Pemetrexed plus Carboplatin or Cisplatin as Neoadjuvant Treatment of Operable Malignant Pleural Mesothelioma (MPM)

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Abstract. *Aim: The objective of this study was the retrospective evaluation of tolerability and activity of pemetrexed with carboplatin (AC) or cisplatin (AP) as neoadjuvant chemotherapy in a consecutive series of patients with malignant pleural mesothelioma (MPM). Patients and Methods: Patients with operable MPM received three cycles of AC or AP followed by surgery and radiotherapy. Results: Since 2005, 51 patients have been treated with AC (27) and AP (24). We observed higher incidence of grade 3 anaemia, cumulative grade 2-3 asthenia and worsening of performance status in the AP group. Response to AC and AP were; complete: 4% vs. 0%, partial: 18% vs. 17%, stable disease: 74% vs. 79%, progressive disease: 4%; the resection rate was 81% vs. 79%. Conclusion: AC and AP are active and feasible neoadjuvant regimens. Progression-free survival, response, disease control and resection rate were similar in the two treatment groups. The lower tolerability to AP treatment could impair the clinical condition of patients undergoing surgery.*

Malignant pleural mesothelioma (MPM) is an aggressive tumour with poor prognosis and increasing incidence in industrialized countries; the epidemiological data foresee a sharp rise of MPM incidence and mortality in the next fifteen years because of previous exposure to asbestos fibres (1-3). MPM is highly refractory to systemic treatment, responses are of short duration, and complete responses are rarely observed (4). Therapy using cisplatin/pemetrexed demonstrated higher response rate, overall survival and time-to-progression compared to single-agent cisplatin, and has become the golden standard first-line chemotherapy for MPM (5). Carboplatin is considered a valid option in the systemic treatment of advanced pleural mesothelioma, and several phase II studies with this agent combined with gemcitabine or pemetrexed showed activity and a better toxicity profile compared to cisplatin (6-11). An expanded access program on 1,704 chemo-naive patients with MPM confirmed similar response rates, time-to-progression and one-year survival using carboplatin/pemetrexed and cisplatin/pemetrexed (12).

Extrapleural pneumonectomy (EPP), a surgical procedure introduced in the 1970s which implies *en bloc* resection of the parietal pleurae, lung, ipsilateral pericardium and hemidiaphragm, did not improve the incidence of local and distant recurrences and that was the reason for some centers to conceive combined treatments (13). Successful surgical resection after neoadjuvant chemotherapy in stage III-A lung cancer paved the way for several groups to apply this strategy in MPM, aiming at reducing the incidence of distant relapse. Several clinical trials in this setting showed a response rate higher than 30% and an overall survival longer than 20 months in patients who complete the multimodality treatment (14-20). In 2000, we adopted a tri-modality protocol with carboplatin plus gemcitabine as induction chemotherapy, followed by EPP and adjuvant radiotherapy (14). The protocol was feasible, with an acceptable toxicity profile, and activity data were in line with other studies in the same setting (15-20). From June 2005 to December 2007, we used cisplatin plus pemetrexed as a neoadjuvant regimen within a multicentric phase II trial ongoing at our center (21). After the clinical trial, the standard induction chemotherapy was carboplatin plus pemetrexed. The objective of our study was to retrospectively evaluate the tolerability and activity of pemetrexed plus carboplatin or cisplatin in the first-line treatment of a consecutive series of operable patients with resectable MPM.

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Patients and Methods

This study was fully-approved by the Institutional Ethics Committee, and written informed consent was obtained from all patients before beginning chemotherapy.

