



Clinical efficacies of gemcitabine combined with docetaxel single or plus bevacizumab as second-line therapy for malignant pleural mesothelioma

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Background: The aims of this study were to evaluate the clinical efficacies and safety of gemcitabine combined with docetaxel as second-line therapy for malignant pleural mesothelioma (MPM), and to compare the effect of combining with bevacizumab or not.

Methods: A total of 37 MPM patients were collected, among whom 21 patients were treated with chemotherapy alone (group GD), and 16 patients were treated with chemotherapy + bevacizumab (group A + GD).

Results: Of the 37 patients, 23 patients achieved the control of their disease conditions, including 1 case of complete response (CR), 9 cases of partial response (PR), 13 cases of stable disease (SD), and 14 cases of progressive disease (PD). The progression free survival (PFS) time was 4.5 months, and the overall survival (OS) time was 12.0 months. The objective response rates (ORR) in groups GD and A + GD were 23.8% and 31.3%, respectively, $\chi^2=1.255$, $P=0.145$, and the difference was not statistically significant; the disease control rate (DCR) in groups GD and A + GD were 52.4% and 75.0%, respectively, $\chi^2=3.975$, $P=0.044$, and the difference showed statistically significant. PFS in groups GD and A + GD were 4.0 and 5.4 months, respectively, $\chi^2=4.615$, $P=0.032$. OS in group GD and A + GD was 11.3 and 13.6 months, respectively, $\chi^2=4.484$, $P=0.028$. The difference was statistically significant.

Conclusions: For MPM patients, if the disease proceeds after the first-line treatment (pemetrexed combined with platinum), the chemotherapy regimen of gemcitabine combined with docetaxel can be performed for the patients with better PS scores. The addition of bevacizumab can further improve the efficacies, and the adverse reactions can be tolerated.

Keywords: Gemcitabine; docetaxel; bevacizumab; pleural mesothelioma; second-line chemotherapy

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Introduction

Malignant pleural mesothelioma (MPM) is a rare malignant tumor originating from the pleural mesothelial tissue. There are significant differences in its incidence among different countries in the world: the incidence rate in China is about 0.3/100,000 to 0.5/100,000 (1), the incidence rate in the Netherlands is 1/100,000, while that in Australia is up to 4/100,000 (2). Histologically, MPM can be divided into the epithelium type, the sarcoma type, and the mixed type. Due to difficulties in early diagnosis, extremely high invasiveness, and lacking effective treatment, the prognosis is very poor, and the natural survival period is less than 1 year. At present, treatments against advanced MPM are based on pemetrexed combined with platinum-based chemotherapy (3-6), but the effect is not ideal. Until 2016, the three-stage clinical MAPS study of chemotherapy-based combination with bevacizumab, one anti-vascular drug, confirmed that (7) standard pemetrexed combined with cisplatin alone can extend the median survival period from 16.1 to 18.8 months than that combined with bevacizumab. At present, chemotherapy combined with bevacizumab has been written into the NCCN guidelines (8). However, second-line chemotherapy against MPM still has no standard treatment program currently, and the recommended drugs include gemcitabine, vinorelbine, or docetaxel (9-13), which can be used alone or in combination. However, literature data reveal that for patients with better PS scores, the chemotherapy regimen of two-drug combination can achieve better effect than single-drug chemotherapy (12,13). Our study was designed to confirm the efficacies of gemcitabine combined with docetaxel in treating MPM, and to further explore whether the two-drug chemotherapy-based combination with anti-vascular therapy can further improve the efficacies.

Methods

Patient selection and general information

The clinical data of 37 MPM patients treated in the First Affiliated Hospital of Guangzhou Medical University and applied at least two treatment cycles of gemcitabine combined with docetaxel, together with bevacizumab or not, from March 1, 2010 to March 1, 2016 were retrospectively collected. All the patients were clearly diagnosed as MPM (clinical stage IV) by pathologic evidence, and had complete imaging data for efficacy evaluation. The first-line treatment was the standard protocol of pemetrexed combined with

cisplatin or carboplatin. There were 19 males and 18 females, age from 38 to 70 years, with the median age as 52 years. According to the TNM staging system of MPM issued by the Union for International Cancer Control (UICC, seventh edition), all these 37 patients were classified into clinical stage IV (*Table 1*). This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Guangzhou Medical University [No. 2016(26)]. Written informed consent was obtained from all participants.

