Pemetrexed Combined with Platinum-based Chemotherapy for Advanced Malignant Peritoneal Mesothelioma: Retrospective Analysis of Six Cases

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Abstract. *Background: Malignant peritoneal mesothelioma (PM) is an extremely rare disease. Pemetrexed and platinum have been used for advanced PM following malignant pleural mesothelioma (PLM). Because PM differs considerably from PLM in clinical features, the efficacy and safety of these therapies have yet to be established. Patients and Methods: Six Japanese patients with PM who had been treated with pemetrexed-based chemotherapy in four Institutions were retrospectively identified. Treatment response, progression-free survival, and overall survival were examined. Toxicities of therapy were also evaluated. Results: Three patients with mild ascites achieved clinical benefits (one with partial response and two with stable disease). Treatments with reduced cisplatin or carboplatin for patients with massive ascites were safely performed. Median PFS and OS were 7.2 and 13.1 months, respectively. Grade 3 hematological toxicities appeared in two patients with massive ascites. Conclusion: Selection of chemotherapy based on the patient's condition, such as ascites, might be important for advanced PM.*

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Malignant peritoneal mesothelioma (PM) is a malignant tumor arising from mesothelial cells lining the peritoneum. PM accounts for 25-33% of total mesothelioma cases, with an incidence of one to two cases per million worldwide (1). Compared to pleural mesothelioma (PLM), the incidence of PM is extremely rare. The development of PM is thought to depend on environmental factors related to each patient, and it is estimated that the incidence of PM will reach its peak in 2025 in Japan (2). PM is closely-related to heavy exposure to asbestos, such that 33% of PM cases had a history of exposure to asbestos, which was lower than that for PLM (3). Fifty percent of patients with primary PM had pleural plaque (4). In addition, radiation therapy, ionized radiation, mica, peritonitis, thorium dioxide, and simian virus-40 infection were reported to have some relationship to the incidence of PM (5-7).

Since few reports about specific therapy for PM are available, treatment of PM has been performed on the basis of the results of PLM treatment. A combined-modality therapy consisting of debulking surgery, intraperitoneal chemotherapy, and radiation therapy has been used for PM patients with limited disease. For advanced PM, palliative chemotherapy was thought to be applicable, but prognosis tended to be poor. Treatment for advanced PM is especially challenging because of the clinical features,

Table I. *Patients' characteristics*.

Case	Age, years/ Gender	ECOG PS	Method of diagnosis	Ascites	History of asbestos exposure	Suggestive findings of asbestos exposure
1	62/Male	1	Cytology, ascites	Massive	Construction work	Asbestos lung, plaques, pleural effusion
2	75/Male	2	Cytology, ascites	Massive	None	Asbestos lung, plaques
3	66/Female	1	Histology, omentum	Mild	Construction work	None
4	35/Male	1	Histology, transcutaneous biopsy	Mild	None	None
5	67/Female	1	Histology, pouch of Douglas puncture	Mild	None	Plaques
6	60/Male	2	Cytology, ascites	Massive	Electrical work	Plaques

ECOG PS, Eastern Cooperative Oncology Group performance status.

including rapid tumor progression, lower sensitivity to radiation therapy, and concomitant massive ascites. Therefore, few regimens with cytotoxic agents have shown satisfactory efficacy for PM (8).

Combination chemotherapy was suggested to be more effective than single-agent chemotherapy in a meta-analysis of PLM and PM (9). According to the Expanded Access Program (EAP), both pemetrexed monotherapy and pemetrexed-plus-cisplatin combination therapy (PC) for PM were reported to be effective and feasible (10). The International EAP also reported the effectiveness and feasibility of pemetrexed alone and with platinum combination therapies in a retrospective analysis of 109 PM cases (11). These findings suggested that pemetrexed-based regimens might be effective for PM, which is believed to possess biological features similar to PLM. However, PM is often accompanied by massive ascites and poor performance status (PS), and these previous studies did not provide detailed criteria for selecting chemotherapy regimens based on patients' background characteristics; thus, the probability of performing adequate PC chemotherapy for PM remains uncertain. Thus, six Japanese patients with PM with different backgrounds treated with pemetrexed-plus-platinum combination chemotherapy were evaluated, and the efficacy and safety of the treatments were determined.

