Long Progression-free Survival by Pemetrexed Continuation Maintenance Therapy Following Cisplatin-based Chemotherapy in Malignant Pleural Mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is associated with a poor prognosis. The combination of cisplatin and pemetrexed has been established as a standard chemotherapy that confers a survival benefit. Because the regimen is sometimes hampered by the renal toxicity of cisplatin and no second-line chemotherapy has yet been established, the strategy of administering a higher total dose of pemetrexed to optimize the regimen could be promising. We herein describe the case of a 69-year-old man with MPM who underwent five cycles of cisplatin plus pemetrexed and exhibited a partial response. Because his serum creatinine increased, pemetrexed maintenance therapy (PMT) was adopted, and 18 cycles were successfully delivered and the patient achieved a complete response. This case suggests that PMT could thus be useful for treating MPM.

Key words: cisplatin plus pemetrexed, complete response, malignant pleural mesothelioma, pemetrexed continuation maintenance therapy, progression-free survival

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Introduction

Malignant pleural mesothelioma (MPM) is associated with a poor prognosis even in the cases treated with multi-modality therapies. Although trimodal therapies of neoadjuvant chemotherapy followed by extrapleural pneumonectomy and adjuvant hemithoracic radiation have been vigorously investigated, the benefits of radical surgery remain controversial (1). The only established chemotherapy with a survival benefit in MPM is the combination of cisplatin and pemetrexed (2), which is sometimes hampered by the renal toxicity induced by cisplatin. A strategy in which pemetrexed maintenance therapy (PMT) is administered following cisplatin-based induction chemotherapy could be promising.

We herein report a case of MPM treated by PMT following cisplatin-based induction chemotherapy in which the patient exhibited complete response and achieved an extremely

long progression-free survival.

Case Report

A 69-year-old man with a two-year history of asbestos exposure from 20 years of age, complained of right chest pain. His chest X-ray (Fig. 1) and computed tomography (CT) scan demonstrated diffuse thickening of the right pleura with a pleural effusion (Fig. 2A, B) partly pressing the hepatic capsule through diaphragm without apparent invasion (coronal image, Fig. 2C), and a nodular pleura-based mass projecting into the azygoesophageal recess (Fig. 2A). Thoracentesis was performed, and a cytological examination demonstrated class III with an elevated hyaluronic acid value of pleural effusion score of 153,000 ng/mL. Therefore, a core needle biopsy under ultrasonographic guidance was performed. A histological evaluation revealed papillary stratification and stromal invasion of malignant cells with dense cellularity, suggesting epithelial-type mesothelioma

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Figure 1. Chest X-ray demonstrated diffuse thickening of the right pleura with pleural effusion.

(hematoxylin and eosin staining, Fig. 3A). The immunohistochemical staining was positive for calretinin (Fig. 3B), which confirmed a diagnosis of the epithelial type of MPM.

The International Mesothelioma Interest Group clinical stage was III; T3 (suggested by the thickened pleura pressing the hepatic capsule without apparent invasion and the mass in the azygosophageal recess), N0, M0.

Accordingly, cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) were administered every 21 days for five cycles, thus resulting in a good partial response on day 17 of the third cycle (Fig. 4A, B). Trimodal therapy including extrapleural pneumonectomy after four cycles of chemotherapy followed by adjuvant hemithoracic radiation was described to him and his family in detail, but they rejected this approach, and the combination chemotherapy regimen was continued.

Because an increase in serum creatinine up to 1.56 mg/dL was observed after the fifth cycle and the disease was stable at the time, PMT was adopted. Pemetrexed (500 mg/m²) was administered every 28 days. The interval of pemetrexed administration was reset to 28 days considering the grade four neutropenia observed in the fifth cycle of induction therapy. A complete response was attained on day 25 of the sixth cycle of maintenance therapy (Fig. 4C, D).

The patient's right chest pain disappeared two months after the initial chemotherapy, and he received 18 courses of PMT without progression for 22 months from the initiation of induction chemotherapy. His complete response ended with the emergence of multiple liver metastases, which were detected on day 25 of the 19th PMT cycle.

Discussion

MPM is a locally invasive and very aggressive tumor associated with a poor prognosis, even in the cases treated with multimodality therapy, and it is refractory to different treatment modalities.

Chemotherapy has come to play the most important role

in the management of advanced MPM, considering the results of "Mesothelioma and Radical Surgery randomized feasibility study" (1). This study suggested limited benefits of radical surgery, although trimodal therapies of neoadjuvant chemotherapy followed by extrapleural pneumonectomy and adjuvant hemithoracic radiation were vigorously investigated and were determined to have a promising median survival of 16.8 months in a phase II trial (3).