This is a retrospective review of all patients prospectively evaluated for trimodality therapy between June 2005 and December 2009 at our Institution. A multidisciplinary team composed of a medical oncologist, thoracic surgeon and radiotherapist evaluated all the patients to assess the indication for a multimodal treatment. Eligibility criteria for trimodality treatment were histologically-confirmed diagnosis of MPM; International Mesothelioma Interest Group (IMIG) stage I to III; Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1; adequate bone marrow, hepatic and renal function (calculated creatinine clearance by Cockroft and Gault ≥45 ml/min); measurable disease according to modified Response Evaluation Criteria in Solid Tumor (RECIST) criteria for MPM (22). Baseline staging and re-assessment after the induction treatment was performed with computerized tomography (CT) scan and positron emission tomography (PET)-CT.

Video-assisted thoracoscopic surgery was performed with multiple pleural biopsies and, if indicated, chemical pleurodesis. Mediastinoscopy was performed in cases with radiological suspicion of lymphnode involvement in the contralateral mediastinum.

Patients underwent cardiological assessment and cardio-pulmonary function tests such as spirometry, diffusing capacity of the lung for carbon monoxide (DLCO), blood gas analysis, pulmonary scintigraphy and ergometric tests. Pneumonectomy was not contraindicated according to the British Thoracic Society (BTS) (23). Patients received three cycles of pemetrexed at 500 mg/m^2 and carboplatin (AC) at an area under the concentration time curve (AUC) 5, or cisplatin (AP) at 75 mg/m^2, on day 1 every three weeks. Standard pre-medication for pemetrexed was prescribed. Pemetrexed plus cisplatin was administered from June 2005 to December 2007 according to a clinical trial ongoing at our Center (21); from December 2007 to December 2009, pemetrexed plus carboplatin was the standard induction regimen.

In cases of complete or partial response or stable disease, surgery was performed between 5-8 weeks after the last chemotherapy cycle. EPP consisted of *en-bloc* removal of the pleura, lung, diaphragm, and pericardium. The prosthesis replacement was accomplished in all patients by the Gore-Tex® patch for the pericardium and of Dual Mesh Gore-Tex® patch for the diaphragm. Systematic hilar and mediastinal lymphadenectomy was performed. Pleurectomy/decortication removed the involved pleura and made the underlying lung free to expand and fill the pleural cavity. We defined a complete resection as a resection of all tumoral lesions without macroscopic residues.

Patients who underwent EPP received adjuvant radiotherapy within 8 weeks after surgery. A total dose of 50.4 Gy in 28 fractions (1.8 Gy/fraction) was administered to the whole hemi-thorax and all the surgical incisions with two opposed shielded fields technique, sparing organs at risk. Patients who underwent pleurectomy/decortication received radiotherapy (21 Gy/3 fractions) to the surgical scar.

Radiological response rate was assessed according to modified RECIST criteria for mesothelioma. Haematological and non-haematological toxicity was assessed according to Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (24).

Progression-free survival (PFS) was assessed from the date of the first cycle to the earliest sign of disease progression or death from any cause.

Overall survival (OS) was assessed from the date of the first cycle until death from any cause. The resection rate (RR) was defined as the proportion of completely resected tumors as determined by a surgeon and a pathologist (R0 or R1).

Statistical analysis. Actuarial PFS and OS curves were designed using the Kaplan Meier method. Differences in survival were tested for significance by the log-rank test. Multivariate analysis was performed by the Cox regression proportional hazard model, where overall survival was analysed according to treatment (AC *vs*. AP), ECOG PS (0 *vs*. 1), age (< *vs*. ≥ 70 years), gender (male *vs*. female), histology (epithelioid *vs*. non-epithelioid), IMIG stage (I-II *vs*. III), EORTC prognostic score (good *vs*. poor) (25).

Results

From 2005, 51 patients were included in the study, 27 treated with AC and 24 with AP (Figure 1). There were more males in the AP group and more patients with stage III in AC group (Table I).

Haematological toxicity was recorded for all patients in each group. Toxicity profiles by patient in the intention-to-treat population showed a higher incidence of grade 3 anaemia in the AP (13%) compared to the AC (4%) group, while grade 3 thrombocytopenia was slightly higher in the AC (7%) *vs*. the AP (4%) group. No grade 4 haematological toxicity was observed in the two sub-populations (Table II). Febrile neutropenia occurred in one patient in the AP group, occasional epistaxis in two patients treated with carboplatin.

