

Pneumonitis Related to Docetaxel: Case Report and Review of the Literature

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Abstract. Taxotere has recently been making a noticeable impact on breast, gastric, ovarian, prostate and non-small cell lung cancers. Its side effects include dyspnea, pruritus, skin rashes, fever and hypotension. The patient presented the less common, however potentially fatal, toxicity of pneumonitis. He initially presented with a flu-like illness and hypoxia that was unresponsive to antibiotic treatment and actually progressed. He presented 14 days after his second dose of taxotere, although in retrospect noted symptoms several days prior. Although some patients described in the literature have progressed to respiratory failure requiring mechanical ventilation, this patient responded to steroid treatment and withdrawal of taxotere.

Case Presentation

A 71-year-old white male presented to the Emergency Department at Allen Memorial Hospital in Utah on 19th of June 2006 with dark colored stools, dizziness and diaphoresis. He was found to have hemoglobin of 8.2 g/dl and endoscopy revealed an active bleed from a mass at the distal esophageal junction. Biopsy was consistent with poorly differentiated invasive adenocarcinoma. Staging CT showed thickening of the gastro-esophageal junction and no evidence of metastatic disease. Following imaging, his cancer was determined to be stage IIA T3N0M0.

The patient worked as an innkeeper in New England for 16 years. He had a smoking history of one package of cigarettes

for 20 years, prior to quitting 30 years ago. He drinks socially and has a half a glass of wine daily with dinner.

In July 2006 he was initially started on neoadjuvant treatment with chemoradiation – with 5-FU and cisplatin. This treatment was completed in September 2006. Unfortunately his tumor was found unresectable secondary to scarring on exploratory laparotomy performed. His chemotherapeutic regimen was then switched to taxotere 75 mg per m² every 21 days. He received his first dose on 13th November 2006 and the second on 4th of December 2006.

The patient then presented to the clinic at Yale New Haven Hospital on the 18th of December 2006 with symptoms of congestion, chest tightness, shortness of breath and low grade fever. He noted respiratory symptoms beginning in early December 2006, with gradually worsening dry cough and shortness of breath with talking or exertion. He had a low grade fever of 99°F, HR 95/min, BP 94/54 mmHg and oxygen saturation of 91% in room air. He was taken to the emergency room for further evaluation. Chest X-Ray at that time revealed a new left retrocardiac opacity which was suggestive of atelectasis and/or consolidation. Blood counts were within normal limits at that time except for a mild anemia with hemoglobin of 10.8 g/dl. The performed CT angiogram of the chest excluded pulmonary embolus but found bilateral upper lobe ground glass opacities. He was admitted and treated for presumed pneumonia with ten days of moxifloxacin. However, his symptoms continued and he was re-admitted to the hospital on 2nd January 2007. A chest CT was performed which showed interstitial lung disease most suggestive of nonspecific interstitial pneumonia (NSIP) (Figures 1, 2). The patient was again treated with moxifloxacin for ten days. However, concern was raised for chemotherapy-related pneumonitis, specifically due to taxotere, so the drug was discontinued and the patient was seen by a pulmonologist. Pulmonary function technicians were unable to perform pulmonary function tests due to the patient's vigorous cough. Arterial blood gases at that time revealed a pH of 7.46, PCO₂ of 35 mmHg, HCO₃ of

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Figure 1. Axial CT scan through the upper chest, viewed at lung windows (L:500, W:4000). There is fibrosis in the periphery of the left upper lobe as evidenced by thickening of the intralobular septations (black arrows) and traction bronchiolectasis (white arrows).

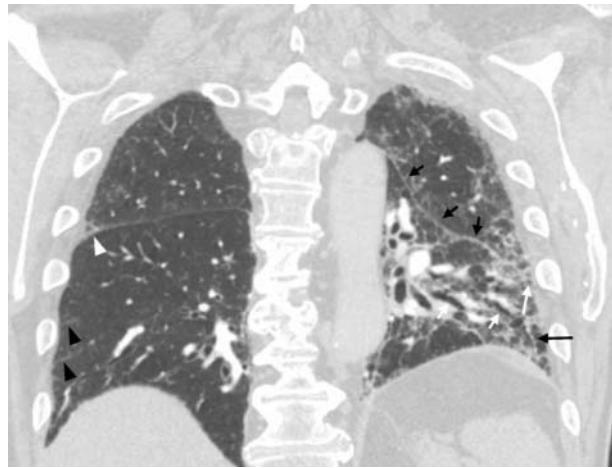


Figure 2. Coronal maximal intensity projection of the chest viewed at lung windows (L:500, W:4000). There is also lower lobe peripheral fibrosis with thickening of the interlobular septations (black arrow), traction bronchiolectasis (white arrow head), and thickening of the left major fissure (black arrow head). This distribution of peripheral fibrosis is suggestive of non-specific interstitial pneumonitis (NSIP), which can be seen secondary to chemotherapy. Note that there may also be early NSIP changes in the right lung.