Grouping

A total of 21 patients were applied the protocol of gemcitabine combined with docetaxel (group GD), and 16 patients were further applied bevacizumab (group A + GD).

Treatment

Medicine include: Gemcitabine (Eli Lilly, USA, registration No. H20110535), Docetaxel (Docetaxel injection, Aventis, UK, registration No. H20090647), and bevacizumab (Avastin, Roche, Switzerland, registration No. JS20100049). The specific medication protocol was as follows: gemcitabine, 1,000 mg/m² iv gtt, days 1-14; docetaxel, 60 mg/m² iv gtt, days 1-14; one treatment course was 28 days; group A + GD: 7.5 mg/kg, days 1-14, until the disease progressed or up to six courses.

Criteria for evaluating efficacies

Referring to the RECIST (v 1.1), the outcomes were divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD); the objective response rate (ORR) = ratio of the patients with CR + PR to the whole patients in the same group; the disease control rate (DCR) = ratio of the patients with CR + PR + SD to the whole patients in the same group. The long-term efficacy mainly recorded the progression free survival (PFS) time, which was the period from the start of applying the second-line medication to the progress or death. The overall survival (OS) time was the period from the start of applying the second-line medication to death or the final follow-up.

Criteria for evaluating adverse reactions

The adverse reactions were graded using the CTCAE

Table 1 Comparison of general information between the two groups

Characteristic	A + GD (n=16) [n (%)]	GD (n=21) [n (%)]
Age (years), median [range]	53 [38–70]	52 [41–69]
Gender		
Male	10 (62.50)	12 (57.14)
Female	6 (37.50)	9 (42.86)
History of contacting asbestos	3 (18.75)	4 (19.05)
Smoking	5 (31.25)	7 (33.33)
Pathological type		
Epithelium	10 (62.50)	15 (71.43)
Sarcoma	2 (12.50)	3 (14.29)
Mixed	4 (25.00)	3 (14.29)
Clinical staging		
Stage IV	16 (100.00)	21 (100.00)
ECOG PS scores		
0	6 (37.50)	8 (38.10)
1	10 (62.50)	13 (61.90)
First-line medication		
Pemetrexed + cisplatin	13 (81.25)	15 (71.43)
Pemetrexed + carboplatin	3 (18.75)	6 (28.57)
Local treatment		
Pleura adhesion fixation	6 (37.50)	9 (42.86)
Palliative chemotherapy	3 (18.75)	4 (19.05)

GD, gemcitabine combined with docetaxel; A, Avastin; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

(version 4.0, grade 0–4). The specific adverse reactions are shown in *Table 2*. No patient occurred adverse reaction-induced withdrawal during treatment. There was no significant difference in the bone marrow suppression, gastrointestinal adverse reactions, fatigue, alanine aminotransferase increase, stomatitis, peripheral neuritis, hair loss, rash, or other common chemotherapy toxicities between the two groups, but the incidence of proteinuria in group GD and A + GD were 14.29% and 50.00%, respectively ($P=0.035$), bleeding in groups GD and A + GD were 14.29% and 43.75%, respectively ($P=0.048$), and hypertension in groups GD and A + GD were 14.29% and 43.75%, respectively ($P=0.048$).

Statistical analysis

SPSS17.0 was used for the statistical analysis, the patients' general information used the descriptive table; Pearson's Chi-Square test was used to treatment efficacies (ORR, DCR) and adverse reactions between the two groups; randomization was stratified according to disease stage, Eastern Cooperative Oncology Group performance status (ECOG PS), sex etc.; the survival analysis used the Kaplan-Meier method, with the test level $\alpha=0.05$.