No grade 4 non-haematological toxicity was shown, grade 3 diarrhøea (4%) and asthenia (4%) were reported in the AC and AP cohorts respectively. Grade 2 nausea, vomiting and asthenia were more common in patients treated with cisplatin compared to the group who received carboplatin (Table III). Moreover, we observed neurotoxicity in one (4%) patient treated with cisplatin.

Chemotherapy dose reduction was applied to two (8%) patients in the AP arm, because of hypercreatininaemia and febrile neutropenia respectively.

Furthermore, we assessed cumulative non-haematological toxicity and ECOG PS impairment during chemotherapy. We observed that cumulative grade 2-3 asthenia was commoner in the AP (21%) than in the AC (7%) subpopulation. Worsening of PS occurred in 29% and 17% of patients treated with AP and AC, respectively.

Response assessment after induction chemotherapy with carboplatin and cisplatin respectively showed one (4%) *vs*. 0 (0%) complete responses (CR); 5 (18%) *vs*. 4 (17%) partial responses (PR); 20 (74%) *vs*. 19 (79%) cases of stable disease (SD) and one case (4%) with progressive disease (PD) in both subgroups. The response rate was 22% *vs*. 17% in the AC and AP groups, respectively; the disease control rate was 96% in

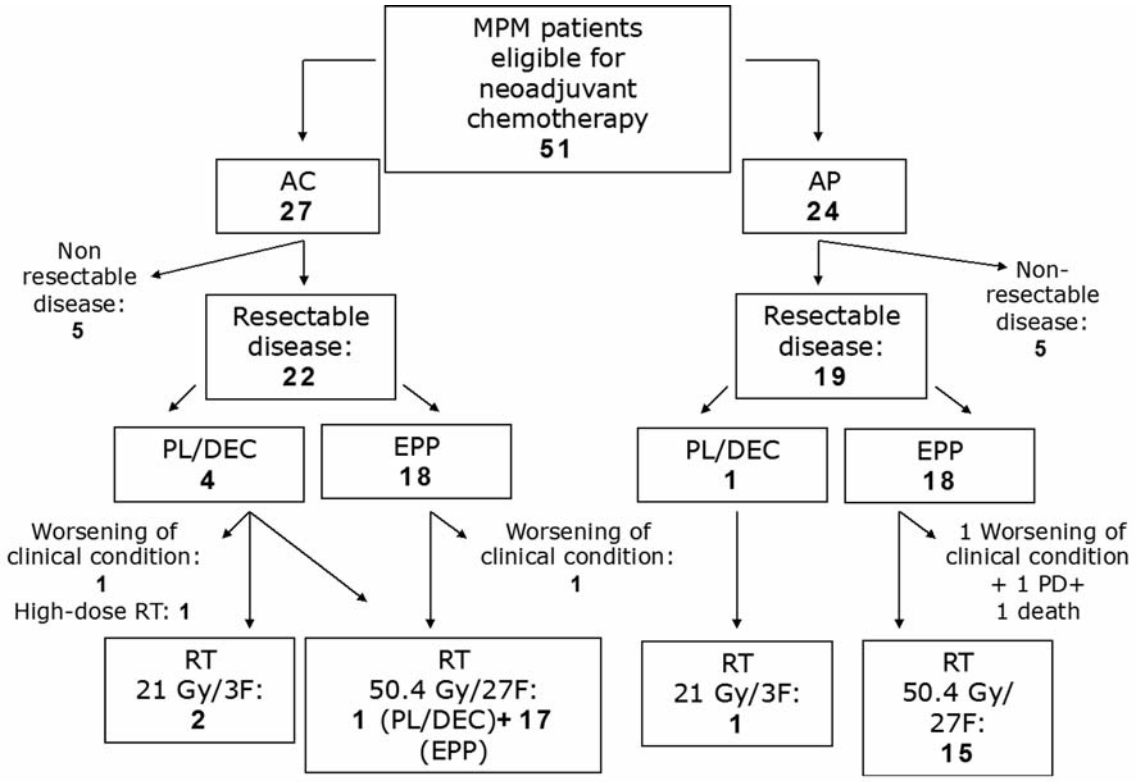

Figure 1. *Study design. PD: Progressive disease; PL/DEC: pleurectomy/decortication; EPP: extrapleural pneumonectomy; RT: radiotherapy; F: fractions; AC: pemetrexed/carboplatin; AP: pemetrexed/cisplatin.*

both treatment groups. The RR was 81% compared to 79% in patients treated with AC and AP, respectively.

Among the 22 operable patients in the AC group, 18 underwent EPP and four pleurectomy/decortication. In the AP group, surgery consisted of 18 EPPs and one pleurectomy/decortication. One (4%) patient in the AP group died postoperatively (day 16), subsequently to acute endocarditis. Patients who underwent EPP received adjuvant radiotherapy (50.4 Gy/28 fractions) to the hemithorax in 17 (63%) and 15 (83%) cases in the AC and AP group, respectively. The main reasons for reducing dose or not administering radiotherapy were worsening of clinical condition and progressive disease at the time of radiotherapy assessment. After pleurectomy/decortication, two (50%) patients in the AC group and one (100%) in the AP group received radiotherapy 21 Gy/3 fractions to the surgical scar. Among patients in the AC group, one received 50.4 Gy/28 fractions because of pathological findings of mediastinal lymph node involvement and another patient did not receive radiotherapy because of their poor clinical condition.

