Successful Salvage Chemotherapy with Gemcitabine and Vinorelbine in a Malignant Pleural Mesothelioma Patient Previously Treated with Pemetrexed

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The role of second-line and salvage chemotherapy in malignant pleural mesothelioma treatment is not yet established. We report a case of relapsed malignant pleural mesothelioma in which the patient failed to respond to pemetrexed-based chemotherapy but was successfully treated with gemcitabine and vinorelbine. The patient underwent a left extrapleural pneumonectomy. Three years later she developed anterior chest wall and retroperitoneal masses. Histological findings revealed metastases from the malignant pleural mesothelioma. Although two cycles of carboplatin plus pemetrexed chemotherapy were administered, she had progressive disease. Then, 1000 mg/m² gemcitabine and 25 mg/m² vinorelbine were administered every 2 weeks. The chemotherapy regimen was tolerated well, and the tumors were remarkably reduced. She was treated with 12 cycles of gemcitabine plus vinorelbine, and 8.5 months of progression-free survival was observed. Gemcitabine plus vinorelbine chemotherapy may be a candidate regimen for salvage chemotherapy against malignant pleural mesotheliomas.

Key words: malignant pleural mesothelioma – salvage chemotherapy – gemcitabine – vinorelbine

INTRODUCTION

Advanced malignant pleural mesothelioma (MPM) is fatal and few chemotherapeutic options are available. Combined therapy with cisplatin plus pemetrexed is considered to be standard chemotherapy for patients with untreated advanced MPM (1). However, since the improvements in response and survival after this therapy are modest, subsequent chemotherapy with new therapeutics is warranted in cases of MPM relapse. Here, we report a case of recurrent MPM in which the patient successfully responded to salvage chemotherapy with a combination of gemcitabine and vinorelbine.

CASE REPORT

In September 2004, a 40-year-old woman was admitted to our hospital for the investigation of left pleural masses and effusion. Percutaneous biopsy was performed and the tumor was diagnosed as MPM (epithelial type) on the basis of the histological findings, including calretinin immunostaining. No obvious evidence of asbestos exposure was noted. She had clinical stage II disease according to the International Mesothelioma Interest Group staging system (2) and underwent a left extrapleural pneumonectomy. Since mediastinal lymph node metastases were detected, two cycles of carboplatin [area under the curve (AUC) 5] and gemcitabine (1000 mg/m²) were administered as adjuvant therapy. Carboplatin was used instead of cisplatin because of her insufficient renal function (creatinine clearance, 50.1 ml/min). She also received adjuvant radiotherapy (42 Gy) at the chest drainage site to prevent local recurrence. In December 2007, a chest computed tomography (CT) scan revealed a mass in the left anterior chest wall and left renal hilar lymphadenopathy (Fig. 1A and B), both of which showed...
positive accumulation in F-18 fluorodeoxyglucose positron emission tomography (FDG-PET). In February 2008, the anterior chest wall tumor and retroperitoneal tumor were surgically removed. These were histologically diagnosed as metastases from MPM (Fig. 1C and D). Two cycles of carboplatin (AUC 3) plus pemetrexed (350 mg/m²) chemotherapy were administered as adjuvant therapy. The dosages of carboplatin and pemetrexed were reduced in this series, because myelosuppression, including neutropenia and thromcytopenia higher than grade 3 [National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 guidelines (3)], and neutropenic fever were observed during the previous carboplatin plus gemcitabine chemotherapy. However, grade 3 thrombocytopenia and grade 4 neutropenia were observed during the therapy despite administration of these doses of carboplatin and pemetrexed. Thus, dose escalation was limited. An abdominal CT scan after two cycles of carboplatin plus pemetrexed therapy revealed an enlarged soft-tissue tumor near the left adrenal gland, indicating a progressive disease. Gemcitabine plus docetaxel therapy was then administered. However, she developed an allergic reaction to docetaxel during the initial administration of the drugs and chemotherapy was discontinued. In December 2008, she complained of left lower back pain, and an abdominal CT scan revealed a swollen lymph node on the dorsal side of the inferior vena cava in addition to an enlarged retroperitoneal soft-tissue tumor (Fig. 2A and B). She was treated with oxycodone and admitted to our hospital for salvage chemotherapy in February 2009. She had an Eastern Cooperative Oncology Group performance status of 1. Intravenous gemcitabine (1000 mg/m²) and vinorelbine (25 mg/m²) were administered every 2 weeks. The chemotherapy regimen was well tolerated. The main side effects were grade 2 neutropenia and phlebitis. No toxicities higher than grade 3 were observed. After the first cycle of chemotherapy, she continued to receive gemcitabine and vinorelbine therapy every 2 weeks as an outpatient. Her lower back pain gradually improved and she no longer required oxycodone. After four cycles of gemcitabine plus vinorelbine, the tumors showed significant reduction, corresponding to a partial response. An abdominal CT scan revealed further reduction of the tumors after eight cycles (Fig. 2C and D). She was treated with 12 cycles of gemcitabine plus vinorelbine, and 8.5 months of progression-free survival was observed.

