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A Retrospective Study of Palliative Cisplatin-Based Doublet Chemotherapy for Malignant Pleural Mesothelioma

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Abstract

Objectives: Cisplatin-based doublet-chemotherapy is the standard palliative treatment for malignant pleural mesothelioma (MPM) supplemented with palliative radiotherapy when indicated by symptoms. This work aims to study the epidemiologic characteristics and overall survival rates of patients with MPM treated with palliative chemotherapy in one institution year 2000 - 2010.

Materials and Methods: Review of journals. Data were structured using the Aarhus Lung Cancer Register and statistics were analyzed using SPSS software.

Results: The median age of the 80 patients (70 males and 10 females) at diagnosis was 63 years (range 40-80). 46% of the patients had epithelioid histological subtype. As first line treatment 21 patients received cisplatin/vinorelbine iv., 29 patients received cisplatin/pemetrexed and 11 patients received pemetrexed as monotherapy. Median overall survival (mOS) for the whole group was 13.1 months (95% CI 10.1-16.2). We found no significant difference in mOS between patients treated with cisplatin/vinorelbine (mOS 17.0 months, 95% CI 12.6-21.4) and cisplatin/pemetrexed (mOS 14.0 months, 95% CI 8.9-19.1), p=0.598. Patients with epithelioid subtype had a significantly better mOS (15.2 months, 95% CI 11.6-18.8) compared to patients with non-epithelioid subtype (8.9 months, 95% CI 5.6-12.2), p=0.026.

Conclusion: Subtype of histology is significantly associated with survival in MPM. Patients with epithelioid histology have a better prognosis than patients with non-epithelioid subtype. Our results show no significant difference in overall survival in patients who received different cisplatin-based doublet-regimes. The survival rates in this retrospective study are comparable to other published data. Randomized trials exploring cisplatin-based doublet regimens like cisplatin/pemetrexed and cisplatin/vinorelbine po. are needed.

Keywords: malignant pleural mesothelioma, palliative chemotherapy, palliative radiotherapy, cisplatin, pemetrexed, vinorelbine

1. Introduction

Malignant Pleural Mesothelioma (MPM) is a rare but highly aggressive cancer with a poor prognosis. In Europe approx. 5000 new cases occur yearly, probably resulting in more than 250.000 deaths over the next 40 years (Peto, Decarli, La Vecchia, Levi, & Negri, 1999). MPM is associated with exposure to asbestos (Carbone, Kratzke, & Testa, 2002). The success of curatively intended trimodality therapy, which includes major surgery (extrapleural pneumonectomy, EPP) combined with neoadjuvant chemotherapy and adjuvant radiotherapy, is limited, and is therefore only recommended for a highly selected group of patients. Pleurectomy/decortication (P/D) is another surgical treatment option that seems to improve survival (Kaufman & Flores, 2011; Stahel, Weder, Lievens, Felip, & ESMO Guidelines Working Group, 2010). As a result of these circumstances the majority of patients with MPM are treated with palliative chemotherapy and radiotherapy. Cisplatin, pemetrexed and vinorelbine are some of the previously studied chemotherapeutics in MPM. Other active drugs include raltitrexed and gemcitabine (Ellis et al., 2006; Tsao, Wistuba, Roth, & Kindler, 2009). Cisplatin acts by interaction with DNA and forms DNA adducts, primarily intrastrand crosslink adducts leading to apoptosis. Pemetrexed is a multitargeted antifolate that inhibits thymidylate synthase, glycinamide ribonucleotide formyltransferase and dihydrofolate reductase, which leads to inhibition of the synthesis of thymidine and purine nucleotides. Vinorelbine is a semisynthetic vinca alkaloide synthetized on the basis of Catharanthus Roseus. The

drug acts primarily by interaction with microtubule dynamics, which leads to mitotic arrest or cell death. Among others, older age, poor performance status, male gender and non-epithelioid subtype are found to be poor prognostic factors (Edwards et al., 2000; Nojiri et al., 2011).

