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Assessment of Docetaxel- and Paclitaxel-Related Diffuse Parenchymal Lung Disease: Two Case Reports

Dosetaksel ve Paklitakselin Neden Olduğu Diffüz Parankimal Akciğer Hastalığı: İki Olgu Sunumu

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Abstract

Previous studies have reported the development of hypersensitivity pneumonia, interstitial pneumonia and organized pneumonia, two parenchymal lung diseases that are clinically and radiologically interchangeable, secondary to docetaxel and paclitaxel (Taxane) use. Parenchymal lung diseases secondary to docetaxel treatment are rare, but may have serious and even fatal consequences, and any delay in diagnosis and treatment can result in a poor prognosis. Docetaxel treatment should be discontinued and corticosteroid therapy should be initiated as soon as lung involvement becomes a concern. We present here two different cases who developed diffuse parenchymal lung toxicity associated with Taxane use, considering the information in literature.

Keywords: *Docetaxel, paclitaxel, pulmonary toxicity, pneumonia.*

Öz

Dosetaksel ve paklitaksel (taksan grubu) kullanımına bağlı olarak literatürde, hipersensitivite pnömonisi, intersitisyel pnömoni ve organize pnömoni geliştiği bildirilmiştir. Bu grup hastalıklar diffüz parankimal akciğer hastalıkları içinde ele alınmakta olup bu hastalıklar arasında klinik ve radyolojik olarak geçişkenlik olabilmektedir. Taksan grubu tedavisine sekonder gelişen diffüz parankimal akciğer hastalıkları nadir görülür fakat ciddi ölümcül sonuçları olmaktadır. Tanıda gecikme ve geç tedaviye başlama kötü prognoza neden olmaktadır. Akciğer tutulumu olduğu anda ilaç tedavisi kesilmeli ve kortikosteroid tedavi başlanmalıdır. Bu yazıda, iki farklı olgu ile taksol kullanımına bağlı gelişen diffüz parankimal akciğer toksisitesi literatür bilgileri eşliğinde sunulmuştur.

Anahtar Kelimeler: *Dosetaksel, paklitaksel, pulmoner toksisite, pnömoni.*

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Paclitaxel and docetaxel (a semisynthetic derivative of paclitaxel) are taxane-group anti-neoplastic agents with antitumor properties that increase the aggregation of microtubules in the cell, preventing depolymerization and forming stable microtubule communities. Taxane therapy has been linked to such adverse effects as peripheral neuropathy, bone marrow suppression (mainly neutropenia), arthralgias, myalgias, interstitial pneumonia, organza pneumonia, noncardiogenic pulmonary edema and skin reactions. We present here two case reports, discussing lung toxicities in the first case who was diagnosed with breast cancer and who underwent docetaxel chemotherapy, and a second case who was diagnosed with NSCLC and who was placed on paclitaxel chemotherapy, due to the rarity of their conditions.

CASE

Case 1: A 50-year-old female patient underwent a protective mastectomy after being diagnosed with invasive ductal carcinoma, with a T2N1MO staging. Following mastectomy, the patient was placed on 100mg/m^2 docetaxel therapy every three weeks but developed a cough and shortness of breath after the third cycle with no fever, and the family physician prescribed non-specific antibiotherapy. The complaints persisted, leading her to be referred to the pulmonology polyclinic, where significant exertional dyspnea was identified during her initial examination. A complete blood count showed normal WBC and neutrophil levels. HGB was 10.1.

A lung radiograph revealed increased bilateral reticular densities in all zones of both lungs. The patient was admitted to the ward for monitoring. She had no fever, while arterial blood gas measurements showed moderate hypoxia (pO_2: 55.3 mmHg). Thorax CT revealed no pulmonary embolism, while extensive ground glass densities and reticulonodular involvement were noted in both lungs (Figure 1). The serum cytomegalovirus (CMV) antibody, legionella antibody/antigen, and anti-human immunodeficiency virus (HIV) antibody were all negative, and C-ANCA, P-ANCA, ANA, ANTI DS DNA, ANTI AMA, ASMA, total Ig E and RF levels were normal.

No bronchoscopy or lavage could be performed since the patient had respiratory distress. Differential diagnoses of infection and metastasis were ruled out based on clinical, radiological and laboratory data, and prednisolone therapy was initiated at a dose of 1 mg/kg as the patient developed lung damage secondary to docetaxel treatment. As the patient started to recover from respiratory distress, the steroid therapy decreased gradually and stopped at the end of one month.

Check-up radiographs showed almost complete recovery of the lung parenchyma.