The median PFS was not significantly different (p=0.204) in patients treated with AC (63 weeks) *vs*. those treated with AP (57 weeks) (Figure 2).

The median OS was higher for patients treated with AC 111 weeks for than for patients treated with AC 66 weeks (p=0.013) (Figure 3).

Different factors could explain survival data, for example, a larger number of female the patients with epithelioid histology and a good prognostic score in the AC group (Table I).

When we analyzed patients' features, histology had a significant impact on OS in the univariate analysis (p=0.006). The median OS of patients affected by epithelioid mesothelioma was 111 weeks, compared to 48 weeks for non-epithelioid mesothelioma (data not shown).

The multivariate analysis confirmed that non-epithelioid histology (p=0.048; hazard ratios=2.682; confidence interval CI 95%=1.010-7.124; standard error=0.498) was significantly associated with a worse outcome, whereas ECOG PS, EORTC prognostic score, age, gender and stage were not significant.

When we considered the impact of treatment for epithelioid mesothelioma on patient outcome, no difference in terms of OS was observed between the two subgroups (AC: 117 weeks *vs*. AP 82 weeks; p=0.054) (Figure 4). We observed a trend towards a longer overall

Table I. *Patients' characteristics*.

First-line chemotherapy	AC (n=27)	AP (n=24)
Median age, years (range)	63(43-75)	64(40-75)
Gender		
Male	18 (67%)	20 (83%)
Female	9 (33%)	4 (17%)
PS		
0	5 (19%)	7 (29%)
1	22 (81%)	17 (71%)
Stage at diagnosis		
I	3 (11%)	4 (16%)
II	5 (19%)	10 (42%)
III	19 (70%)	10 (42%)
EORTC prognostic score		
Poor	9 (33%)	10 (42%)
Good	18 (67%)	14 (58%)
Histology		
Epithelioid	21 (78%)	17 (71%)
Sarcomatoid	4 (15%)	5 (21%)
Biphasic	2 (7%)	2 (8%)

PS: Performance Status; AC: pemetrexed/carboplatin; AP: pemetrexed/cisplatin.

Table II. *Haematological toxicity by patient in the intention-to-treat population according to common toxicity criteria for adverse events version 3.0*.

