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CASE REPORT

Complete remission and fatal interstitial pneumonitis related to nab-paclitaxel in refractory small cell lung cancer: A case report and review of the literature

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Abstract

For refractory or resistant small cell lung cancer (SCLC), there is no standard treatment. We report a case of refractory SCLC achieving complete remission and then developing fatal interstitial pneumonitis after treatment with single-agent nab-paclitaxel. The relevant literature has also been reviewed. In terms of effectiveness, evidences exists that some refractory or resistant SCLC patients respond to paclitaxel, including nab-paclitaxel and solvent-based paclitaxel. Paclitaxel-related fatal interstitial pneumonitis is an uncommon event, with five fatal cases reported in the literature. It appears to occur in weekly paclitaxel-treated patients and develop during the middle-to-late phase of treatment. Therefore, further randomized clinical trials should be encouraged. In our case, positive immunohistochemical analysis for caveolin-1 in the tumor vascular endothelia suggests that the complete response may have been facilitated by enhanced transportation of paclitaxel through the tumor vascular barrier via caveolin-1, despite being negative for secreted protein acidic and rich in cysteine (SPARC) in tumor cells. Further molecular investigations of gp60, caveolin-1 and SPARC will shed light on tailored treatment in this setting.

Introduction

Patients with small cell lung cancer (SCLC) often eventually relapse after initial chemotherapy with cisplatin plus etoposide or irinotecan. Intravenous topotecan is the only agent authorized in Europe and USA with the specific indication for sensitive and relapsed SCLC. For refractory or resistant SCLC, however, there is no standard treatment. Since solvent-based paclitaxel (Cremophor-based paclitaxel, Taxol, Bristol-Myers Squibb, Princeton, NJ, USA) has been reported to have single-agent activity in some relapsed and refractory SCLC patients,[1] nab-paclitaxel (a solvent-free, nanoparticle albumin-bound paclitaxel, Abraxane, American BioScience Inc., Santa Monica, CA, USA), which shares identical anticancer components with solvent-based paclitaxel, is also worth considering for some refractory or resistant SCLC patients.[2] Accordingly, nab-paclitaxel was administered to a patient with refractory SCLC in our hospital. We observed both complete remission and fatal interstitial pneumonitis, and herein present the case for discussion.

Case report

A 73-year-old heavy-smoking male patient without remarkable medical history was diagnosed at a local hospital with pathological stage IIIB (pT4ipsN2M0) adenocarcinoma of the left upper lobe after lobectomy and mediastinal lymph node dissection. Carboplatin and gemcitabine were then prescribed, but later withheld after one cycle of treatment due to the presence of grade 4 thrombocytopenia.

He was referred to our department complaining of a subcutaneous mass on the left chest wall measuring 3.5 cm; it was later removed by a surgeon in our hospital and confirmed as metastatic SCLC. The slide from the local hospital was then

reviewed by pathologists and was also confirmed as SCLC (Fig 1a). Baseline positron emission tomography (PET) computed tomography (CT) in our hospital showed a huge mass located at the left hilum encroaching on adjacent large vessels, mediastinal lymph nodes enlargement, and chest wall involvement (Fig 1b). The patient tolerated two cycles of irinotecan plus carboplatin well, but on the basis of PET-CT evaluation had progression of disease according to the Response Evaluation Criteria in Solid Tumors (Fig 1c). As refractory SCLC was diagnosed, single-agent nab-paclitaxel (100 mg/m^2, weekly) was recommended. Two cycles later, he achieved complete remission (Fig 1d). On the 5th day after the response was confirmed, he developed exacerbated dyspnea and maintained SpO_2 of over 90% with mask oxygenation. Serum D-dimer was normal and, therefore, pulmonary embolism was excluded. A left ventricular ejection fraction of 65% ruled out cardiac insufficiency. Velcro crackles found in the bilateral base of the lungs strongly pointed to a possible diagnosis of interstitial pneumonitis, which was also indicated later by repeated chest CT scans (Fig 1e). No bacteria, fungi, tuberculosis bacteria, erythrocytes or tumor cells were found in smears and cultures of bronchoscopy lavage fluid. Because of the patient's reluctance, biopsy was not performed. In addition, before entering the intensive care unit the patient's temperature was normal and the blood neutrocyte count was approximately normal. Since nab-paclitaxel-related interstitial pneumonitis was clinically diagnosed, the therapeutic process against the complication focused on: (i) resolving interstitial pneumonitis with methylprednisolone of 1 g per day for 3 consecutive days; (ii) protecting the residual normal lung tissue with ambroxol hydrochloride and urinary trypsin inhibitor; (iii) preventing lung infection with levofloxacin, imipenem/cilastatin (1:1), and caspofungin acetate; and (iv) life support care with mechanical ventilation plus total parenteral nutrition along with other symptom-relieving medicines. One week later, the patient deteriorated rapidly and finally succumbed to respiratory failure. We performed immunohistochemistry for both secreted protein