Patients and Methods

Study population. The present study selected Japanese patients who were diagnosed at four Institutions from July 2007 through March 2012 as having malignant PM cytologically or histologically and who had first-line systemic chemotherapy using the pemetrexed plus platinum combination. They were investigated for basic characteristics and efficacy and safety of the chemotherapies. Measurable and non-measurable lesions were evaluated by computed tomographic (CT) or magnetic resonance imaging (MRI), and tumor response was assessed using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 (12). Overall survival (OS) and progression-free survival (PFS) were defined as the time from the starting date of chemotherapy to the date of death and to the first documentation of disease progression. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: for men, eGFR (ml/min/1.73 m^2)=194 × $Cr^{-1.094}$ × age $^{-0.287}$; for women, eGFR=194 × Cr $^{-1.094}$ × age $^{-0.287}$ × 0.739. The amount of ascites was categorized into three groups: mild ascites was defined as ascites located only around the liver or in the pelvic cavity; massive ascites represented a large amount of ascites present from the pelvic cavity to the liver; and medium ascites was the presence of ascites that was neither mild nor massive.

Treatment. The PC treatment schedule was intravenous infusion of pemetrexed (500 mg/m^2/day, on day 1) and cisplatin (75 mg/m^2/day, on day 1), repeated every three weeks. In pemetrexed-plus-carboplatin therapy (PCB), pemetrexed was administered in the same way, and intravenous infusion of carboplatin [area under the concentration–time curve (AUC)=5] on day 1 was administered. Treatments were administered until disease progression, unacceptable toxicity, or the decision to discontinue by the patient or the investigator. All patients took folic acid at 1,000 mg orally every day beginning approximately one to two weeks before the first dose of pemetrexed until three weeks after termination of pemetrexed. A 1,000 μg injection of vitamin B12 was administered intramuscularly approximately one to two weeks before pemetrexed and repeated every nine weeks. Toxicity was evaluated based on National Cancer Institute (NCI) Common Terminology Criteria of Adverse Events (CTC-AE), version 4.0 (13).

Results

Baseline characteristics. Six patients (four males, two females) with PM were treated during the period from July 2007 to March 2012 (Table I). Their median age was 62 (range=35-75) years. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 1 in four patients and 2 in bio-patients. Five patients were treated with palliative chemotherapy, and the other patient underwent chemotherapy after debulking surgery (patient 3). Three patients were diagnosed by cytological examination of ascites punctures. For the other patients, histological diagnoses were obtained by a surgical specimen for patient 3, transcutaneous tumor biopsy for patient 4, and pouch of Douglas puncture for patient 5. Four patients showed pleural plaque on chest CT, suggesting a history of exposure to asbestos. Two patients (1 and 2) showed

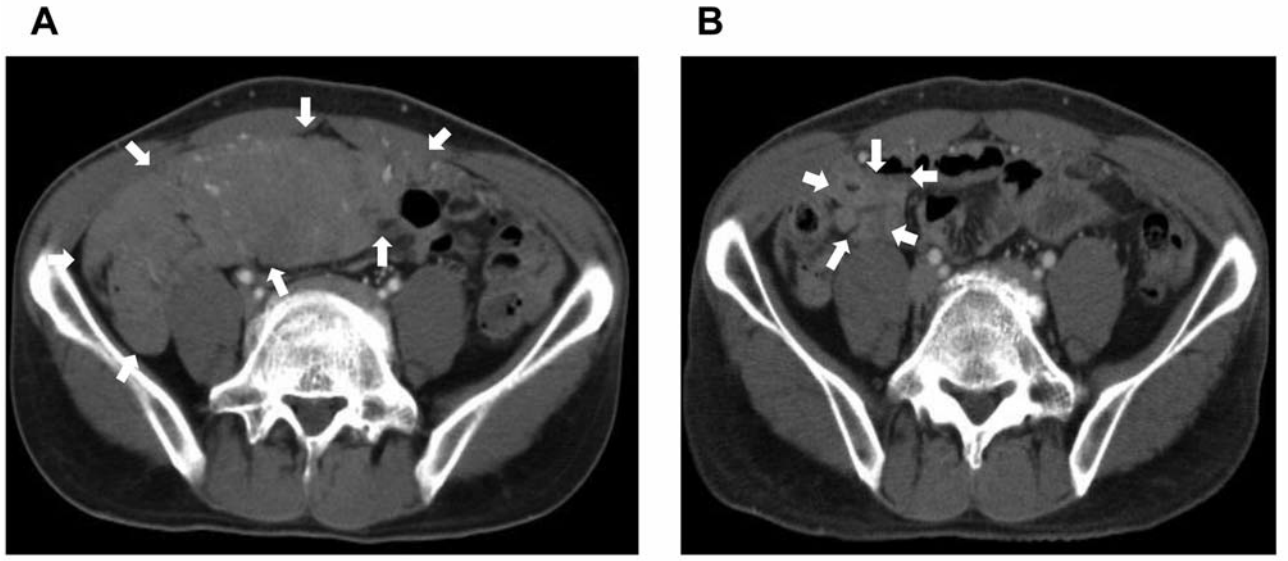

Figure 1. *Representative abdominal computed tomographic (CT) images of patient 4 are shown. The partial response of the tumor was revealed by CT images before (A) and after (B) six cycles of chemotherapy. Arrows indicate the abdominal tumor.*

