A Retrospective Study of Chemotherapy with and without Pemetrexed in Malignant Pleural Mesothelioma

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Abstract. Background: The current standard first-line chemotherapy for malignant pleural mesothelioma (MPM) is pemetrexed and cisplatin. However, other regimens, with or without a platinum agent, are reported to be effective in the treatment of MPM. Patients and Methods: Patients who were diagnosed with MPM and treated with chemotherapy between January 1999 and June 2010 at the Osaka Prefectural Medical Center for Respiratory and Allergic Diseases were studied, and the outcomes of these patients were retrospectively analyzed in relation to therapy. Results: In total, 48 patients with MPM (42 men and 6 women) treated with chemotherapy were included in the current analysis. The median survival time (MST) and one-year survival rate in the pemetrexed-containing group were 541 days and 63.2%, respectively. The MST and one-year survival rate in the non-pemetrexed group were 516 days and 66.7%, respectively. Overall survival did not differ significantly with respect to the pemetrexed-containing regimen. Conclusion: The superiority of pemetrexed-containing regimens is equivocal. Non-pemetrexed-containing regimens may be potent alternatives.

Malignant pleural mesothelioma (MPM) is a rare form of malignancy that originates from the mesothelium. It is known to be associated with asbestos exposure (1). Despite recent advances, the prognosis of this disease remains poor, and a median survival of 6-12 months is reported (2-4). Surgery, radiation, chemotherapy, and multimodal therapy are treatment options for MPM, but evidence for the efficacy of these treatments is insufficient (1, 2, 5).

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Results

In total, 48 MPM patients (42 men and 6 women) treated with chemotherapy were included in the current analysis. Their backgrounds are listed in Table I. The median age at diagnosis was 67 years. The epithelioid type was predominant. Most of the patients had good performance score. Twenty-three patients were treated with chemotherapy containing pemetrexed (pemetrexed-containing group) and the remaining patients were treated with chemotherapy that did not contain pemetrexed (non-pemetrexed-containing group). Baseline characteristics of each group did not differ significantly (Table II). The first line regimens used in each group are listed in Tables III and IV.

Survival analysis for chemotherapy. The MST and one-year survival rate in the pemetrexed-containing group were 541 days and 63.2%, respectively, while those in the non-pemetrexed group were 516 days and 66.7%, respectively (Figure 1). Overall survival did not differ significantly between the two groups ($p=0.65$).

Surgical therapy. Surgery was performed in eight patients. Six patients were treated with extrapleural pneumonectomy (EPP), and two patients were treated with pleurectomy/decortication (P/D). Neoadjuvant chemotherapy with gemcitabine–cisplatin was administered to both of the patients treated with P/D, and neoadjuvant chemotherapy with pemetrexed–cisplatin was administered to all of the patients treated with EPP. Survival did not differ significantly between the patients treated with surgery and those treated without surgery ($p=0.19$). However, there was a trend for improved survival in patients who underwent surgery (Figure 2).

Survival analysis for histologic type. Survival of the patients with the epithelioid type was significantly better than the one of patients with the non-epithelioid type ($p=0.0038$). The MST and one-year survival rate of the patients with the epithelioid type were 789 days and 76.7%, respectively, and...
these of patients with the non-epithelioid type were 306 days and 38.3%, respectively (Figure 3).

Univariate and multivariate analysis. The results of univariate analysis are presented in Table V. Significant factors of poor prognosis include non-epithelioid type, advanced stage, and presence of chest pain. Factors demonstrating \( p<0.1 \) in univariate analysis were included in multivariate analysis using the Cox model; none of the factors reached statistical significance (Table VI).

Discussion

In this retrospective study, survival was similar in patients receiving pemetrexed and in patients receiving other agents. There was a trend for improved survival with surgery, which did not reach statistical significance. On univariate analysis, non-epithelioid type, advanced stage, and presence of chest pain were suggested to be related to poor survival outcome, although in multivariate analysis, these factors did not reach statistical significance.

The current standard first-line chemotherapy is pemetrexed plus cisplatin. In a systematic review by Ellis et al., which included 119 trials (8 randomized trials and 111 phase II trials), it was suggested that response rates with combination chemotherapy are higher than those with single agents and that platinum-containing regimens lead to higher response rates compared with non-platinum-containing regimens. This review concluded that chemotherapy with pemetrexed and cisplatin is recommended for patients with advanced MPM (14). However, most of the studies included in this systematic review are noncomparative phase II trials, and pemetrexed–cisplatin has only been demonstrated to be superior to cisplatin monotherapy.

Some other agents, used with or without platinum, are reported to be effective in the treatment of MPM. Among non-pemetrexed-containing regimens, gemcitabine–cisplatin is also often administered. The response rate and MST of this regimen are reported to be 12-48% and 9.4-13 months, respectively (7, 8). Lee et al. retrospectively analyzed data for 81 patients with MPM who were treated with pemetrexed–cisplatin or gemcitabine–cisplatin and reported that survival outcomes of patients treated with these regimens did not differ (17). Carboplatin is considered to be a potent alternative to cisplatin. In a phase II study, the response rate and MST of gemcitabine–carboplatin were reported to be 24% and 10.6 months, respectively (9).

Vinorelbine, a semisynthetic vinca alkaloid, has also been shown to be effective in the treatment of MPM. In a phase II study of 29 chemotherapy-naïve patients, the response rate and MST of single-agent vinorelbine were reported to be 24% and 10.6 months, respectively (12). Vinorelbine may be used in combination with platinum agents. Sørensen et al. evaluated the efficacy of vinorelbine–cisplatin and reported MST and median time to progression to be 16.8 months and 7.2 months (response rate, 29.6%), respectively (13). Recently, in a randomized phase III trial of 409 patients from 76 centers performed by the Medical
Research Council, active symptom control (ASC) alone was compared to ASC plus chemotherapy (mitomycin–vinblastine–cisplatin, or weekly vinorelbine) (18). In this study, the additional benefit of chemotherapy on ASC was not demonstrated, but a survival advantage was suggested for ASC plus vinorelbine compared to ASC alone, although it was not statistically significant. The authors concluded that the efficacy of vinorelbine deserves further investigation.

Standard surgical options in the treatment of MPM include EPP and P/D. Lower local recurrence rate and higher distant recurrence rate of EPP compared to P/D are reported. The role of surgical resection for the treatment of MPM and the optimal surgical procedure remain controversial since microscopically complete resection is difficult, and these surgical treatments have relatively high rates of morbidity and mortality (4). No randomized trial has evaluated the efficacy of surgical treatment in MPM. Lee et al. performed phase II trials in 77 MPM patients, evaluating the efficacy of adjuvant pemetrexed plus cisplatin followed by EPP and radiation. In this study, patients who completed all therapy had a good prognosis, with an MST of 29.1 months and a two-year survival rate of 61.2% (19).

Limitations of the current study include its retrospective design and small sample size. In addition, non-pemetrexed-containing regimens were mostly used prior to 2007, when pemetrexed became available in Japan. Moreover, in this study, the response to chemotherapy was not evaluated.

In conclusion, the superiority of pemetrexed-containing regimens is equivocal. As some agents other than pemetrexed have been shown to be effective in the treatment of MPM, non-pemetrexed-containing regimens may be potent alternatives, particularly for patients unable to tolerate pemetrexed-containing chemotherapy. Chemotherapy in MPM may not be necessarily confined to pemetrexed-containing regimens.
References


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