The Efficacy of the Frontline Platinum-based Combination Chemotherapy in Malignant Peritoneal Mesothelioma

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Objective: Malignant peritoneal mesothelioma is a rare neoplasm that accounts for ~1 per 1 million has limited data regarding its frontline therapy. We investigated the treatment outcomes in patients with malignant peritoneal mesothelioma receiving frontline cisplatin-based combination chemotherapy.

Methods: We analyzed 14 patients with malignant peritoneal mesothelioma who had been treated by frontline cisplatin-based combination chemotherapy between January 2005 and March 2009. The chemotherapeutic agent added to platinum was gemcitabine in one patient, cyclophosphamide–doxorubicin in three patients and pemetrexed in 10 patients.

Results: The confirmed overall response rate was 35.7% and the disease control rate was 71.4%. In all patients, two complete responses and three partial responses were observed (overall response rate, 35.7%). Stable disease was observed in five patients (35.7%). The median progression free survival was 4.4 months (95% CI, 0.6–9.0) and the median overall survival was 20.1 months (95% CI, 12.7–28.5). There was significant differences for progression free survival (P = 0.031) according to the different chemotherapeutic agents (pemetrexed versus non-pemetrexed agents) added to platinum. Grade 3 or 4 hematologic toxicities included leukopenia in one patient and anemia in three patients. There were no Grade 3 or 4 non-hematologic toxicities or treatment-related deaths.

Conclusion: The platinum-based combination chemotherapy showed moderate activity and a favorable toxicity profile as a frontline treatment for patients with malignant peritoneal mesothelioma. Pemetrexed in combination with platinum showed improved survival outcomes as compared with other combination regimens combined with platinum.

Key words: platinum – peritoneal mesothelioma – pemetrexed

INTRODUCTION

Mesothelioma is a neoplasm of serosal surfaces. It may involve the pleura, less frequently the peritoneum and in a small percentage of cases the pericardium. Primary malignant peritoneal mesothelioma is a rare clinical entity that accounts for ~1 per 1 million. Symptoms include abdominal pain, vomiting, constipation, fever and weight loss. Owing to the rarity of the disease, there were only few papers on the therapy for malignant peritoneal mesothelioma. Currently, there are no standard treatments for this disease (1–3). Therapy includes surgical and medical treatment, each of these alone or in combination. Intensive multimodality approaches that combine cytoreductive surgery with intraperitoneal chemotherapy, with or without radiotherapy have been proved to be able to considerably improve the survival in selected cases (4–11). However, cytoreductive surgery is not always possible for patients with extensive
intraperitoneal disease and these intensive multimodality approaches are often associated with high morbidity and mortality rates.

The role of chemotherapy in malignant peritoneal mesothelioma has continued to be challenging. However, most available cytotoxic agents have been tested in patients with malignant peritoneal mesothelioma with rather disappointing results. A systematic review published in 2002 performed a meta-analysis of all prospective clinical trials published in the literature from 1965 to 2001 relative to the treatment of malignant mesothelioma of pleural or peritoneal origin. In terms of antitumor response rate, thus, this meta-analysis suggested cisplatin to be the most active agent, and the combination of cisplatin with doxorubicin the most active regimen (12).

Pemetrexed is a novel multitargeted antifolate with broad antitumor activity, including lung, colon bladder, cervical and breast cancer (13). Pemetrexed also showed effective antitumor activity in advanced pleural mesothelioma and was the first agent approved for treatment of advanced pleural mesothelioma. In a pivotal Phase III trial, the combination of pemetrexed plus cisplatin provided patients with significantly improved survival when compared with cisplatin alone (14).

Additionally, pemetrexed alone or in combination with cisplatin has been reported to be active and safe in patients with malignant peritoneal mesothelioma (1). Gemcitabine is also known to be active in patients with malignant peritoneal mesothelioma both as a single agent and in combination with cisplatin (15–17). Tanida et al. (18) reported that combination chemotherapy with cisplatin and gemcitabine revealed favorable tumor reduction and long-term survival in patients with malignant peritoneal mesothelioma.

Because of the rarity of malignant peritoneal mesothelioma, no evidence based standard treatment of this disease has been reported to date (1–3). We investigated the treatment outcomes in patients with malignant peritoneal mesothelioma receiving frontline platinum-based combination chemotherapy (platinum plus pemetrexed, cisplatin plus gemcitabine and platinum plus doxorubicin–cyclophosphamide).

PATIENTS AND METHODS

PATIENTS

Between January 2005 and March 2009, 14 patients with malignant peritoneal mesothelioma were treated with frontline platinum-based combination chemotherapy at the Samsung Medical Center, Seoul, Korea. All patients were pathologically confirmed of malignant peritoneal mesothelioma. The following clinical data were collected from the medical records of each patient: physical examination, surgical and pathologic reports and imaging. Medical information including chemotherapy regimens, dose of cytotoxic agents, response, toxicity profile and the date of progression, last follow-up and deaths were collected.

