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Comparison of cisplatin plus pemetrexed and cisplatin plus gemcitabine for the treatment of malignant pleural mesothelioma in Japanese patients

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ABSTRACT

Background: Cisplatin plus pemetrexed is a standard front-line chemotherapeutic regimen for inoperable malignant pleural mesothelioma (MPM). However, no clinical trials have compared the efficacy of cisplatin plus pemetrexed and cisplatin plus gemcitabine, which may be comparable based on previous phase II study results. This study aimed at evaluating the efficacy of cisplatin plus pemetrexed and comparing it with that of cisplatin plus gemcitabine in Japanese MPM patients.

Methods: From July 2002 to December 2011, 13 and 17 consecutive patients with inoperable MPM were treated with cisplatin plus gemcitabine and cisplatin plus pemetrexed, respectively, at the Shizuoka Cancer Center. We reviewed the medical charts of these patients and evaluated their characteristics as well as data regarding drug toxicity and antitumor efficacy.

Results: The response rates were 15% and 35% in the cisplatin plus gemcitabine and cisplatin plus pemetrexed groups, respectively ($P=0.4069$), while disease control rates were 77%, and 82%, respectively ($P=0.9999$). Progression-free survival was significantly higher with cisplatin plus pemetrexed (median, 215.5 days) than with cisplatin plus gemcitabine (median, 142.5 days) ($P=0.0146$; hazard ratio [HR], 0.3552). Overall survival showed a tendency towards being superior with cisplatin plus pemetrexed (median, 597.5 days) compared with cisplatin plus gemcitabine (median, 306.5 days) ($P=0.1725$, HR, 0.5516). Hematological toxicities, especially thrombocytopenia and neutropenia, tended to be more frequent and severe in the cisplatin plus gemcitabine group.

Conclusions: Cisplatin plus pemetrexed may be superior and should continue to be the standard front-line chemotherapeutic regimen for inoperable MPM.

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1. Introduction

The combination of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) given every 3 weeks was established as a standard-of-care front-line regimen after the largest phase III trial conducted in patients with chemotherapy-naïve malignant pleural mesothelioma (MPM) revealed an improvement in survival over cisplatin alone [1]. The combination regimen had a response rate of 41.3%, median time to progression of 5.7 months, and median overall survival (OS) of 12.1 months. However, the combination of cisplatin and gemcitabine has demonstrated comparable response and survival rates in several phase II trials [2–6], with response rates of 12–48% and median OS times of 9.4–13 months. However, no clinical trial has compared the efficacies of cisplatin plus pemetrexed and cisplatin plus gemcitabine; therefore, the question remains whether cisplatin plus gemcitabine is comparable to cisplatin plus pemetrexed in treating MPM patients.

Pemetrexed alone or in combination with cisplatin is also used worldwide for the treatment of non-squamous non-small-cell lung cancer (NSCLC) [7]. Pemetrexed alone or in combination with cisplatin has shown increased efficacy in East Asian non-squamous NSCLC patients compared to Western populations [8,9]. However, there have been few reports examining the efficacy of cisplatin plus pemetrexed for MPM in East Asian patients including Japanese patients. Therefore, it is unclear whether the efficacy of pemetrexed in combination with cisplatin for the treatment of MPM is better in East Asian patients than in Western populations.

The objective of our retrospective analysis was to evaluate the efficacy of cisplatin plus pemetrexed in the treatment of MPM in Japanese patients and to compare its efficacy with that of cisplatin plus gemcitabine.

2. Patients and methods

2.1. Patient selection

We reviewed 13 and 17 consecutive patients with inoperable MPM who were treated with cisplatin plus gemcitabine and cisplatin plus pemetrexed, respectively, as first-line chemotherapy at the Shizuoka Cancer Center between July 2002 and December 2011. Tumor stage was determined according to the classification system of the International Mesothelioma Interest Group [10] This study was approved by institutional review board of Shizuoka Cancer Center (Approval date: November 26, 2012; Approved #: 24-J100-24-1-3). Written informed consent was not required, because this study is retrospective.

2.2. Chemotherapy

2.2.1. Cisplatin plus gemcitabine

Cisplatin (80 mg/m^2) and gemcitabine (1000 mg/m^2) were administered intravenously on day 1 and on days 1 and 8. The treatment cycles were repeated every 3 weeks for a maximum of 6 cycles. Generally, the doses of cisplatin and gemcitabine were reduced in the event of grade 4 hematological toxicity or grade ≥3 severe non-hematological toxicity during the previous treatment cycle. The dose of cisplatin was also reduced in the event of a creatinine elevation generally equal to ≥1.5 mg/dL. When the white blood cell, neutrophil, or platelet counts were below 2000 mm^{-3}, 1000 mm^{-3}, or 75,000 mm^{-3}, respectively, or if an active infection was present, the administration of gemcitabine on day 8 was omitted.

2.2.2. Cisplatin plus pemetrexed

Cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) were administered intravenously on day 1. The treatment cycles were repeated every 3 weeks for a maximum of 6 cycles. Generally, the doses of cisplatin and pemetrexed were reduced in the event of grade 4 hematological toxicity or grade ≥3 severe non-hematological toxicity during the previous treatment cycle. The dose of cisplatin was also reduced in the event of creatinine elevation generally equal to ≥1.5 mg/dL. Patients were instructed to take a daily 1-g multivitamin supplement containing 500 mg of folate beginning 1 week prior to day 1 of cycle 1 until study discontinuation. Vitamin B12 (1000 mg) was intramuscularly injected starting 1 week prior to day 1 of cycle 1 and repeated every 9 weeks until the treatment ended.

2.2.3. Supportive care

All patients received prophylactic antiemetic therapy consisting of a 5-HT3 antagonist, aprepitant, metoclopramide, and dexamethasone according to the American Society of Clinical Oncology guidelines [11]. Aprepitant was approved for use in October 2009 in Japan. Granulocyte colony-stimulating factor was used when patients with febrile neutropenia or grade 4 neutropenia required its administration depending on the judgment of the physician in charge.

2.3. Evaluation of efficacy and toxicity

Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, ver. 1.0 [12]. Acute adverse events were evaluated until 4 weeks after the last chemotherapy administration or until the patient's death in accordance with the Common Terminology Criteria for Adverse Events ver. 3.0 [13].

2.4. Statistical analysis

To analyze progression-free survival (PFS) and OS, survival curves were drawn using the Kaplan–Meier method. The PFS was calculated from the date of initiation of the chemotherapy to the date of disease progression or death from any cause. The PFS was censored at the date of the last visit for those patients who were still alive without any documented disease progression. The OS was calculated from the date of initiation of the chemotherapy to the date of death and was censored at the date of the last visit for patients whose deaths could not be confirmed. The PFS and OS were compared using the log-rank test according to the chemotherapeutic regimens (cisplatin plus gemcitabine vs. cisplatin plus pemetrexed). Cox proportional hazards models were used to calculate the hazard ratio (HR). To evaluate