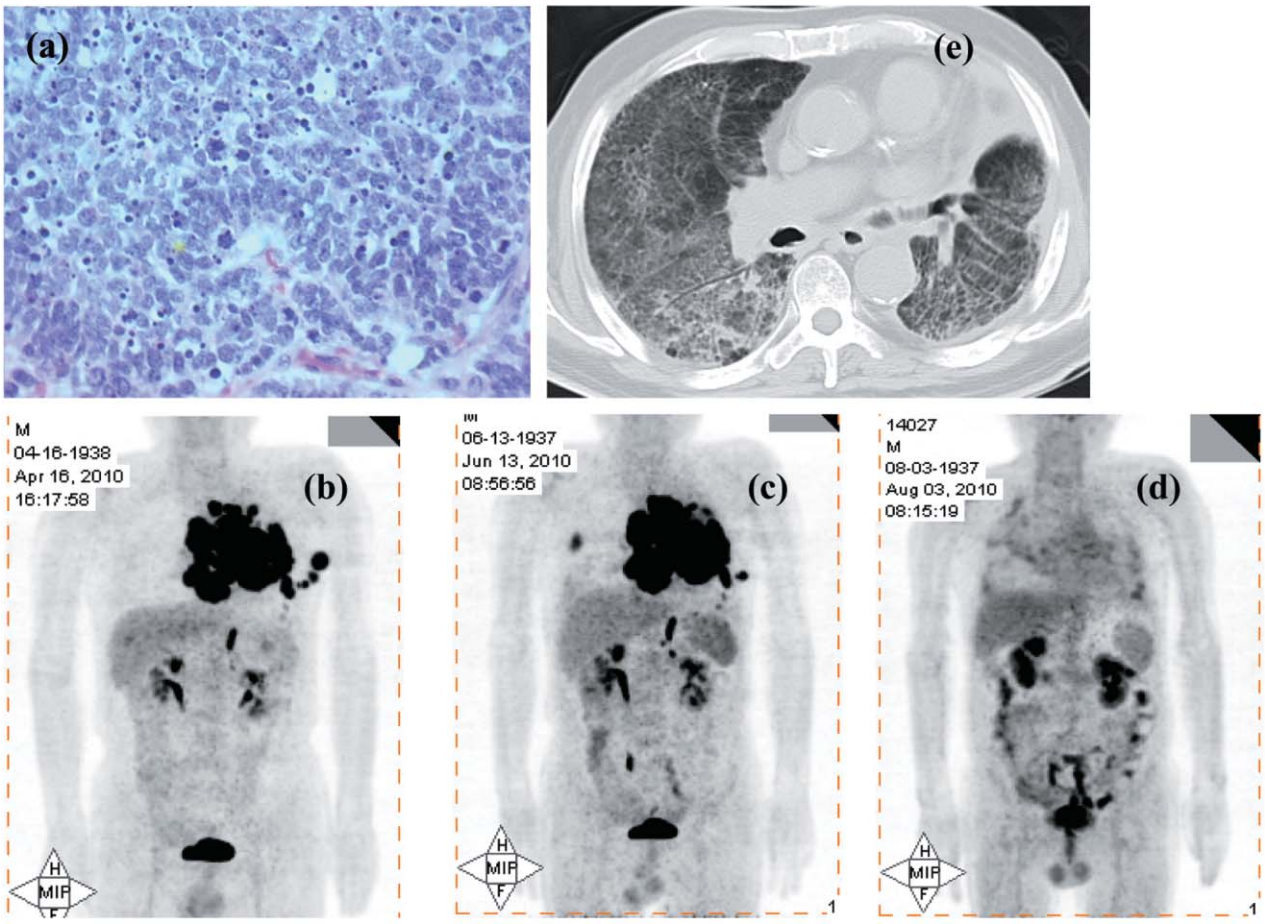

Figure 1 (**a**) Hematoxylin and eosin staining, 400×. Morphology of resected tissue showing the typical characteristics of small-cell lung cancers. (**b**) Positron emission tomography/computed tomography film of baseline. (**c**) Progression of disease after two cycles of irinotecan plus carboplatin. (**d**) Complete remission after two cycles of nab-paclitaxel. (**e**) Extensive bilateral areas of ground-glass attenuation on computed tomography scan.

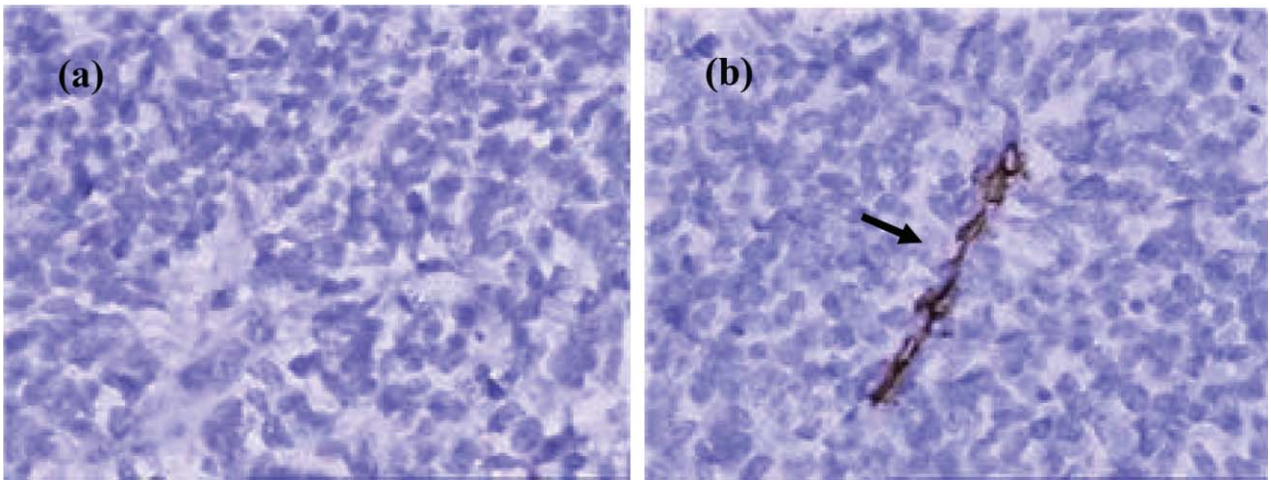

Figure 2 Immunohistochemical analysis of paraffin-embedded resected tissue, 400×. Tumor cells are negative for secreted protein acidic and rich in cysteine (**a**), vascular endothelia are positive for caveolin-1 (**b**).

acidic and rich in cysteine (SPARC) and caveolin-1 proteins on the resected subcutaneous mass, which was negative for SPARC (antibodies from ab14174; Abcam, Cambridge, UK) in tumor cells(Fig 2a) and positive for caveolin-1 (antibodies from #3238; Cell Signaling Technology, Danvers, MA, USA) in tumor vascular endothelia (Fig 2b).

Discussion

To our knowledge, this is the first reported case of refractory SCLC achieving complete remission and then developing into fatal interstitial pneumonitis after single-agent nab-paclitaxel treatment.