CHEMOTHERAPY, RESPONSE AND TOXICITY

The platinum-based combination chemotherapy regimens used were as follows: pemetrexed plus platinum (PP), cyclophosphamide–doxorubicin plus platinum (CAP) and gemcitabine plus platinum (GP). The PP regimen consisted of intravenous (iv) pemetrexed 500 mg/m² daily on day 1 over ~10 min and iv cisplatin 75 mg/m² on day 1 over 1 h of each treatment; CAP, iv cyclophosphamide 500 mg/m² on day 1 over 1 h, iv doxorubicin 50 mg/m² on day 1 over 30 min and iv cisplatin 50 mg/m² on day 1 over 1 h of each treatment; and GP, iv gemcitabine 1000 mg/m² on day 1 and 8 over 30 min and iv cisplatin 70 mg/m² on day 1 over 1 h. Folic acid supplement was administered orally beginning 1–2 weeks before the first dose of pemetrexed and continued daily until the patient discontinued treatment. Vitamin B12 was administered by intramuscular injection 1–2 weeks before the first dose of pemetrexed and repeated every 9 weeks until the patient discontinued therapy. Treatment cycles of all these regimens were repeated every 21 days. All responses required confirmation by imaging studies at 6 weeks or more after the initial documented response. Responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Toxicity was graded according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 2.0. The severity of any toxicities not defined in NCI-CTC were graded as 1 = mild, 2 = moderate, 3 = severe or 4 = very severe.

STATISTICAL ANALYSIS

We investigated the treatment outcomes in patients with malignant peritoneal mesothelioma receiving frontline platinum-based combination chemotherapy. Treatment outcomes were estimated as response rate, progression free survival (PFS), overall survival (OS) and toxicities. The response was determined according to RECIST 1.0. PFS and OS were defined as the duration from the first treatment to the date of disease progression or death, respectively. Both PFS and OS were estimated using the Kaplan–Meier method. The efficacy analysis was based on the intent to treat population. The proportional hazards model was used to make survival comparisons controlling for each chemotherapy regimen. Statistical significance was defined as a two sided $P < 0.05$.

RESULTS

PATIENTS CHARACTERISTICS

From January 2005 to March 2009, 14 patients with malignant peritoneal mesothelioma were treated with frontline platinum-based combination chemotherapy. The clinical characteristics of these patients are shown in Table 1. The median age of patients was 54 years (range, 40–69), and the male/female ratio was 1.0:1.8. The median ECOG performance status was 1 (0–2) and all patients had advanced
metastatic disease. All (100%) of patients revealed the pathologic type of epithelial mesothelioma and ascites. Five patients received prior debulking operation. Any patients did not receive prior radiotherapy. The regimens of the frontline chemotherapy used in this study are listed Table 1 and all of these patients received platinum-based combination chemotherapy. The chemotherapeutic agent added to platinum was gemcitabine in one patient, cyclophosphamide–doxorubicin in three patients and pemetrexed in 10 patients.

### RESPONSE RATE

Among all the 14 patients, two complete responses and three partial responses were observed (overall response rate, 35.7%). Stable disease was observed in five patients (35.7%) and progressive disease in five patients (28.6%); RESPONSE RATE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall (n = 14)</th>
<th>Treatment group</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pemetrexed + platinum</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>No. of patients</td>
<td>5</td>
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<tr>
<td></td>
<td>% of total</td>
<td>37.7</td>
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<tr>
<td>Disease control rate</td>
<td>No. of patients</td>
<td>10</td>
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<td></td>
<td>% of total</td>
<td>71.4</td>
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<tr>
<td>PFS, months</td>
<td>Median</td>
<td>4.4</td>
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<td>95% CI</td>
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<td>OS, months</td>
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<td>95% CI</td>
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Table 2. Objective response and survival

<table>
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<tr>
<th>Parameter</th>
<th>Overall (n = 14)</th>
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Table 2). The disease control rate was 71.4% and all 14 patients were assessable for treatment response. The differences in response rates were not observed according to the patients’ baseline characteristics (age, sex, performance status, pathological types, prior surgery and chemotherapy regimen).

### SURVIVAL

All 14 patients were included in the survival analysis on intent to treat basis. The median PFS was 4.4 months (95% CI, 0.6–9.0) and median OS was 20.1 months (95% CI, 12.7–28.5; Fig. 1). There was significant differences for PFS ($P = 0.031$) according to the different chemotherapeutic agents (pemetrexed versus non-pemetrexed agents) added to platinum (Fig. 2). However, in multivariate analysis, any clinical characteristics (age, sex, performance status, pathological types, prior surgery and chemotherapy regimen) did not have the role as independent predictive factor for PFS and OS. The PFS and OS curves are shown in Fig. 1.