Toxicity	AC (%)	AP (%)
Leucopenia		
G1	14 (52)	16 (67)
G2	10 (37)	10 (42)
G3	2 (7)	2 (8)
G4	0 (0)	0 (0)
Neutropenia		
G1	14 (44)	7 (29)
G2	10 (37)	7 (29)
G3	3 (11)	4 (17)
G4	0 (0)	0 (0)
Anaemia		
G1	19 (70)	17 (71)
G2	4 (15)	5 (21)
G3	1 (4)	3 (13)
G4	0 (0)	0 (0)
Thrombocytopenia		
G1	11 (41)	6 (25)
G2	4 (15)	1 (4)
G3	2 (7)	1 (4)
G4	0 (0)	0 (0)

AC: Pemetrexed/carboplatin; AP: pemetrexed/cisplatin.

survival in the AC compared to the AP group for the subgroup of elderly patients (>70 years) (p=0.064, data not shown), although median survival was not reached in patients treated with AC.

Table III. *Non-haematological toxicity by patient in the intention-to-treat population according to common toxicity criteria for adverse events version 3.0*.

Toxicity	AC (%)	AP (%)
Nausea		
G1	6 (22)	9 (38)
G2	2 (7)	7 (29)
G3	0 (0)	0 (0)
G4	0 (0)	0 (0)
Vomiting		
G1	2 (7)	2 (8)
G2	1 (4)	2 (8)
G3	0 (0)	0 (0)
G4	0 (0)	0 (0)
Asthenia		
G1	7 (26)	2 (8)
G2	2 (7)	4 (17)
G3	0 (0)	1 (4)
G4	0 (0)	0 (0)
Anorexia		
G1	2 (7)	5 (21)
G2	0 (0)	1 (4)
G3	0 (0)	0 (0)
G4	0 (0)	0 (0)
Constipation		
G1	4 (15)	4 (17)
G2	1 (4)	0 (0)
G3	0 (0)	0 (0)
G4	0 (0)	0 (0)
Diarrhøea		
G1	0 (0)	0 (0)
G2	0 (0)	0 (0)
G3	1 (4)	0 (0)
G4	0 (0)	0 (0)

AC: Pemetrexed/carboplatin; AP: pemetrexed/cisplatin.

Different treatments other than chemotherapy could have an impact on patient prognosis; in fact, we performed a higher number of pleurectomies/decortications in the AC group (18%) compared to the AP group (5%). Furthermore, second-line treatment after disease progression was administered to 58% of the patients in the AC group and to 37% in the AP group.

Discussion

Treatment of MPM is still a matter of debate and clinical trials are currently ongoing to define the best option of care.

Platinum-based chemotherapy plus gemcitabine or pemetrexed for 3-4 cycles, followed by surgery and postoperative high-dose radiotherapy demonstrated the best results in terms of OS and PFS (14-20). Multimodal treatment time is long, and remarkable clinical and psychological distress at the end of this invasive approach was shown; this

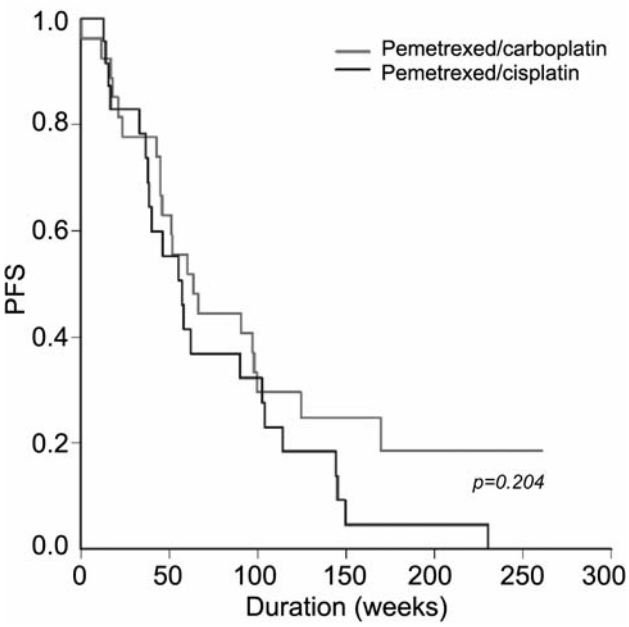

Figure 2. *Median progression free-survival (PFS) in patients treated with pemetrexed/carboplatin and with pemetrexed/cisplatin.*