Due to the relatively small number of patients diagnosed with MPM, only few randomized trials concerning palliative chemotherapy exists. Combination chemotherapy have been reported having higher response rates than single agent therapy, and platinum-containing regimes had better outcomes compared to non-platinum containing regimes (Ellis et al., 2006; Porpodis et al., 2013). A landmark randomized phase III trial (n = 456) by Vogelzang et al. demonstrated that the combination of cisplatin and pemetrexed was superior to cisplatin alone when given to chemotherapy-naïve patients with MPM (mOS 12.1 months vs. 9.3 months, p= 0.020, response rate 41.3% vs. 16.7%) (Vogelzang et al., 2003). This platinum-based doublet-regime is now established as the standard-of-care frontline regime against which other frontline regimes are evaluated. The combination cisplatin/vinorelbine iv. has been studied in a phase II study, where a mOS of 16.8 months (range 0.5-46.4+) and a response rate of 29.8% was determined (Sorensen, Frank, & Palshof, 2008). As second line treatment, monotherapy with vinorelbine is an option based on a study finding the drug moderately active and with acceptable toxicities (Stebbing et al., 2009).

The aim of this retrospective study is to explore the tumor and patient characteristics and survival rates related to type of treatment in a cohort of patients with inoperable MPM referred to Aarhus University Hospital in Denmark year 2000-2010. Our hypothesis is that the median overall survival rates are comparable for the two cisplatin-based doublet-regimens explored in this study. We also expect older age, male gender and non-epithelioid histology to be significant factors of poor prognosis.

2. Materials and Methods

At the Department of Oncology at Aarhus University Hospital (Denmark) the standard first line palliative chemotherapy until 2007 was cisplatin (100mg/m^2 every 4 weeks) and vinorelbine (25mg/m^2 iv. given weekly). The standard first line treatment after 2007 has been cisplatin (75mg/m^2 every 3 weeks) and pemetrexed (500mg/m^2 every 3 weeks supplemented with folic acid and vitamin B-12). Patients with contraindications for cisplatin were treated with pemetrexed (500mg/m^2 every 3 weeks) as monotherapy in first line. Monotherapy with vinorelbine (25mg/m^2 iv. given weekly or 60/80mg/m^2 po. day 1 and 8) was used as second line treatment, alternatively pemetrexed (500mg/m^2 every 3 weeks) if the patient was unexposed to this drug. If severe thoracic pain or symptoms of airway compression was conspicuous, palliative radiotherapy (20 Gy/4 fractions, 15 Gy/3 fx or 8 Gy/1 fx) was offered prior to or concomitant with the initiation of palliative chemotherapy.

A total of 80 consecutive patients diagnosed with inoperable malignant pleural mesothelioma, who referred to Department of Oncology at Aarhus University Hospital for palliative treatment in the period 2000 and 2010, were reviewed. Disease stage was classified according to the Staging Manual in Thoracic Oncology 2009 by IASLC. Response to treatment and subsequent determination of disease control rate (complete response + partial response + stable disease) and response rate (complete response + partial response) was based upon the author's review of the imaging reports using the modified RECIST criteria for response to treatment in MPM (Byrne & Nowak, 2004). The survival period was determined from the date of diagnosis confirmed by the pathologist until the date of death or April 11, 2013. Survival time was estimated using the Kaplan-Meier method, and log-rank test was used to compare survival between groups. A univariate Cox proportional hazards regression analysis was performed for each factor.

Data were structured using the Aarhus Lung Cancer Register and were analyzed using IBM® SPSS® Statistics software version 21.0 for Windows.

3. Results

Baseline characteristics for the 80 included patients are listed in Table 1. The majority were males (88%) and the median age at diagnosis was 63 (range 40-80). The most frequent histological subtype was epithelioid (46%). Most patients had an advanced stage of disease (39% in stage IV). The majority were in good performance status (PS). 48% of the patients didn't have any comorbidity at all, and 16% had 2 comorbidities or more. The most frequent type of comorbidity was cardiovascular disease. 7.5% had cancer previously.