Results

Evaluation of short-term efficacies

Among the 37 patients, 23 patients achieved the control of their disease conditions, including 1 case of CR, 9 cases of PR, 13 cases of SD, and 14 cases of PD, with ORR as 27.0%, DCR as 62.2%, and PFS as 4.5 months. The OS was 12.0 months. Further analysis showed that the ORR in groups GD and A + GD were 23.8% and 31.3%, respectively, $\chi^2=1.255$, $P=0.145$, and the difference was not statistically significant; the DCR in groups GD and A + GD were 52.4% and 75.0%, respectively, $\chi^2=3.975$, $P=0.044$, and the difference showed statistically significant. The short-term efficacy evaluation is shown in *Table 3*.

Evaluation of long-term efficacies

The long-term efficacy evaluation is shown in *Table 3*. The PFS of the 37 patients was 4.5 months, with OS as 12.0 months. Further analysis showed that the PFS in groups GD and A + GD were 4.0 and 5.4 months, respectively, $\chi^2=4.615$, $P=0.032$, and the difference was statistically significant. The survival curves of the two groups are shown in *Figure 1A*, with the OS as 11.3 and 13.6 months, respectively, $\chi^2=4.484$, $P=0.028$, and the difference was statistically significant. The survival curves are shown in *Figure 1B*.

Evaluation of adverse reactions

The specific adverse reactions are shown in *Table 2*. No patient occurred adverse reaction-induced withdrawal during treatment. There was no significant difference in the bone marrow suppression, gastrointestinal adverse reactions, fatigue, alanine aminotransferase increase, stomatitis, peripheral neuritis, hair loss, rash, or other common chemotherapy toxicities between the two groups, but the incidence of proteinuria in groups GD and A + GD

Table 2 Observation of adverse reactions of second-line GD protocol with/without bevacizumab

Adverse event	A + GD (n=16), grade (%)		GD (n=21), grade (%)	
	0-2	≥3	0-2	≥3
Bone marrow depression				
Leukopenia	31.25	0	38.10	0
Thrombocytopenia	18.75	0	28.57	0
Anemia	31.25	0	28.57	0
Digestive tract responses				
Nausea or vomiting	31.25	0	28.57	0
Diarrhea	6.25	0	14.29	0
Urinary system responses				
Serum creatinine increase	18.75	0	14.29	0
Proteinuria*	50.00	0	14.29	0
Cardiovascular responses				
Hypertension*	43.75	0	14.29	0
Cardiac insufficiency	6.25	0	4.67	0
Bleeding & thrombus				
Hemoptysis or hematuria*	43.75	0	14.29	0
Thrombus	18.75	0	14.29	0
Others				
Fatigue	31.25	0	38.10	0
SGPT increase	31.25	0	28.57	0
Stomatitis	18.75	0	28.57	0
Peripheral neuritis	31.25	0	28.57	0
Hair loss	62.50	31.25	52.38	33.33
Rash	31.25	0	38.10	0

*, P<0.05. GD, gemcitabine combined with docetaxel; A, Avastin; SGPT, serum glutamic pyruvate transaminase.

Table 3 Observation of clinical efficacies of second-line GD protocol with/without bevacizumab

Group	n	CR	PR	SD	PD	ORR (%)	DCR (%)	PFS (months)	OS (months)
A + GD	16	1	4	7	4	31.25	75.0	5.4	13.6
GD	21	0	5	6	10	23.81	52.38	4.0	11.3
χ^2	-	-	-	-	-	1.255	3.975	4.615	4.484
P	-	-	-	-	-	0.145	0.044	0.032	0.028

GD, gemcitabine combined with docetaxel; A, Avastin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival.