24 mmols/L, PaO₂ of 74 mmHg and oxygen saturation of 95%, indicating a mild respiratory alkalosis without compensation and a slight reduction in PO₂ with an A-a gradient of 33 mm Hg (normal 10-12 mm Hg). He was felt to most likely have a combination of radiation pneumonitis and chemotherapy toxicity rather than infection. Open lung biopsy was offered, but given the patient's age, history of cardiovascular disease and high likelihood that the presentation was due to non-infectious etiology, the patient opted for a more conservative approach. He was started on 60 mg of prednisone daily. At his follow-up visit approximately two weeks later, he noted improvement in his dry cough (grade 1 from grade 2, according to Common Toxicity Criteria Adverse Events 3.0 scale) and his dyspnea reduced to grade 1 from grade 3 according to CTCAE 3.0. Pulmonary function test performed at this time revealed a moderately severe restrictive ventilatory defect with a moderate reduced diffusing capacity for carbon monoxide (DLCO) of 65%.

Given the marked improvement on prednisone therapy as well as the rapid onset of the respiratory symptoms and no evidence of metastatic pulmonary disease, it was felt that the patient had chemotherapy induced lung injury – secondary to taxotere. He was treated with a prednisone taper, to which he responded well.

Discussion

Docetaxel is a taxoid derived semisynthetically from the European yew *Taxus baccata*. It stabilizes microtubules against depolymerization and thereby blocks cells in metaphase of the cell cycle (1). It has shown utility in gastric, breast, ovarian and non-small cell lung cancer. However,

docetaxel, as well as fellow class-member paclitaxel, carry toxicities (2). The most common side-effects are hypersensitivity reactions related to the vector of delivery. In early trials, of paclitaxel and docetaxel 30-40% of patients experienced type I hypersensitivity reactions. An activation of the complement or direct activation of mast cells/basophils by paclitaxel or its cremophor has been proposed (3). Docetaxel is formulated in a non-ionic surfactant polysorbate 80, the presence of which has been implicated in acute hypersensitivity reactions. As a consequence, a cremophor-free formulation of paclitaxel in which nanoparticles are conjugated to albumin molecules has been developed. Unfortunately, no polysorbate-free formulation of docetaxel is near completion (4). An additional side-effect unique to docetaxel is fluid retention and pleural effusion secondary to capillary leak syndrome (5).

Paclitaxel is associated with pulmonary toxicity (6,7). Pulmonary infiltrates have been reported 48 hours after initiation of treatment. In most cases the symptoms and radiological findings resolved within 24-96 hours following initiation of steroid therapy. Unlike paclitaxel, dyspnea with docetaxel has been less well documented. Docetaxel-induced pneumonitis is characterized by a later onset of respiratory deterioration and a longer duration of symptoms. In some cases pulmonary toxicity has been fatal. An early case report by Read *et al.* reviewed four patients with interstitial pneumonitis related to docetaxel (8). All presented with acute dyspnea and fever 1-2 weeks after receiving the drug,

and all developed respiratory failure requiring mechanical ventilation. Broad-spectrum antibiotics and corticosteroids were ineffective. Another report by Mileshkin *et al.* discussed two patients with severe interstitial pneumonitis following high-dose cyclophosphamide, thiotepa, and docetaxel (9). High-dose methylprednisolone did bring about a dramatic response in those cases. Similarly, Merad *et al.* reported two patients with docetaxel-related pneumonitis who recovered after treatment with corticosteroids (10).

However, the mechanism of pneumonitis due to taxanes is unclear. A specific pulmonary antigen expressed by the tumor may cause the proliferation of cytotoxic T-cells (10). Additionally, reactive oxygen metabolites have been associated with direct lung injury. Although these metabolites form spontaneously, it is felt that docetaxel could increase their production (10). Moreover, the prolongation of docetaxel toxicity may indicate the immunomodulatory effects of taxanes, with the resulting pulmonary insult lasting the lifespan of the leukocytes (7).

More severe interstitial pneumonitis has been reported in patients treated with docetaxel and gemcitabine in combination (11) and also with concomitant thoracic radiation therapy (12). The high effectiveness and easiness of administration has made docetaxel a widely used chemotherapy agent. Although it is generally well tolerated, patients must be carefully monitored with chest X-rays, pulmonary function tests and CT scans when unexpected respiratory symptoms and pulmonary infiltrates appear. Discontinuation of the therapy, until diagnosis of the cause is available, is recommended. If infection and tumor spread in the lungs are excluded, an aggressive pulmonary support and use of corticosteroids must be attempted.

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