Table 1. Baseline patient and tumor characteristics for all patients

Patients and tumor characteristics (all patients) N = 80	
Median age at diagnosis (range)	63 (40-80)
Gender (male/female)	80 (70/10)
Histology	
Epithelioid	37 (46%)
Sarcomatoid	14 (17%)
Biphasic	23 (30%)
Subtype not specified	6 (7%)
Stage	
I	15 (19%)
II	12 (15%)
III	21 (26%)
IV	31 (39%)
Unknown	1
Performance status at first line treatment	
0	25 (31%)
1	41 (51%)
2	7 (9%)
3	1 (1%)
Unknown	6 (8%)
Performance status at second line treatment	
0	4 (12%)
1	24 (71%)
2	5 (15%)
3	1 (3%)
Unknown	0
Comorbidities (number)	
0	38 (48%)
1	29 (36%)
≥2	13 (16%)
Comobidity (type)	
COPD	4 (5%)
Cardiovascular	22 (27.5%)
Diabetes Mellitus	3 (4%)
Previous Cancer	6 (7.5%)
Cerebrovascular	4 (5%)
Others	18 (22.5%)

COPD: Chronic Obstructive Pulmonary Disease.

Cisplatin and vinorelbine was given to 21 patients and cisplatin and pemetrexed was given to 29 patients as the first palliative treatment. 14 patients received pemetrexed as monotherapy in first line (Table 2). None of the patients underwent surgery for MPM. Of the 11 patients who received palliative radiotherapy as first treatment, only 2 patients were treated with doublet chemotherapy afterwards. 20 Gy in 4 fractions was given to 5 patients as first treatment. The remaining 6 patients who received palliative radiotherapy as first treatment received other palliative radiation doses. The most common clinical indication for giving palliative radiotherapy was thoracic

pain (5 out of 11 patients). 34 patients received second line treatment, predominately palliative radiotherapy (Table 2). Also for this group of patients, 20 Gy in 4 fractions was the most frequently used fractionation and thoracic pain was the most common symptom.

Table 2. Type of palliative treatment in first and second line

Palliative treatment	First treatment	Second treatment
Cisplatin/vinorelbine	21	1 (1^{+})
Cisplatin/pemetrexed	29	1 (1^{+})
Pemetrexed	14	10 (1^{+})
Vinorelbine	0	2
Palliative radiotherapy	11	20
Patients treated	75	34
No treatment	5	46

$^{+}$: Given after palliative radiotherapy in first line

The patient and tumor characteristics, categorized by type of treatment, are listed in Table 3. The group who received pemetrexed as monotherapy were generally elderly (median age 75) and had a lower WHO performance status than the patients who received combination chemotherapy. The distribution of histological subtypes in the groups treated with cisplatin/pemetrexed or cisplatin/vinorelbine was significantly uneven, as more patients with a non-epithelioid histology were present in the cisplantin/pemetrexed group (69% vs. 33%, p=0.021). There was also a higher frequency of patients with advanced disease in the cisplatin/pemetrexed group than in the cisplatin/vinorelbine group (72% vs. 48%) although not reaching statistically significance (p=0.087).

Table 3. Patient and tumor characteristics according to type of 1st line treatment

	Cisplatin/Pemetrexed (n=29)	Cisplatin/Vinorelbine (n=21)	p-value	Pemetrexed (n=14)	Radiotherapy (n=11)
Median age (range)	63 (41-78)	62 (64-73)		75 (53-80)	63 (48-80)
≤70	23 (79%)	19 (90%)	0.168		7
>70	6 (21%)	2 (10%)	0.441		4
Male	25 (86%)	19 (90%)	1.0	12	10
Female	4 (14%)	2 (10%)		2	1
PS 0	16 (55%)	7 (33%)	0.158	1 (7%)	1 (9%)
PS ≥ 1	13 (45%)	14 (67%)		10 (71%)	5 (45%)
PS ≥ 2				3 (21%)	4 (36%)
Unknown					1 (9%)
Epithelioid	9 (31%)	14 (67%)	0.021	6 (43%)	5 (45%)
Non-epithelioid	20 (69%)	7 (33%)		8 (57%)	6 (55%)
Stage			0.087		
I or II	8 (28%)	11 (52%)		4 (29%)	3 (27%)
III or IV	21 (72%)	10 (48%)		10 (71%)	8 (73%)
Comorbidity (number)			0.093		
0	12 (41%)	14 (67%)		3 (21%)	8 (73%)
≥ 1	17 (59%)	7 (33%)		11 (79%)	3 (27%)
Full dose	18 (62%)	7 (33%)	0.085		
Reduced dose	11 (40%)	14 (67%)			

P-values were calculated using two-sided Fisher's exact test (Wilcoxon's signed-rank test was used for age). PS: Performance status. NOS: Non-otherwise specified.