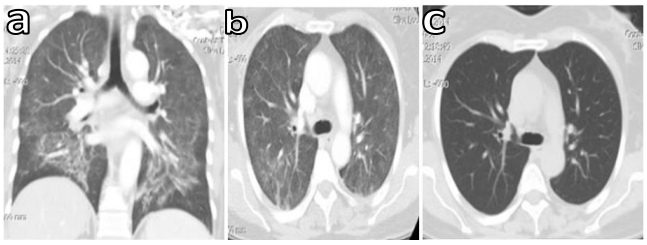

Figure 1: Thorax CT images prior to, and after treatment: an increase in ground glass appearance and interstitial reticulonodular densities can be seen with protected regions of sub-pleural and costophrenic sinuses (a and b). Lung parenchyma appears completely normal 1 month after corticosteroid therapy (c)

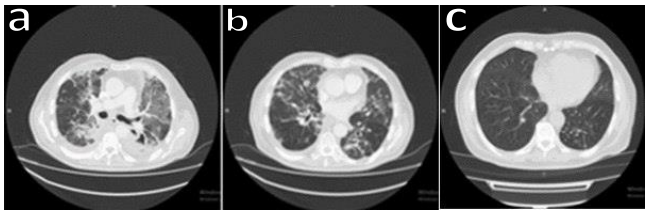

Figure 2: Areas with slightly ground glass density and fibrotic recessions extending to the pleura observed in both lungs (a and b). On control Thoracic CT, near-complete improvement in lung parenchyma was detected (c)

Case 2: A 71-year-old female patient diagnosed with NSCLC, with a staging of T3N2MO, was started on RT and CT treatment. After surgery, the patient was treated with 100 mg/m^2 paclitaxel once every three weeks, and complaints of cough and dyspnea developed after the third course. An emergency physician started the patient on non-specific antibiotic treatment, who had no fever, and she was referred to the pulmonology polyclinic after her complaints did not regress. The patient was hospitalized in an external center and followed up with pneumonia treatment many times, but no decrease was noted, and the frequent emergency applications continued. The patient was presented with dyspnea during her initial examination in the polyclinic. Hb:9 g/dL RDW: 20.9% HCT: 30.7% RBC: 3,42x104 MCH: 26.3 pg Plt: 40x103. A lung radiograph showed increased bilateral reticular density in all zones of both lungs, and the patient was admitted to the ward for monitoring. She had no fever, while arterial blood gas measurements revealed moderate hypoxia. Thoracic CT showed marked emphysematous changes in the upper lobes in both lungs, and ground-glass density areas, pleural parenchymal sequelae, fibrotic retraction and bronchiectatic changes in the superior lower lobe of the left lung. Areas with slight ground glass densities and fibrotic recessions extending into the pleura were observed in both lungs. (Figures 2a and b)

The serum cytomegalovirus (CMV) antibody, legionella antibody/antigen and anti-human immunodeficiency virus (HIV) antibody were negative. Considering the clinical,

radiological and laboratory data, differential diagnoses of infection and metastasis were ruled out.

Prednisolone therapy was initiated at a dose of 1 mg/kg, as the patient had developed lung damage secondary to paclitaxel treatment. After the respiratory distress regressed, the steroid therapy was gradually reduced at the end of one month.

Thoracic CT revealed a near-complete improvement in the lung parenchyma (Figure 2C).

DISCUSSION

Docetaxel is a chemotherapeutic agent used for the treatment of breast, head and neck, gastric, prostate and non-small cell lung cancers. Cells that cannot pass into the mitotic phase during the cell cycle cannot divide and are directed to apoptosis by the G1 control point. There have also been studies showing that paclitaxel inhibits blc-2 by binding to a protein called blc-2, which blocks apoptosis, thus allowing apoptosis to continue (1,2). The most common side effects of docetaxel include neutropenia, hypersensitivity reactions, mucosal inflammation (stomatitis), peripheral neuropathy and fluid retention. Cases of docetaxel-related hypersensitivity, and interstitial and organized pneumonia have been reported, and while pulmonary side effects are rare, they remain as potentially fatal complications of docetaxel therapy. Docetaxel-related pneumonia is characterized by prolonged symptoms and respiratory distress (3). It has been shown that patients with NSCLC treated with a combination of docetaxel with other chemotherapeutic agents or radiotherapy can develop drug-related lung damage (4,5).

In Von Hoff et al.'s (6) study of mice with human pancreatic cancer xenografts, Nab-PTX alone and in combination with GEM consumed the desmoplastic stroma, whereas in mice receiving Nab-PTX plus GEM, the intratumoral concentration of GEM was 2.8 times greater than in those who received GEM alone.

