

Case Report

Interstitial Lung Disease Following Single-Agent Nanoparticle Albumin-Bound Paclitaxel Treatment in Patients with Advanced Non-Small Cell Lung Cancer

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Keywords

Interstitial lung disease · Nanoparticle albumin-bound paclitaxel · Non-small cell lung cancer · Single-agent treatment

Abstract

Interstitial lung disease (ILD) is a serious and potentially fatal adverse event in lung cancer therapy. Nanoparticle albumin-bound paclitaxel (nab-PTX) is a novel, solvent-free formulation of paclitaxel (PTX). Although the incidence of nab-PTX-induced ILD is not clear, it is generally considered that this formulation presents a similar risk of developing ILD as PTX. Here, we report 3 patients who developed severe ILD following treatment with nab-PTX. We draw attention to the risk of developing drug-induced ILD following nab-PTX treatment, and highlight that this novel formulation might therefore not be as safe as PTX with respect to the development of ILD.

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Introduction

Nanoparticle albumin-bound paclitaxel (nab-PTX) is an albumin-bound formulation of paclitaxel (PTX). In first-line therapy for patients with advanced non-small cell lung cancer (NSCLC), nab-PTX in combination with other platinum reagents showed significant efficacy in improving patients' prognosis as well as reducing toxicity profiles [1–3]. PTX-induced interstitial lung disease (ILD) occurs in approximately 1% of treated patients [4, 5]; thus, PTX is considered relatively safe with respect to the risk of developing drug-induced ILD. Although the incidence of nab-PTX-induced ILD is not clear, it is generally thought that this formulation presents a similar risk of developing ILD as PTX.

To date, only one study has evaluated the development of nab-PTX-induced ILD in clinical trials [6]. Here, we present case reports of 3 patients who developed severe ILD following treatment with nab-PTX. Our reports highlight the risk of developing drug-induced ILD following nab-PTX therapy and indicate that this novel formulation might therefore not be as safe as PTX with respect to the development of ILD.

Case Reports

Case 1

A 71-year-old male ex-smoker, who was diagnosed with stage IV NSCLC (adenocarcinoma), received a platinum-based doublet regimen (carboplatin, pemetrexed, and bevacizumab) as initial chemotherapy until progression. nab-PTX (100 mg/m²) was subsequently used as a second-line regimen. On day 23 of the second cycle of nab-PTX treatment, he developed grade 1 fever and grade 3 dyspnea. Computed tomography (CT) scanning revealed hyperplasia of interlobular septa, nodular shadows, and ground glass opacity, which suggested a pattern of hypersensitivity pneumonia (Fig. 1). There was no elevation of tumor markers and the size of the target lesion was stable. Cultures of sputum, blood, and mycobacterium were all negative. The results of serological testing for *Candida* antigen and *Aspergillus* antigen were negative. (1→3)β-D-glucan was not elevated. Although all infectious disease tests were negative, and antibiotics were started prophylactically (tazobactam/piperacillin 13.5 g/day). Serum KL-6 level was 985 U/mL. Since the respiratory condition had deteriorated, bronchoscopy could not be performed. Clinically, we diagnosed nab-PTX-induced ILD. The drug lymphocyte stimulation test (DLST) was not conducted. Steroid treatment (prednisolone 0.5 mg/kg) was immediately initiated and the ILD symptoms quickly improved. Then steroid treatment was decreased. As there was no alternative anticancer agent for lung cancer, a minimum dose for the remainder of nab-PTX treatment was started. We explained the risk of exacerbation of ILD and obtained the patient's consent. nab-PTX treatment was continued for two further cycles until progression, and the ILD was not exacerbated during the remaining treatment.

Case 2

A 74-year-old male ex-smoker, who was diagnosed with stage IV NSCLC (squamous carcinoma), received a platinum-based doublet regimen (carboplatin, tegafur/gimeracil/oteracil) as initial chemotherapy and nab-PTX (100 mg/m²) as a second-line regimen. On day 24 of the first cycle of nab-PTX, he developed grade 1 fever and grade 3 dyspnea. There was no elevation of tumor markers and the size of the target lesion was stable. Cultures of sputum, blood, and mycobacterium were all negative. The results of serological

testing for *Candida* antigen and *Aspergillus* antigen were negative. (1→3)β-D-glucan was not elevated. Although all infectious disease tests were negative, antibiotics were started prophylactically (meropenem 3 g/day). Serum KL-6 level was 334 U/ml. Since the respiratory condition had deteriorated, bronchoscopy could not be performed. CT scanning showed scattered ground glass opacity and hyperplasia of bronchovascular bundles, which suggested a pattern of hypersensitivity pneumonia (Fig. 2). Clinically, we diagnosed nab-PTX-induced ILD. DLST was not conducted. He was immediately given steroid treatment (prednisolone 0.5 mg/kg). ILD improved and steroid treatment was decreased to a maintenance level. As there was no alternative anticancer agent for lung cancer, a minimum dose of nab-PTX treatment was started. We explained the risk of exacerbation of ILD and obtained patient's consent. nab-PTX was continued for two further cycles until progression. During the remaining nab-PTX treatment, the patient's ILD did not worsen.