The median overall survival (mOS) for the whole cohort was 13.1 months (95% confidence interval (CI) 10.1-16.2). The mOS estimates with regard to the type of first line chemotherapy reveals no significantly difference between the two cisplatin-based doublet regimens. The group treated with cisplatin/pemetrexed: had a mOS of 14.0 months (CI 8.9-19.1) compared to 17.0 months (CI 12.6-21.4) for patients in the group treated with cisplatin/vinorelbine, p = 0.598 (Figure 1). No statistically significant difference in mOS either occurred if the survival analysis were based on the time from of referral to the Department of Oncology or "date of first treatment" to death (data not shown). Disease control rate (DCR) (complete response + partial response + stable disease) was 59% for patients treated with cisplatin/pemetrexed and 48% for patients treated with cisplatin/vinorelbine. However, the difference was not statistically significant, p=0.388. Response rates (complete response + partial response) were 28.6% and 17% respectively, also not reaching statistically significance, p=0.712. The 14 patients who were treated with pemetrexed as monotherapy in first line had a mOS of 7.5 months (CI 4.1-10.8), and the 11 patients who received radiotherapy as the first treatment had a mOS of 13.5 months (CI 2.6-24.4). Only 3 of these patients were offered palliative chemotherapy afterwards (Table 2). The group of patients with epithelioid subtype had a mOS of 15.2 months (CI 11.6-18.8) in contrast to the group with non-epithelioid subtype (biphasic + sarcomatoid + subtype not specified) whose mOS was 8.9 months (CI 5.6-12.2). This result was statistically significant, p=0.026 (Figure 2). Non-epithelioid subtype was associated with statistically significant HR of 1.779 (p=0.028) in the univariate analysis, but no significant hazard ratios were found for any of the other potential prognostic factors (Table 4).

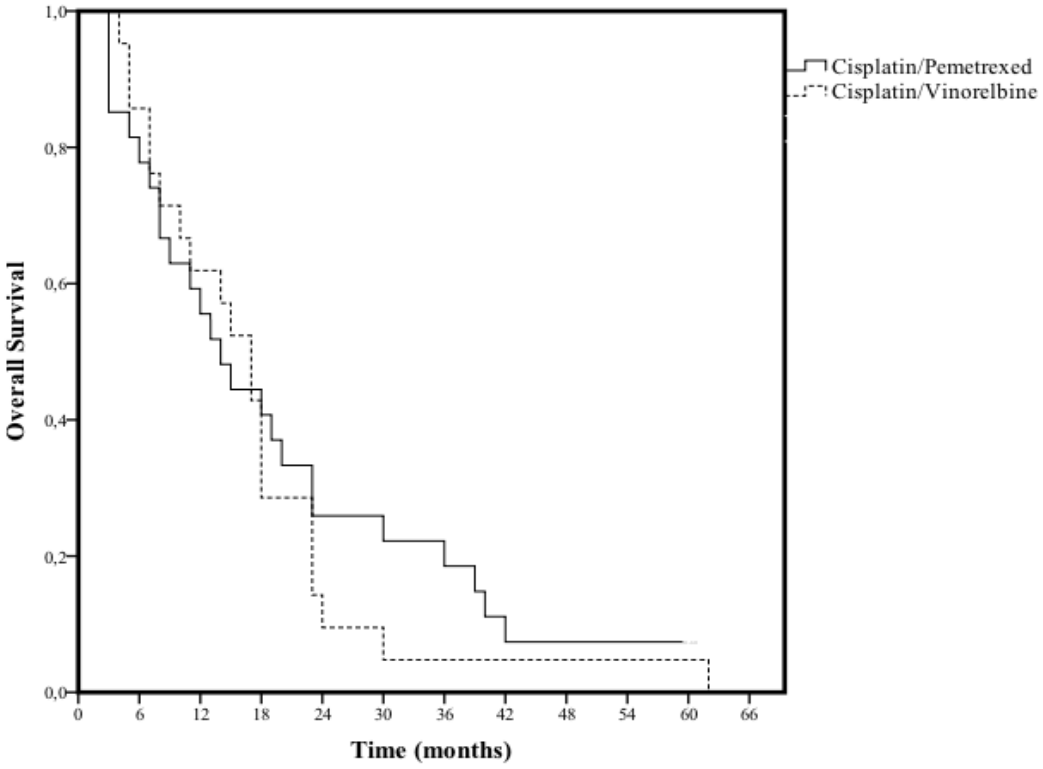

Figure 1. Kaplan-Meier survival curves of patients treated with cisplatin/pemetrexed (n=21) or cisplatin/vinorelbine (n=29) as first line palliative chemotherapy (p=0.598)