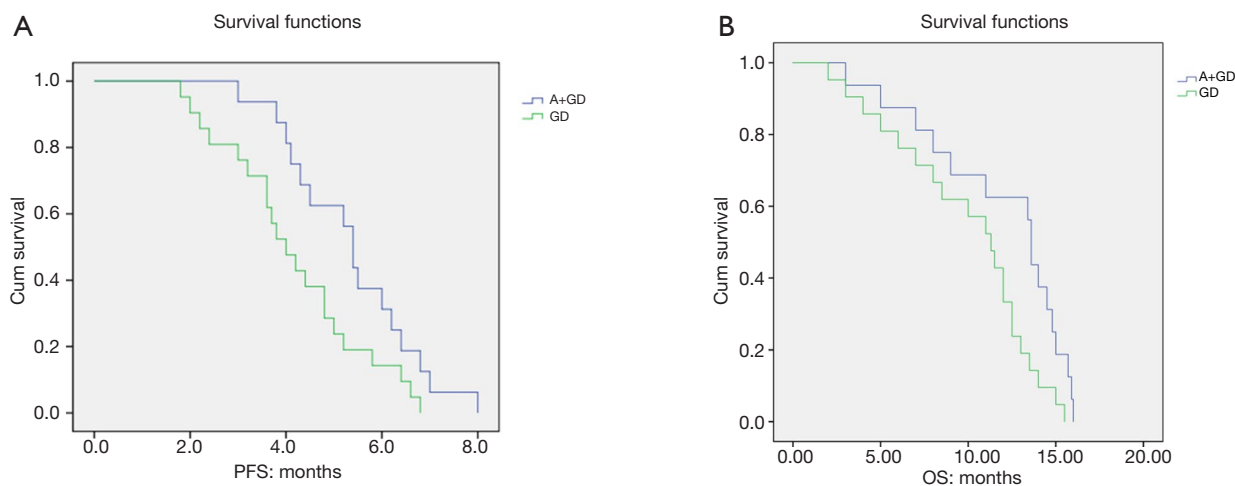


Figure 1 Survival analyses. (A) The PFS in groups GD and A + GD were 4.0 and 5.4 months, respectively, $\chi^2=4.615$, $P=0.032$, and the difference was statistically significant; (B) the OS in groups GD and A + GD were 11.3 and 13.6 months ($P=0.028$), and the difference was statistically significant. A, Avastin; GD, gemcitabine combined with docetaxel; PFS, progression free survival; OS, overall survival.

were 14.29% and 50.00%, respectively ($P=0.035$), bleeding in groups GD and A + GD were 14.29% and 43.75%, respectively ($P=0.048$), and hypertension in groups GD and A + GD were 14.29% and 43.75%, respectively ($P=0.048$).

Discussion

MPM is a rare malignant tumor originating from the pleural mesothelial tissue. Histologically, MPM can be divided into the epithelium type, the sarcoma type, and the mixed type. Due to difficulties in early diagnosis, extremely high invasiveness, and lacking effective treatment, the prognosis is very poor, and the natural survival period is less than 1 year. At present, treatments against advanced MPM are based on pemetrexed combined with platinum-based chemotherapy (3-6), but the effect is not ideal. In 2003, Vogelzang *et al.* (3) reported that the third-stage clinical results of first-line pemetrexed combined with cisplatin or cisplatin alone, the median survival period was extended from 9.3 to 12.1 months, so that the chemotherapy of pemetrexed combined with cisplatin has been confirmed as the first-line standard chemotherapy protocol. However, due to cisplatin's serious toxicities in the digestive tract and kidneys, its clinical applications have been limited to a certain limit. In 2006, Ceresoli *et al.* (4) firstly reported the second-stage clinical results of carboplatin, replacing cisplatin, in treating MPM and considered that pemetrexed combined with carboplatin for MPM has good tolerance, with the median survival time as

12.7 months, and the effect had no significant difference from the standard protocol of pemetrexed combined with cisplatin. Subsequently, Castagneto *et al.* (5) and Katirtzoglou *et al.* (6) also reported the two-stage clinical studies and had obtained the similar results. Therefore, in clinical practice, pemetrexed combined with carboplatin can also be used as the first-line standard protocol, especially for those MPM patients that can't tolerate cisplatin. So far, pemetrexed combined with platinum is still the first-line chemotherapy standard protocol against MPM. Until 2016, the three-stage clinical MAPS study of chemotherapy-based combination with anti-vascular drugs confirmed that (7) standard pemetrexed combined with cisplatin alone can extend the median survival period from 16.1 to 18.8 months than that combined with bevacizumab. Currently, this joint protocol has been widely used as the first-line treatment toward non-operable MPM patients, and has been written into the NCCN guidelines (8). However, there is no standard treatment protocol of second-line chemotherapy for MPM currently, the recommended drugs mainly include gemcitabine, vinorelbine, or docetaxel (9-13), and these drugs can be used singly or combinedly. However, literature data have pointed out that as for the patients with better PS scores, the treatment protocol of combining two chemotherapy drugs can achieve better efficacies than single-drug chemotherapy. For example, Zucali *et al.* (12) reported that the protocol of gemcitabine combined with vinorelbine achieved the results of 2.8-month time to progress (TTP) and 10.9-month OS, and Tourkantonis