The current standard of care is a platinum-based chemotherapy regimen, and the combination of cisplatin and pemetrexed established by a phase III trial in 2003 is the only protocol demonstrating survival benefit to date (2). In the trial, the median number of cycles was six, ranging from one to 12 cycles, and the median survival time and progression-free survival of cisplatin plus pemetrexed arm were 12.1 and 5.7 months, respectively. However, this regimen is sometimes hampered by the renal toxicity of cisplatin, and no role for second-line chemotherapy has been established to date. The approach to optimize chemotherapy by administering a higher total dose of pemetrexed, which is the key drug in MPM management, could be promising. This optimization could be attained by employing PMT following cisplatin-based induction chemotherapy, which has already been established in the management of advanced non-squamous non-small-cell lung cancer (NSCLC) (4).

Pemetrexed is a multitargeted antifolate that inhibits multiple enzymes, such as thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycylamide ribonucleotide formyltransferase, involved in purine and pyrimidine synthesis. TS and DHFR expressions negatively correlate with the treatment efficacy of pemetrexed in NSCLC patients, and patients with low TS and DHFR expression levels tend to have a longer median progression-free survival (5, 6). In particular, up-regulation of TS gene expression plays an important role in acquired pemetrexed resistance in NSCLC (7).

On the other hand, there are few molecular investigations of MPM, and elevated TS expression is related to both intrinsic and acquired resistance to the combined treatment of pemetrexed and platinum (8).

Pemetrexed as a single agent to treat MPM has shown fair activity in a phase II trial; the response rate and median overall survival were 14.1% and 10.7 months, respectively (9). Its anti-tumor activity, even as a single agent, is the theoretical basis of the current PMT strategy.

In the current case, a cisplatin plus pemetrexed regimen was introduced as neoadjuvant chemotherapy; however, the patient and his family rejected extrapleural pneumonectomy and adjuvant hemithoracic radiation. Therefore, the combination chemotherapy was continued, and PMT was adopted due to the renal toxicity of cisplatin, which had been established in the management of NSCLC. A complete response was attained on day 25 of the sixth cycle of PMT, thus suggesting the anti-tumor activity of pemetrexed as a single agent. The toxicity of PMT in the current case with renal dysfunction was negligible and tolerable.

Figure 2. Chest CT demonstrated diffuse thickening of the right pleura with a nodular pleura-based mass projecting into the azygoesophageal recess (A). Pleural effusion was observed (B), and the coronal image clearly showed the thickened pleura partly pressing hepatic capsule through the diaphragm around the costophrenic angle without apparent invasion (C).

Figure 3. Histological findings of core-needle biopsy revealed papillary stratification and stromal invasion of malignant cells with dense cellularity, suggesting epithelial-type mesothelioma (A: Hematoxylin and Eosin staining, 200×). The immunohistochemical staining was positive for calretinin (B: 200×).

The evidence of a survival benefit in MPM patients has been demonstrated following a cisplatin plus pemetrexed regimen (2); however, the optimal cycle of cisplatin-based chemotherapy has not been clarified. Considering the anti-tumor activity of pemetrexed as a single agent (9), developing a strategy to administer a higher total dose of pemetrexed to patients with cisplatin-induced renal dysfunction could lead to clinical benefits.

The molecular mechanism of the current case is still only theoretical given the lack of data regarding molecular markers, such as TS (5-8) and excision repair cross-complementation group 1 (ERCC1) (10), which are said to negatively correlate with the response to pemetrexed and

cisplatin, respectively. The basic mechanism of the exceptionally favorable outcome in the current case could be putatively explained by the low TS expression in the MPM tissue, considering the previously described molecular mechanism related to pemetrexed effectiveness and resistance (5-8). Given the extremely long progression-free survival, TS gene up-regulation could not have occurred in accordance with the pemetrexed treatment (8).

The current report is the first pemetrexed continuation maintenance therapy (CMT) following cisplatin-based induction chemotherapy with a long documented progression-free survival. There is one investigation (11) of carboplatin-based induction chemotherapy that has not proven a survival bene-

Figure 4. Chest CT obtained on day 17 of the third cycle of induction chemotherapy (A, B). The images demonstrate shrinkage of the nodular pleura-based mass in the azygoesophageal recess (A) and the disappearance of diffuse pleural thickening, except for the area around the costophrenic angle (B). Chest CT obtained on day 25 of the sixth cycle of PMT (C, D). The images show the disappearance of the nodular pleura-based mass in the azygoesophageal recess (C) and the thickened pleura around the costophrenic angle (D).

fit in MPM.

Taken together, although the standard of care for MPM is the combination of cisplatin and pemetrexed and PMT still remains experimental, the adoption of PMT following cisplatin-based induction chemotherapy appears very promising, and further investigation is urgently needed. The optimization of an induction chemotherapy protocol and the indication criteria should be validated by phase III trials in patients with various responses to induction chemotherapy, as is case with non-squamous NSCLC.

We described a case of MPM treated by PMT following cisplatin-based induction chemotherapy, with a complete response and an extremely long progression-free survival. The use of higher total dose of pemetrexed by adopting PMT to avoid cisplatin toxicity could be promising.

The optimization of an induction chemotherapy protocol and histology-specific indication criteria should be validated by phase III trials.

The authors state that they have no Conflict of Interest (COI).

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