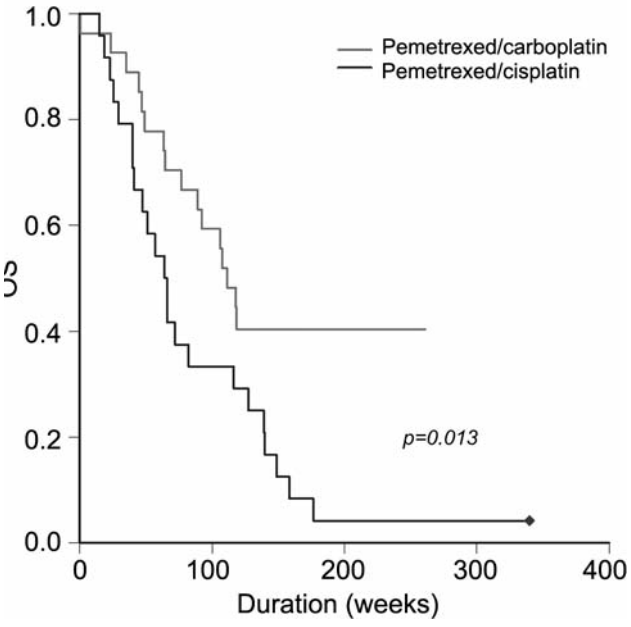

Figure 3. *Median overall survival (OS) of patients treated with pemetrexed/carboplatin and with pemetrexed/cisplatin.*

is the reason to look for stronger evidence of the benefits of this approach. Recent results from the Mesothelioma and Radical Surgery (MARS) trial showed that EPP offers no benefit compared to no radical surgery in terms of OS and PFS, with a considerable rate of perioperative morbidity and mortality, worse quality of life and higher incidence of serious adverse events (26). Although several limitations affected the MARS trial (small number of patients, heterogeneity of chemotherapy regimens), the specific trial raised the issue of a less invasive approach as a suitable treatment for patients with MPM. These results are supported by previous data by Flores *et al*. on a consecutive series of more than 600 patients, where different outcomes between EPP and pleurectomy/decortication were investigated. Results showed a longer survival when patients underwent pleurectomy/ decortication compared to EPP (27), although the study was unable to draw a definitive conclusion regarding the best surgical approach. To date, no randomized prospective clinical trial to define the best chemotherapy regimen in the neoadjuvant setting has been performed. Carboplatin is often preferred to cisplatin in the systemic treatment of cancer because it has a lower incidence of neurotoxicity, nephrotoxicity, nausea and vomiting (28). The poor clinical condition of patients with MPM underlines the need for a well-tolerated chemotherapy regimen which preserves good quality of life and performance status, especially in elderly people. When carboplatin substituted cisplatin in patients not eligible for surgery, comparable

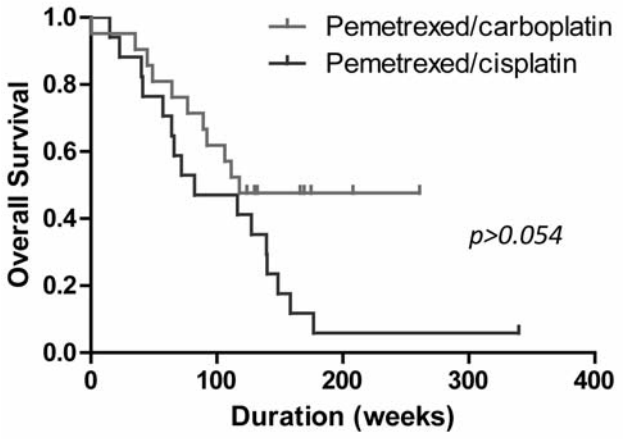

Figure 4. *Median overall survival in patients affected by epithelioid mesothelioma, treated with pemetrexed/cisplatin and pemetrexed/carboplatin.*