et al. (13) reported that the protocol of gemcitabine combined with docetaxel achieved the results of 7-month TTP and 16.2-month OS.

Although the current clinical guidelines (8) recommend that pemetrexed combined with platinum, together with bevacizumab or not, can both be used as a first-line standard protocol for non-operable MPM patients. However, because bevacizumab needs patients to pay their own expense in China, so its first-line applications have been limited. Therefore, the first-line treatment toward all the patients enrolled into our study was pemetrexed combined with cisplatin while no bevacizumab was applied. In addition, some patients were detected the mutation of the epidermal growth factor receptor (*EGFR*) gene, and all the results showed wild-type. Because all the patients had better PS scores (0 to 1 point), we chose the second-line two-drug protocol. The reasons of selecting the protocol of gemcitabine combined with docetaxel were mainly the following aspects: (I) second-line chemotherapy still has no standard treatment protocol, and currently recommended drugs mainly include gemcitabine, vinorelbine, or docetaxel (9-13); (II) although certain literature has reported that vinorelbine has a certain effect as second-line chemotherapy for MPM (9-12), it still needs special treatment because of its vascular toxicity (14), so anti-vascular drugs such as bevacizumab can't be considered shortly after deep vein catheterization (15); therefore, we did not choose vinorelbine; (III) not only Tourkantonis *et al.* (13) once reported that the protocol of gemcitabine combined with docetaxel achieved the results of 7-month TTP and 16.2-month OS, but also Ralli *et al.* (16) also reported in 2009 that the protocol of gemcitabine combined with docetaxel achieved the results of 7-month TTP and 15-month OS. Based on the above reasons, we chose gemcitabine combined with docetaxel as the second-line protocol. Our previous studies (17) have found that for the non-small cell lung cancer patients with *EGFR* mutation, the third-line bevacizumab combined with pemetrexed can significantly increase the efficacies of pemetrexed than pemetrexed alone, as well as can further extend the PFS and OS of late non-small cell lung cancer. Therefore, we believe that the combination of chemotherapy and anti-vascular therapy, even the second-line chemotherapy, can further improve the therapeutic effect of first-line pemetrexed combined with platinum in MPM patients who have not been applied bevacizumab yet. The results of this study show that the effective rates in groups A + GD and GD are 31.25% and 23.81%, respectively, and there is no statistical

significance between the two groups. The disease-control rates are 75.00% and 52.38%, respectively ($P=0.044$), and there exists statistical significance between the two groups. The further observation of long-term efficacies reveals that the PFS in groups A + GD and GD were 4.0 and 5.4 months, respectively ($\chi^2=4.615$, $P=0.032$), and there was significant difference between the two groups. The OS was 11.3 and 13.6 months, respectively ($\chi^2=4.484$, $P=0.028$), and there was significant difference between the two groups. As for the adverse reactions in the two groups, the incidence of proteinuria, hypertension, and bleeding in group A + GD was significantly higher group GD, but no patient was withdrawn due to adverse reactions, consistent with the reports about the adverse effects of bevacizumab in treating MPM (7,18) or other solid tumors (19,20).

Conclusions

In summary, as for advanced MPM, the patients that progress after first-line standard pemetrexed combined with cisplatin and have better PS scores can be applied the second-line protocol of gemcitabine combined with docetaxel. Moreover, our study reveals for the first time that the addition of bevacizumab based on such treatment can further improve the disease control rate and prolong the PFS and OS.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2018.01.05>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was conducted with approval

from the Ethics Committee of Guangzhou Medical University [No. 2016(26)] and written informed consent was obtained from all patients.

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