**DISCUSSION**

We report the case of a patient with relapsed MPM successfully treated with gemcitabine and vinorelbine. Gemcitabine has shown some activity in combination with platinum compounds in first-line chemotherapy for patients with MPM (4–8). In addition, several studies on gemcitabine as a single agent have been reported with response rates ranging from 0 to 31% (9–11). Vinorelbine as platinum-doublet (12) or single-agent (13,14) chemotherapy in patients with untreated MPM has also been reported. The response rates of single-agent vinorelbine were 16% (13) and 24% (14) in these trials. However, the role of second-line and salvage chemotherapy in MPM treatment is not yet established, and to our knowledge, there are few prospective trials of second-line chemotherapy in pemetrexed-pretreated patients. Under the circumstances, vinorelbine as single-agent treatment (15)
and gemcitabine plus oxaliplatin chemotherapy (16) in pemetrexed-pretreated patients have been studied. Zucali et al. (17) administered gemcitabine and vinorelbine as second-line chemotherapy to 30 patients who showed progressive disease after pemetrexed-based chemotherapy. Gemcitabine (1000 mg/m²) and vinorelbine (25 mg/m²) were administered on days 1 and 8 every 3 weeks, and a 10% partial response and 43.3% disease-control rate were achieved in the study. On the basis of these reports, we administered gemcitabine and vinorelbine in the present case and observed marked tumor reduction. We think that gemcitabine plus vinorelbine chemotherapy may be a candidate regimen for salvage chemotherapy against relapsed MPM.

The present patient failed to respond to carboplatin plus pemetrexed chemotherapy prior to gemcitabine plus vinorelbine therapy. However, the dosages of carboplatin and pemetrexed used previously were insufficient, and the response to the chemotherapy was evaluated as progressive disease. In addition, although she was previously treated with gemcitabine, the response to carboplatin plus gemcitabine therapy could not be evaluated as there were no assessable lesions. Therefore, the efficacy of previous gemcitabine treatment in this case was unclear.

In terms of toxicities, Zucali et al. (17) reported that neutropenia and thrombocytopenia higher than grade 3 were observed in 11 and 4% of patients, respectively, and that other toxicities were mild in the above-mentioned study. In the present case, previous chemotherapy using carboplatin combined with gemcitabine or pemetrexed caused severe hematological toxicities. However, a combination of gemcitabine and vinorelbine exhibited an acceptable toxicity profile including hematological and non-hematological toxicities, and serial chemotherapy could be continued in an outpatient setting. Meanwhile, in this case, the metastatic lesions developed as the chest wall and retroperitoneal tumors after an extrapleural pneumonectomy. These tumors were histologically diagnosed as metastases from MPM, and no other metastases were detected. The patterns of clinical progression of this case, including lymphadenopathy of renal hilum or dorsal side of the IVC and retroperitoneal soft-tissue tumor, were considered to be unusual as metastatic MPM. Thus, the present case also seemed to have rare metastases in the clinical manifestation of MPM.

In summary, the clinical course presented here suggested that gemcitabine and/or vinorelbine could be active against MPM that has been previously treated with pemetrexed. The optimal chemotherapy regimen or the role of salvage chemotherapy in MPM treatment needs to be evaluated in prospective clinical trials.

Conflict of interest statement
None declared.

References