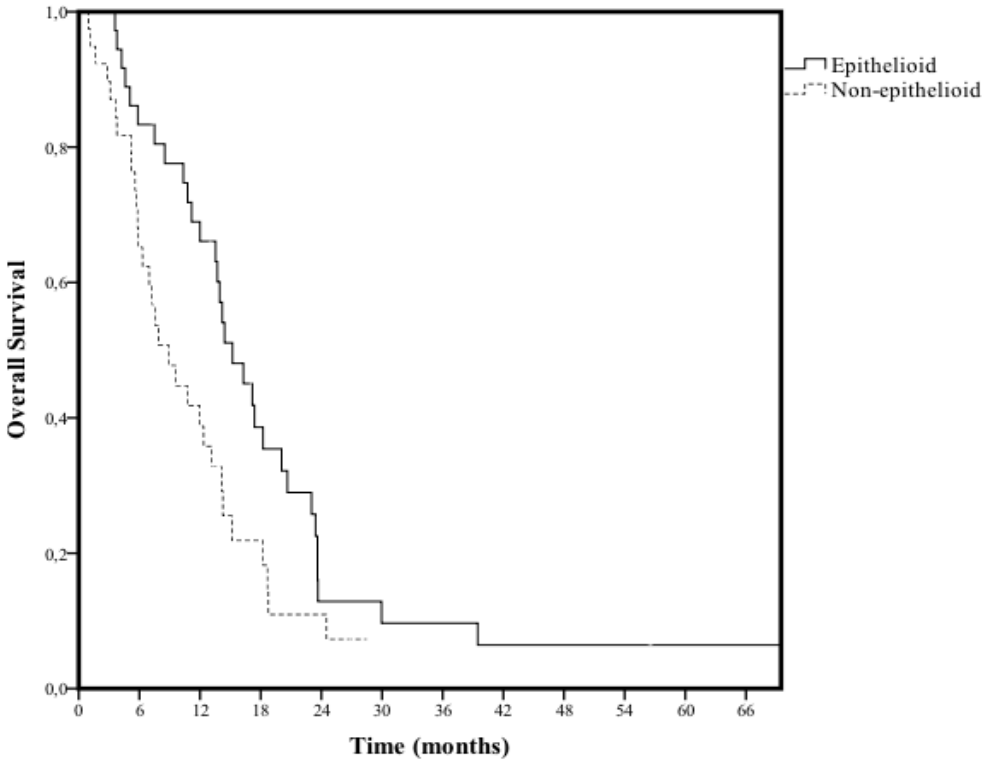

Figure 2. Kaplan-Meier survival curves of patients with epithelioid subtype (n=37) and non-epithelioid subtype (n=43) (p=0.026)

Table 4. Cox regression univariate analysis

Variable	HR (95% CI)	p-value
1 or more comorbid diseases	1.27 (0.768-2.092)	0.353
Non-epithelioid subtype	1.779 (1.064-2.976)	0.028
Male gender	1.097 (0.501-2.402)	0.818
Stage III or IV	1.019 (0.626-1.659)	0.939
Age > 70	1.30 (0.705-2.405)	0.395
Palliative radiotherapy as first treatment	0.928 (0.470-1.835)	0.831

HR: Hazard ratio. CI: Confidence interval.

4. Discussion

In our single-institution retrospective study no statistically significant difference in overall survival, disease control rate or response rate between the platinum-based doublet regimens cisplatin/pemetrexed and cisplatin/vinorelbine iv., as first line palliative chemotherapy for MPM, was determined. Non-epithelioid histology predicted a statistically significant worse prognosis compared to epithelioid subtype. These results confirmed the initial hypothesis of our study, but older age and gender were not found to be significant prognostic factors.