The process underlying drug-related lung damage is not fully understood. According to one hypothesis, docetaxel causes hypersensitivity-type lung damage by stimulating a proliferation of cytotoxic T cells which act against the pulmonary antigens produced by the tumor. It has been further suggested that docetaxel causes damage through its reactive oxygen metabolites (3). Interstitial pneumonia is the most common form of diffuse parenchymal lung toxicity discussed in literature. Ochoa et al. (7) analyzed 30 case reports (12 NSCLC, 12 breast CA, 4 prostate CA, 2 gastrointestinal carcinomas) published prior to 2012 and found an overall mortality rate of 40%, while two case reports published later described the development of interstitial pneumonia in three patients with NSCLC, all three of whom recovered under corticosteroid therapy (8,9).

Interstitial involvement appears to be more common in patients with NSCLC. The incidence of docetaxel-related interstitial involvement is 4.6%, however, this rate rises to 25.9% in patients with prior interstitial changes. Docetaxel is not recommended for NSCLC patients with interstitial changes, as demonstrated by CT (chest computed tomography) (10). A study of 40 patients (35 patients diagnosed with breast cancer, and none with lung cancer) newly started on docetaxel treatment reported significant decreases in DLCO, FEV1, FEV1/FVC and HRCT scores after treatment. Despite the significant decreases in pulmonary function tests and HRCT scores, none of the patients developed respiratory symptoms in the study (11).

The diagnosis of hypersensitivity pneumonia secondary to docetaxel and paclitaxel treatment is made based on the exclusion of other potential causes. In an article reporting four cases, the diagnosis of hypersensitivity pneumonia was made based on the presence of diffuse interstitial infiltration, a lack of response to antibiotherapy, the exclusion of metastatic tumors, potential hypersensitivity reactions to other medications, and rare infectious agents such as CIMV, HIV or legionella (12). A case of docetaxel hypersensitivity pneumonia that resulted in mortality has also been reported in which docetaxel treatment was continued despite the development of lung symptoms, and the diagnosis was subsequently made based on autopsy results (13). Since the diagnosis in that case was delayed, it is likely that treatment was begun at the late stage of the disease, which may have contributed to a lack of treatment response. Hypersensitivity pneumonia has been described previously in five patients in literature, all of whom, including four with NSCLC and one with breast cancer, had a mortal course (12,13).

Organized pneumonia can also develop as a result of docetaxel treatment (14–16).

Laboratory results, radiological findings and bronchoalveolar lavage can be helpful in a differential diagnosis to rule out infections and malignancies, but do not lead to a definitive diagnosis. It has been previously reported that a transition from docetaxel-related pulmonary fibrosis to organized pneumonia may occur (15). Previous cases of docetaxel-related organized pneumonia have been treated with steroids and discontinuation of treatment. All three cases described in literature developed in patients with lung carcinoma who recovered upon corticosteroid therapy.

Broncho Alveolar Lavage (BAL) was not performed in either of the cases in the present study, no diagnostic lung tissue biopsy could be carried out, and carbon monoxide diffusion capacity (DLCO) test results of the lung were unavailable, which can be considered limitations of the present study.

CONCLUSION

The most significant challenge encountered in cases of docetaxel- and paclitaxel-related pneumonia is the complexity of differential diagnoses. The first diagnosis that comes to mind in such patients is pneumonia due to the immunosuppression associated with chemotherapy and antibiotherapy, and this can result in a loss of time, increasing the risk of mortality. In patients undergoing docetaxel treatment, the symptoms should be questioned, and steroid therapy should be initiated immediately. Docetaxel is a common chemotherapeutic agent owing to its ease of use, its high efficacy and its high tolerance among patients. Docetaxel-related lung damage should be considered particularly in patients with respiratory symptoms and confirmed pulmonary infiltrations. Since neutropenia is common in this patient group, the diagnosis should not be mistaken for infections or radiation pneumonia when docetaxel is used in combination with radiotherapy for the treatment of lung cancer. Since docetaxel can result in organized pneumonia, the condition can incorrectly be considered as a lack of response to treatment or progression when docetaxel is used for the treatment of lung cancer. In such cases, the initial action must be the cessation of docetaxel treatment, after which potential infections, hypersensitivities and interstitial lung diseases must be ruled out. It should be remembered that docetaxel-related interstitial pneumonia can have fatal consequences if there is a delay in differential diagnosis and treatment. Early diagnosis, the discontinuation of docetaxel and the administration of corticosteroid therapy may allow complete recovery.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.Y., H.Ç., M.Ç., M.Y.Ş., F.E., N.S.; Planning and Design - G.Y., H.Ç., M.Ç., M.Y.Ş., F.E., N.S.; Supervision - G.Y., H.Ç., M.Ç., M.Y.Ş., F.E., N.S.; Funding - G.Y., H.Ç.; Materials - G.Y., H.Ç.; Data Collection and/or Processing - G.Y., H.Ç.; Analysis and/or Interpretation - G.Y., H.Ç.; Literature Review - G.Y., H.Ç.; Writing - G.Y., H.Ç.; Critical Review - G.Y., H.Ç.

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