reticular, nodular shadows and a ground-glass appearance, which were compatible with asbestos lung. Three out of the four patients with pleural plaque had long histories of asbestos exposure: construction workers using asbestos for 30 years (patients 1 and 3), and an electrical worker with 20 years' experience (patient 6). The lung lesions of patient 2 worsened during chemotherapy and were diagnosed as exacerbation of asbestos lung. All patients had ascites on CT, three of whom had massive ascites requiring drainage for symptom relief and for prevention of chemotherapy-induced adverse events. Measurable lesions in the peritoneal cavity and outside of the peritoneal cavity including the lung, diaphragm and lymph nodes, were observed in all patients. Two patients showed tumor calcification (patients 3 and 6).

Treatment. All six patients were administered pemetrexed-plus-platinum doublet systemic chemotherapy (Table II). The median treatment number was 6.3 (range=3-12) courses. Five patients were administered PC and one patient received PCB because of cardiac dysfunction based on a history of acute myocardial infarction. Doses of cisplatin were decreased in patient 2 because of massive ascites with mild renal insufficiency. In patient 1, reduced doses of cisplatin were administered because of massive ascites without renal insufficiency, but which was carefully continued for 12 cycles. The doublet chemotherapies were terminated because of disease progression in patient 2, peripheral neuropathy in patient 3, and excess accumulated dose of cisplatin in three patients. Maintenance chemotherapy with pemetrexed was administered to three patients after the doublet therapy. Treatment dose reduction during therapy due to toxicity was performed in patient 6, in which carboplatin was reduced to 400 mg because of CTC-AE grade 2 nausea and vomiting.

Efficacy and safety. All patients were evaluable for tumor response. Best overall tumor responses were partial response (PR) in two patients and stable disease (SD) in four patients. Median PFS was 7.2 months, and median OS was 13.1 months. PC showed good tumor control, including one PR and two SD for the patients with PS 1 and mild ascites (patients 3-5). The representative CT images of patient 4 who had PR are shown (Figure 1). Patient 2 with poor PS or massive ascites was unable to continue planned PC therapy and had no treatment response. The other patient with a poor general condition (patient 6) was safely administered PCB and maintained SD. Patients 1, 3 and 6 received 3-8 cycles of maintenance therapy using single-agent pemetrexed. Vinorelbine or vinorelbine-plus-gemcitabine was used for second-line chemotherapy in two patients.

In terms of hematological toxicities, two patients had grade 3 leukopenia, two had grade 3 neutropenia, and two had grade 3 anemia (Table III). All of them had massive ascites. Blood transfusion was performed in one patient. No grade 4 hematological toxicity occurred. Grade 1 or 2 increments of serum creatinine, aspartate aminotransferase, and alanine aminotransferase, peripheral neuropathy, vomiting, fatigue, anorexia, and alopecia occurred in several patients. Prominent decreases of eGFR after chemotherapy were found in two patients with massive ascites (1 and 2) and in one patient with mild ascites treated with PC. No eGFR change was observed in the patient with massive ascites who was treated with PCB.

Table II. *Efficacy and safety profile.*

Case	Dose (mg/m^2)	Cycles	eGFR		Toxicity G3/4	ORR	PFS (days)	Subseq. Tx (courses)	OS (days)
			Before	After					
1	Pem (500) Cis (60)	12	88.3	45.1	Leukopenia Neutropenia Anemia	PR	310	Pem (3) VNR (10)	438
2	Pem (500) Cis (25)	3	58.8	26.5	Leukopenia Neutropenia Anemia	SD	85	BSC	104
3	Pem (500) Cis (75)	5	94	64.6	-	SD	329	Pem (11)	429
4	Pem (500) Cis (75)	6	126.9	52	Anemia	PR	167	GEM+ VNR (16)	915+
5	Pem (500) Cis (75)	6	76.4	51.9	-	SD	184	BSC	231
6	Pem (500) Carb (AUC=5)	6	83.8	85.3	-	SD	218	Pem (4)	248

Subseq. Tx, Subsequent therapy; Pem, pemetrexed; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); before, before chemotherapy; after, after chemotherapy; PFS, progression-free survival; OS, overall survival; VNR, vinorelbine; GEM, gemcitabine; Cis, cisplatin; Carb carboplatin; AUC, area under the concentration-time curve; BSC, best supportive care.