Case 3

A 59-year-old male ex-smoker, whose disease had relapsed following surgery for stage IIIB NSCLC (adenocarcinoma), was treated with a platinum-based doublet regimen (cisplatin and vinorelbine) and concurrent radiation therapy as a first-line regimen, followed by another platinum-based doublet regimen (carboplatin, pemetrexed, and bevacizumab); nab-PTX was subsequently given as a third-line regimen. On day 24 of the second cycle of nab-PTX therapy, the patient developed grade 1 fever and grade 3 dyspnea. CT scanning revealed consolidation with an air bronchogram and interlobular ground glass opacity, which suggested a pattern of organizing pneumonia (Fig. 3). There was no elevation of tumor markers and the size of the target lesion was stable. Cultures of sputum, blood, and mycobacterium were all negative. The results of serological testing for *Candida* antigen and *Aspergillus* antigen were negative. (1→3)β-D-glucan was not elevated. Although all infectious disease tests were negative, antibiotics were started prophylactically (tazobactam/piperacillin 13.5 g/day). Since the respiratory condition had deteriorated, bronchoscopy could not be performed. Clinically, we diagnosed nab-PTX-induced ILD. DLST was not conducted. Steroid treatment (prednisolone 0.5 mg/kg) was immediately initiated, and ILD temporarily improved. nab-PTX treatment was discontinued and a minimum dose of steroid was maintained; however, the patient's condition worsened and he developed infectious pneumonia. Despite steroid pulse therapy, the patient died of respiratory failure approximately 6 months after developing ILD.

Discussion

ILD is a serious and potentially fatal condition associated with lung cancer therapy and its development has been associated with treatment with several anti-cancer agents. Given that PTX-induced ILD occurs in approximately 1% of treated patients [4, 5], this drug is considered to present a low risk of development of ILD. nab-PTX is a novel, solvent-free formulation of PTX that shows significant efficacy in improving patients' prognosis, with a reduced toxicity profile, when administered in combination with carboplatin. However, the risk of developing ILD following nab-PTX treatment remains largely unknown.

No incidence of ILD was reported as an adverse event in the largest phase III clinical trial of nab-PTX in patients with NSCLC conducted to date [1]. Furthermore, a phase I/II study of nab-PTX as a first-line single agent did not report any adverse events related to ILD [7]. Two phase II studies have investigated nab-PTX as a second-line regimen [6, 8]. In one of the

phase II studies, 2 patients developed ILD but neither case was fatal. According to our case reports, although the number of cases was too small to be conclusive, male gender and ex-smoker status might represent risk factors for developing ILD. One patient underwent radiation therapy, although the relevance of a relationship between radiation therapy and the onset of ILD is unclear. Furthermore, an investigation of the risk of administering nab-PTX therapy to lung cancer patients with a history of ILD would be beneficial.

The present study was limited in size and data were collected retrospectively. Additionally, no bronchoalveolar lavage or lung biopsy were performed to confirm ILD. Each pattern was evaluated using only CT.

Although the incidence of ILD is relatively low, it might be premature to consider nab-PTX as having a similar safety profile to PTX with respect to the development of this condition. Therefore, further studies to investigate the relationship between nab-PTX and ILD are warranted.

Statement of Ethics

The material in the manuscript has been acquired according to modern ethical standards and written informed consent of the patients has been obtained.

Disclosure Statement

None of the authors have any conflict of interest to declare.

Author Contributions

All authors contributed equally to the literature search, data collection (including figures), and manuscript writing.

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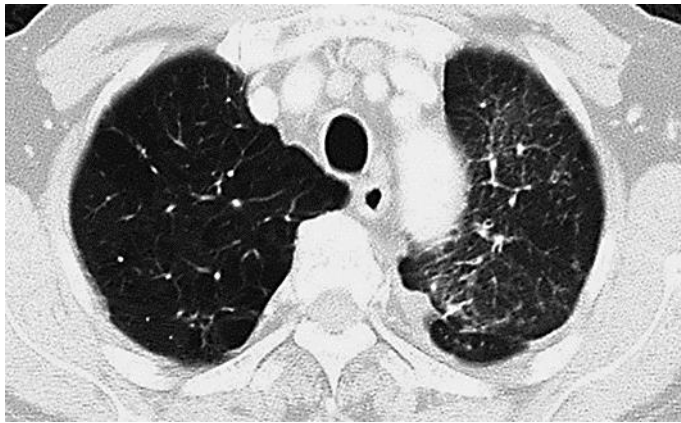


Fig. 1. Plain chest computed tomography of case 1. Hyperplasia of interlobular septa, nodular shadows, and ground glass opacity, which suggest a pattern of hypersensitivity pneumonia.

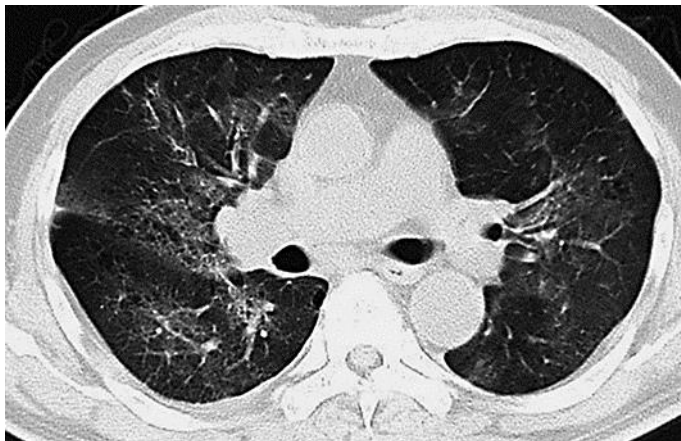


Fig. 2. Plain chest computed tomography of case 2. Scattered ground glass opacity and hyperplasia of bronchovascular bundles, which suggest a pattern of hypersensitivity pneumonia.



Fig. 3. Plain chest computed tomography of case 3. Consolidation with an air bronchogram and interlobular ground glass opacity, which suggest a pattern of organizing pneumonia.