Repetitive responses to nanoparticle albumin-bound paclitaxel and carboplatin in malignant pleural mesothelioma

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Abstract
Malignant pleural mesothelioma (MPM) is a rare tumor with a poor prognosis. Although cisplatin plus pemetrexed is the standard chemotherapy for patients with unresectable MPM, few agents are available for MPM patients who do not tolerate pemetrexed. Here, we report the first case of an MPM patient for whom the combination of nanoparticle albumin-bound paclitaxel and carboplatin (nabPC) repetitively achieved tumor regression. A 76-year-old man was diagnosed with epithelioid MPM. One cycle of carboplatin plus pemetrexed and two cycles of gemcitabine were administered but failed to inhibit tumor progression. By contrast, four cycles of nabPC resulted in a good response. Upon disease progression, four cycles of nabPC were performed again and resulted in a modest response. In conclusion, based on the present case, nabPC is a potential alternative chemotherapeutic agent for MPM, especially for MPM patients who do not tolerate pemetrexed.

Introduction
Malignant pleural mesothelioma (MPM) is an uncommon tumor with a poor prognosis and is associated with previous exposure to asbestos. Cisplatin plus pemetrexed is the standard first-line chemotherapy for patients with advanced MPM [1]. One of the main clinical problems of MPM management is that few agents have been shown to have efficacy against MPM [1]. Here, we report the first case of an MPM patient for whom the combination of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and carboplatin (nabPC) repetitively achieved tumor regression.

Case Report
A 76-year-old man with a 35-pack-year smoking history and a history of asbestos exposure presented with a high-grade fever and right chest pain. A chest radiograph showed consolidation in the right lower lobe of the lung with pleural effusion. Although his fever improved with an injection of ceftriaxone, his chest pain and pleural effusion did not. Chest computed tomography (CT) revealed interlobular septal nodules and pleural thickening. Video-assisted thoracoscopy with a pleural biopsy was performed 1 month after the first medical examination. Immunohistochemical staining of the biopsy samples indicated the diagnosis of epithelioid MPM; the samples were positive for mesothelial markers such as calretinin, vimentin, and cytokeratins 5/6, and were negative for epithelial cell markers such as thyroid transcription factor-1 and Ber-EP4. Positron emission tomography-CT revealed multiple metastases in the mediastinal lymph nodes, including the contralateral mediastinal nodes. Thus, the patient was diagnosed with stage IV MPM (pT2N3M0) based on the tumor-node-metastasis (TNM) staging system.

The patient did not undergo surgery or radiotherapy. Carboplatin with a target area under the curve (AUC) of 5 mg/mL/min and 500 mg/m² pemetrexed was administered on day 1 along with folinic acid and vitamin B12
supplements. A maculopapular rash, which was judged as grade 3 according to CTCAE v4.0, appeared on day 5 and resulted in withdrawal of the chemotherapy by the first cycle. Second-line chemotherapy included two cycles of 1000 mg/m² gemcitabine on days 1 and 8 every 4 weeks. A CT scan taken after two cycles of gemcitabine demonstrated tumor progression (Fig. 1A–C). Because his ECOG-PS (Eastern Cooperative Oncology Group performance status) remained grade 1, he was treated with the combination of carboplatin with a target AUC of 6 mg/mL/min on day 1 and 100 mg/m² nab-paclitaxel on days 1, 8, and 15 every 4 weeks. Drastic decreases in interlobular nodules and pleural thickness were achieved (Fig. 1D–F) Repeated administration of nab-paclitaxel worsened the patient’s peripheral sensory neuropathy, resulting in withdrawal of the chemotherapy by the fourth cycle.

The patient remained progression free for 5 months, at which time he redeveloped chest pain. A chest CT performed 2 months later confirmed an increase in pleural thickness and interlobular nodules due to disease progression (Fig. 2A–C). Rechallenge with nabPC was conducted at the same dose used previously. A modest decrease in pleural thickness and interlobular nodules was achieved without any grade 3/4 hematological adverse effects (Fig. 2D–F). As with the previous treatment with nabPC, peripheral sensory neuropathy led to withdrawal of the therapy by the fourth cycle.

Discussion

Here, we report a case of an MPM patient for whom tumor regression was repetitively achieved with nabPC. Paclitaxel inhibited the growth of mesothelioma xenografts. Phase 2 trials of paclitaxel (200 mg/m² or 250 mg/m² every 3 weeks) in MPM were carried out based on this result, but these studies identified a low response rate (0%–9%) [2]. The combination of carboplatin and paclitaxel (PC) was reported to achieve complete remission in a patient with malignant peritoneal mesothelioma [3]. Nab-paclitaxel is a 130 nm particle form of paclitaxel that was developed to deliver paclitaxel as a suspension of albumin particles in saline. To date, nabPC is proven to achieve higher response rates than PC in the treatment of non-small-cell lung cancer [4]. Nab-paclitaxel also has the following advantages over paclitaxel: a shorter infusion time, a standard infusion set, and no requirements for steroid or antihistamine premedications to prevent hypersensitivity reactions. In the
In the present case, a drastic response was achieved using nabPC as a third-line chemotherapy agent for a patient with advanced MPM.

MPM is a rare and aggressive neoplasm, and a large cohort study of MPM in England and Wales reported a median overall survival of 9.5 months [5]. The combination of cisplatin and pemetrexed is considered to be the standard first-line chemotherapy regimen for unresectable MPM because this regimen is known to have promising activity in MPM [1]. Furthermore, the cisplatin, pemetrexed, and bevacizumab triplet has been shown to result in significantly longer survival times in patients with unresectable MPM compared with cisplatin plus pemetrexed [1]. Pemetrexed, gemcitabine, and vinorelbine are all recommended regimens for second-line chemotherapy in MPM according to the NCCN guidelines [1]. Because the treatment options for patients with MPM that is especially intolerant to pemetrexed are limited, new chemotherapy regimens are desired. To the best of our knowledge, this is the first case report of treatment with nabPC repetitively achieving effective tumor regression in MPM.

In conclusion, the present case suggests that nabPC is a potential alternative chemotherapy agent for MPM. We hope that the results reported here will aid in the treatment of MPM patients, especially those who do not tolerate pemetrexed. Further prospective studies regarding the efficacy of nabPC in MPM patients should be conducted.

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Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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