Discussion

The present study examined the safety and efficacy of systemic chemotherapies in six Japanese patients with PM. Although several clinical studies examining the efficacy of pemetrexed-plus-platinum combination chemotherapy for PM exist, a prospective study suitable for establishing standard therapy has not been carried-out because of the low incidence of PM. Caretni *et al*. reported the results of a retrospective analysis of 109 cases of PM in EAP (11). They showed that overall response rates to single-agent pemetrexed, PC, and PCB were 20.0%, 24.1%, and 12.5%, respectively. CTC-AE grade 3 and 4 toxicities were observed more frequently in the pemetrexed-monotherapy group. This group included older patients (median age of 62.0 years in the pemetrexed group, 56.0 years in the PC group, and 58.5 years in the PCB group) and a higher proportion of patients with Karnofsky performance status less than 80% (44.7% in the pemetrexed group, 29.7% in the PC group and 29.4% in the PCB group). This suggested that lower efficacy and severer adverse events might depend on poorer general condition (11). However, detailed patient background data including tumor burden and ascites were not available in that study.

In the present study, the median PFS of first-line pemetrexed-plus-platinum combination chemotherapy in these six patients was 7.2 months, and the median OS was 13.1 months, both poorer than in previous reports. These results might be due to the limited number of patients, including two cases with poor general condition. However, two patients had successfully achieved PR, and one of them survived for 30.5 months after diagnosis, suggesting that the combination chemotherapy could provide efficacy for patients who are able to tolerate it.

Table III. *Toxicity profile by grade.*

Toxicity	Grade, n			
	1	2	3	4
Hematotoxicity				
Leukopenia	1	1	2	-
Neutropenia	1	1	2	-
Anemia	2	1	3	-
Thrombocytopenia	-	-	-	-
Non-hematotoxicity				
Nausea	1	2	-	-
Vomiting	-	2	-	-
Anorexia	2	1	-	-
Malaise	2	1	-	-
Cr increased	2	1	-	-
AST increased	1	1	-	-
ALT increased	1	1	-	-
Ascites	3	-	3	-
Abdominal distension	-	3	-	-
Pleural effusion	2	-	-	-
Pulmonary fibrosis	2	-	-	-
Peripheral sensory neuropathy	2	-	-	-
Weight loss	2	-	-	-

The first-line combination chemotherapy for PM has shown equivalent efficacy to the treatments for PLM. While pemetrexed-plus-platinum doublets was usually continued until PM disease progression, six cycles of doublet chemotherapy were employed in the treatment of PLM (14). Subsequent single-agent pemetrexed has been an option for maintenance chemotherapy following six cycles of first-line combination chemotherapy (15). In the present study, three patients had six cycles of first-line doublet, and 12 cycles were performed for patient 1, whose dose of cisplatin was reduced. Three patients treated with single-agent pemetrexed as maintenance therapy showed a trend for prolonged survival. These observations suggest that a therapeutic strategy similar to that used for PLM might be applicable for PM.

Carteni *et al*. reported that CTC-AE grade 3 and 4 anemia and neutropenia were observed in 6.4% and 34.6%, of all patients respectively, (11). Three cases (50%) developed grade 3 hematological toxicities in the present study, more than in previous reports. Two out of three (66.7%) patients with grade 3 toxicity had massive ascites, suggesting that the amount of ascites and hematological toxicity might be related. Decreased eGFR tended to appear more clearly in patients with massive ascites. The dose of cisplatin was often reduced in cases of massive ascites because of difficulties in controlling fluid balance and possible retention of cytotoxic agents in the peritoneal effusion. Although dose reduction of cisplatin was performed in patients with massive ascites in the present study, hematological and renal toxicities could not be avoided. On the other hand, while patient 6 had a PS of 2 and had massive ascites, six cycles of PCB and four cycles of single-agent pemetrexed were safely administered with no severe hematological and renal toxicities, and overall survival of 248 days was achieved. In the international EAP for patients with PLM, 752 patients received pemetrexed-plus-carboplatin as first-line treatment, with similar efficacy to that of pemetrexed-plus-cisplatin in the 1-year survival rate (PC=63.1%, PCB=64.0%) and median time-to-progression (7 *vs*. 6.9 months). While hematological toxicities were more common in the pemetrexed-plus-carboplatin group, this might not be directly linked to carboplatin toxicity because of differences in patients' baseline characteristics. PCB was concluded to be a possible choice for patients with PM who are not suitable for cisplatin-based chemotherapy.

Thus, an appropriate treatment regimen should be carefully selected based on the patient's condition, including the amount of ascites and organ function. Establishment of standard chemotherapy against PM is expected to be difficult because of the low incidence of this disease. Thus, retrospective analyses of accumulated clinical observations may be important in order to form a consensus on the clinical standard-of-care. New classes of molecular targeting drugs including anti-epidermal growth factor receptor, anti-angiogenesis, and inhibitors of multikinase, proteasome, and histone deacetylase, are now in clinical trials for malignant mesothelioma (16). Development of safe and effective therapies for PM are also desired based on the results of these trials.

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