results in terms of disease control rate, time-to-disease progression, and OS were found, with no severe non-haematological toxicities and acceptable haematological toxicity rates (6-8). On the basis of the promising results with carboplatin plus gemcitabine in the treatment of unresectable MPM (6), we explored the feasibility of the same protocol in the neoadjuvant setting (14). In that prospective trial, patients who showed disease control after three to four cycles of

chemotherapy with carboplatin/gemcitabine, underwent EPP and postoperative radiotherapy. We recorded a response rate of 33.3% and a disease control rate of 100%; 81% of the study population underwent surgery, while 71% completed the entire trimodality protocol. With appropriate caution in the comparison of different studies, in the present study, both treatment groups showed lower disease control (96% in both groups) and response rate (22% AC; 17% AP), while the RR was in line with previous results (81% AC; 79% AP). Significantly, a higher proportion of patients in the AC group completed the trimodality protocol (74%) compared to patients who received cisplatin (67%). Furthermore, no postoperative morbidity was observed in the previous study and in the group treated with AC, while one (4%) patient in the AP group experienced an acute adverse event and died within two weeks from surgery. These data confirm that a front-line chemotherapy with an acceptable toxicity profile is preferable in the context of a combined approach to prevent impaired clinical conditions after induction treatments. In the current study, with induction carboplatin/gemcitabine, the median time-to-relapse was 16.3 months; AC and AP led to similar PFS (15.7 *vs*. 14 months). The median OS of patients treated with AC (27.7 months) seems in line with survival data of patients who received carboplatin/gemcitabine as induction treatment (25.5 months). The shorter OS in AP group is probably the consequence of a bias due to patients' features (non-epithelioid histology, male gender) and treatments other than chemotherapy (surgical procedure, second-line treatments).

Some of the previous studies of trimodality treatment (14, 17) did not include patients with sarcomatoid histology; in the present study, histology was confirmed as the most important factor influencing patient outcome, and when we analyzed the effect of different treatment schedules on epithelioid MPM, no difference in survival was shown in patients treated with carboplatin *vs*. cisplatin.

Should histology be considered as a selection criteria for trimodality treatment?

In the light of toxicity data of the present study, we believe that the tolerability of drugs administered in the induction phase of a trimodality protocol has its own weight in the successful completion of such an approach. We underline the higher non-haematological toxicity of cisplatin compared to carboplatin, with particular reference to grade 2 nausea, vomiting and asthenia, cumulative grade 2-3 asthenia and worsening of ECOG PS at the last cycle of chemotherapy, for the same PFS, response, disease control and RR. Furthermore, in the AP group, we registered dose reductions in 8% of the patients because of febrile neutropenia and hypercreatininaemia, whereas in the AC group, no dosage reduction was observed. The only case of postoperative mortality occurred in the group of patients treated with cisplatin, due to one case of fatal endocarditis.

On the basis of our results and on recent evidence by other groups (29), we believe that there is a role for pemetrexed plus carboplatin in the neoadjuvant setting; in particular, in elderly patients or patients presenting comorbidities or slightly impaired PS, when surgery may be an option. Prospective randomized trials are required to define the best induction chemotherapy regimen, with particular interest to tolerability, perioperative complications and completion of the entire care pathway.

In the wake of Flores *et al*.'s surgical results (27), where pleurectomy/decortication was better than a more complex resection (EPP), our study also suggests that a 'gentler' approach (pemetrexed plus carboplatin rather than cisplatin) could be better as neoadjuvant chemotherapy of MPM.

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