There is a scarcity of reported refractory SCLC cases responding to nab-paclitaxel. We only found a phase I trial of nab-paclitaxel in combination with gemcitabine in patients with thoracic tumors, in which three out of total six relapsed SCLC patients had partial response that may have been partially attributed to nab-paclitaxel.[3] Since nab-paclitaxel and solvent-based paclitaxel share identical anticancer properties, the response achieved by solvent-based paclitaxel may signify the efficacy of nab-paclitaxel in treating refractory SCLC. As reported in a phase II trial by Yamamoto N *et al*.,[1] two out of 10 refractory SCLC patients had partial responses to weekly single-agent solvent-based paclitaxel treatment. Although there is no high-level evidence to bolster nab-paclitaxel's effectiveness in treating refractory SCLC, combining the results of the above-mentioned studies with the results from our case, we can at least conclude that paclitaxel, including nab-paclitaxel and solvent-based paclitaxel, do confer remission for some cases of refractory SCLC, which usually has a very gloomy prognosis. Future randomized clinical trials designed to evaluate the efficacy and safety of nab-paclitaxel in refractory SCLC should therefore be encouraged. In addition, since nab-paclitaxel has been reported elsewhere to take advantage of the gp60 and caveolae-mediated albumin transport pathway to traverse the endothelial lining of the blood vessel into the tumor wherein it was preferentially retained via tumoral SPARC,[4,5] can nab-paclitaxel treatment for refractory SCLC be tailored by molecular analysis of gp60, caveolin-1, and SPARC? In our case, positive immunohistochemical analysis for caveolin-1 in tumor vascular endothelia suggested that the complete response may have been facilitated by enhanced transportation of paclitaxel through the tumor vascular barrier via caveolin-1, even though immunohistochemistry was negative for SPARC in tumor cells.

Drug-induced interstitial pneumonitis is not rare in cancer chemotherapy and can usually be resolved with corticosteroids. Nevertheless, fatal interstitial pneumonitis caused by paclitaxel is a rare event. Four cases of paclitaxel-related fatal interstitial pneumonitis have been reported: one case by Ostoros *et al*.;[6] two by Shitara *et al*.;[7] and one by Nagata *et al*.[8] In addition, Suzaki *et al*. also reported a case of adenocarcinoma of the lung developing interstitial pneumonitis after treatment with paclitaxel and dying 4 months later of respiratory failure due to progression of both interstitial pneumonitis and lung cancer.[9] We have excluded this case from our review, because death was not exclusively attributed to interstitial pneumonitis, or rather a patient with fatal interstitial pneumonitis could not survive for 4 months. Our case, presenting insidious onset of dyspnea with rapid progression to respiratory failure and extensive bilateral areas of ground-glass attenuation on a chest CT scan, is typically suggestive of interstitial pneumonitis, even though the diagnosis was not certified by pathology. We can also exclude lymphangitic car-

cinomatosis, infection, cardiogenic edema, pulmonary hemorrhage and embolism, which clinically mimic interstitial pneumonitis. From the five cases, we deem that there are two clinical features regarding paclitaxel-induced fatal interstitial pneumonitis which should raise concern. One is the schedule for paclitaxel administration; the other is the timing of onset. All five patients received paclitaxel on a weekly schedule. When treating non-SCLC, as suggested by Chen *et al*. weekly schedules of docetaxel caused lower myelosuppression but more pneumonitis than a 3-week schedule.[10] As both docetaxel and paclitaxel are categorized as taxanes, sharing a similar lung injury mechanism, we wonder whether pneumonitis is more likely to develop on a weekly schedule of paclitaxel than a 3-week schedule. We therefore recommend paclitaxel to be administered with caution on a weekly schedule, especially for those patients at potential high risk of pneumonitis. Second, the timing of onset of fatal interstitial pneumonitis is a relatively delayed event, developing in our case after six administrations, in Ostoros *et al*.'s[6] case also after six administrations, in Shitara *et al*.'s[7] two cases after 11 and 21 administrations, and in Nagata *et al*.'s[8] case after three administrations. We should therefore always be aware of fatal interstitial pneumonitis during management with paclitaxel, especially in the middle to late phase of treatment.

Collectively, some refractory or resistant SCLC patients respond to paclitaxel, including nab-paclitaxel and solvent-based paclitaxel. Further clinical trials are recommended. Molecular analyses of gp60, caveolin-1, and SPARC may shed light on tailored treatment in this setting. In conclusion, from the five cases reported, paclitaxel-related fatal interstitial pneumonitis occurs rarely, and seems to favor a weekly schedule and develop at the middle to late phase of treatment.

Disclosure

No authors report any conflict of interest.

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