### TOXICITY

Toxicities observed during the treatment are listed in Table 3. NCI-CTC Grade 3 or 4 hematologic toxicities included leukopenia in one patient and anemia in three patients. There were no Grade 3 or 4 non-hematologic toxicities or treatment-related deaths.
DISCUSSION

Malignant peritoneal mesothelioma is a rare cancer for which limited data are available to guide physicians in their choices of treatment (1–3). Although there have been some studies on the role of chemotherapy in patients with malignant peritoneal mesothelioma, there has not been consensus for the chemotherapy in patients with advanced malignant peritoneal mesothelioma (1–3,18,19). In large meta-analysis for malignant mesothelioma of pleural or peritoneal origin, polychemotherapy regimens had greater response rates than single agent therapy (23 versus 12%, $P < 0.001$) (12). This meta-analysis also suggested cisplatin to be the most active single agent and the combination of cisplatin with doxorubicin the most active regimen. Thus, Tanida et al. (18) reported that combination chemotherapy with cisplatin and gemcitabine revealed favorable tumor reduction and long-term survival in patients with malignant peritoneal mesothelioma. Recently, antifolates deserve particular mention due
to their emerging role in the treatment of this chemoresistant disease. Janne et al. (1) reported that pemetrexed alone or in combination with cisplatin showed active and safe in patients with malignant peritoneal mesothelioma. A Phase II study on combinations of pemetrexed and gemcitabine in 20 patients with advanced malignant peritoneal mesothelioma reported a response rate of 15% and a median survival time of 26.8 months (20). Our study may provide important guidance for the treatment of patients with advanced malignant peritoneal mesothelioma. Platinum-based combination chemotherapy (PP, CAP and GP) used in our study proved active with an overall response rate of 35.7% and a median survival duration of 20.1 months. Response rates for combination of pemetrexed plus cisplatin in previous reports ranged from 26 to 36% which is comparable to the response rates of our study. In addition, the disease control rate in this study was as much as 71.4%, which is comparable to the rate of 71.2% observed by Janne et al., and the rate of 77% reported by Karthaus et al. in studies using pemetrexed plus cisplatin.

Although this study was conducted retrospectively at a single institution and analyzed a limited and selected group of patients, we found that there was significant differences for PFS ($P = 0.031$) according to the different chemotherapeutic agents (pemetrexed versus non-pemetrexed agents) added to platinum. Response rate for the combination of pemetrexed plus cisplatin in our study was 50% and disease control rate was 80%. The median PFS was 12.3 months and the median OS could have not been achieved. These findings suggested that the combination of pemetrexed plus cisplatin might be a good option in treatment of advanced malignant peritoneal mesothelioma. Median PFS and OS were 1.5 and 6.4 months in the non-pemetrexed group (Fig. 2). These outcomes were substantially lower than other trials involving non-pemetrexed agents. The reason may, at least in part, be related to patient selection. All patients treated with non-pemetrexed agents in this study were male and did not receive debulking surgery. However, it should be kept in mind that the results represent only a small group of patients.

Twelve of 14 patients treated with frontline platinum-based combination chemotherapy experienced disease progression. Eight of 12 patients with disease progression received the second-line chemotherapy. The regimes used as the second-line chemotherapy were as follows; pemetrexed in one patient, PP in three patients, etoposide plus platinum in three patients and vinorelbine plus platinum plus metotrexate in one patient. All four patients with salvage peme- trexed containing regimes had received PP as a frontline treatment.

The platinum-based combination regimen showed a favorable toxicity profile and there were no treatment-related deaths. Although hematologic toxicity was reported, the incidence of Grade 3–4 hematologic toxicity was $\approx 28.5\%$ and there were no febrile neutropenic patients. NCI-CTC Grade 3–4 non-hematologic toxicity was not observed. Other study using the non-platinum-based combination regimen (pem- trexed plus gemcitabine) in advanced malignant peritoneal mesothelioma showed 60% Grade 3–4 neutropenia and over 20% Grade 3–4 non-hematologic toxicity (20).

This study was conducted retrospectively at a single institution and analyzed a limited and selected group of patients. Most patients had good performance status, which suggest that patients with poor performance may have been excluded from receiving chemotherapy. Nevertheless, our report is the study to evaluate the efficacy and tolerability of frontline platinum-based combination chemotherapy in advanced malignant peritoneal mesothelioma only. Moreover, we ana- lyzed the treatment outcomes according to the different chemotherapeutic agents (pemetrexed versus non-pemetrexed agents) added to platinum. Future studies need to evaluate the antitumor activity of different drugs targeting vascular endothelial growth factor and platelet-derived growth factors, as they are known autocrine growth factors in malignant mesothelioma, and epidermal growth factor receptor, which is also highly overexpressed (21). In order to more improve the treatment outcome in advanced malignant peritoneal mesothelioma, a tailored targeted chemotherapy regimen should be developed.

**Conflict of interest statement**

None declared.

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