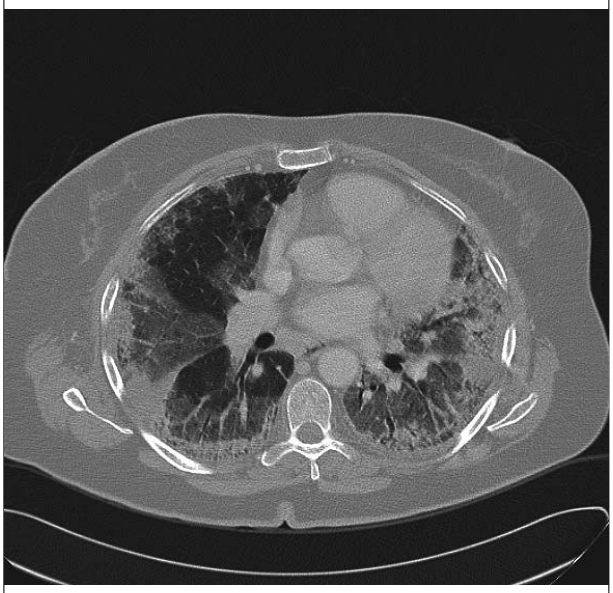


Figure 2. *CT scan showing bilateral airspace consolidations with ground-glass opacities in patchy distribution*



Small ill-defined centrilobular nodules. Predominance in middle and lower lung (205 x 205 mm).

days after the second discharge, should have provoked a wider differential diagnosis than non-neutropenic pneumonia. At that time, high-dose corticosteroids might have prevented the fatal outcome. In this case, prednisone was only started after negative bronchoalveolar lavage on the ICU. In retrospect, it is likely that the symptoms of dyspnoea and fever were, from the first episode, in fact signs of early interstitial pneumonitis. The clinical course and the findings at autopsy are entirely compatible with reported findings in patients with interstitial pneumonitis due to docetaxel.

Our patient was also treated with trastuzumab.[8,9] Trastuzumab-associated pneumonitis has been described, but data are far more sparse than for docetaxel. Just a few of the reported patients were treated with trastuzumab only. In contrast with docetaxel, trastuzumab-associated pneumonitis may develop many months after initiation of treatment and may run a more insidious course. In view of the extensive use of trastuzumab nowadays, trastuzumab-induced pneumonitis, if existent, seems rarer than docetaxel-induced pneumonitis. This leads us to conclude that the pneumonitis in our patient was due to docetaxel.

CONCLUSION

In summary, although pneumonitis is a rare side effect of docetaxel, it is an important to be aware of this specific toxicity, since the first manifestation may mimic an opportunistic pulmonary infection, but early recognition and appropriate treatment may be life saving. With the expanding indications of docetaxel, this side effect may be encountered more often in daily practice. Treatment consists of stopping docetaxel and starting corticosteroids.

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