The current recommendation of cisplatin/pemetrexed as first line palliative chemotherapy for MPM is mainly based on one randomised phase III trial, where this doublet regimen is compared to cisplatin monotherapy(Ellis et al., 2006; Obasaju et al., 2007; Santoro et al., 2008; Stahel et al., 2010; Vogelzang et al., 2003). To our knowledge, no randomized studies exists evaluating cisplatin-based doublet regimens against each other. A recently published retrospective study comparing pemetrexed- versus non-pemetrexed-containing doublet chemotherapy for the treatment of MPM in 48 patients, found median OS rates of 17.8 months and 17.0 months respectively (p=0.65). The patients and tumor characteristics were well balanced between the two groups also in

terms of histological subtype. However, patients undergoing surgery (EPP or P/D) were also included in this study, potentially giving bias to the survival estimates (Higashiguchi et al., 2012). Lee et al. retrospectively compared patients with inoperable MPM either treated with cisplatin/pemetrexed (n=40) or cisplatin/ gemcitabine (n=41), and determined median overall survival rates of 11.2 and 10.7 months respectively (no confidence intervals reported) (Lee, Murray, Anderson, Rao, & Bishop, 2009). None of the mentioned retrospective studies evaluated response rates to chemotherapy. A phase II study, exploring the activity of cisplatin/vinorelbine iv. as first-line palliative chemotherapy for inoperable MPM in 54 patients, reported a mOS of 16.8 months (range 0.5-46.4+ months) and a response rate of 29.6% (Sorensen et al., 2008). The study by Vogelzang et al. determined a mOS rate of 12.1 months (CI 10.0-14.4) for the cisplatin/pemetrexed group, and a response rate of 41.3% (Vogelzang et al., 2003). Toxicity was not evaluated in the present study, but the data from the studies exploring cisplatin/pemetrexed and cisplatin/vinorelbine does not indicate any major differences in the overall toxicity. The previously published mOS estimates and response rates, and the results from our analysis cannot be directly compared due to differences in study design, but they seem reasonably comparable.

The poor prognosis of the group treated with pemetrexed monotherapy in first line could be explained from the clinical characteristics of these patients. They were elderly, had more comorbidity and a higher PS than the patients who received doublet chemotherapy. The physician's choice of treatment was of course based upon these factors. Initial need for palliative radiotherapy due to severe symptoms, doesn't seem to indicate a bad prognosis, since the median overall survival rate for this group was comparable to the survival estimates for patients who received doublet chemotherapy. Patients who received radiotherapy as first line treatment had a non-significant HR of 0.928 (Table 4). However, any conclusion regarding this aspect cannot be drawn, as symptoms weren't explored in our study and due to the small sample size.

The limitations of our work are related to its retrospective design and the small number of patients. The cohort is unselected and therefore differences between groups, potentially affecting the survival statistics comparing types of treatment, occurs. An example of this is the frequency of epithelioid and non-epithelioid subtypes in the cisplatin/pemetrexed and the cisplatin/vinorelbine groups (p=0.021) (Table 3). The higher number of individuals in the cisplatin/vinorelbine group with non-epithelioid subtype could give these patients a worse outcome. Hence, the survival data of our study should be interpreted with caution, although a trend toward comparable survival rates for the two cisplatin-based doublet-regimens (cisplatin/pemetrexed vs. cisplatin/vinorelbine) can be drawn.

Targeted drugs have come into clinical use for many types of cancers like e.g. tyrosine kinase inhibitors (TKIs) for EGFR-mutated non-small cell lung cancer, but for MPM, conventional chemotherapy is still the treatment available for the vast majority of patients. Due to the potential biases of retrospective studies, randomized phase III studies evaluating the efficacy and feasibility of cisplatin-based doublet-regimens like cisplatin/pemetrexed and cispltin/vinorelbine in inoperable MPM are needed. After the introduction of a peroral formulation of vinorelbine for the treatment of e.g. NSCLC (Bartsch, 2006; Depierre et al., 2001; Gralla et al., 2007; Jassem et al., 2001), the cisplatin/vinorelbine po. combination might be a feasible and more administration-friendly alternative to cisplatin/pemetrexed in patients with inoperable MPM.

5. Conclusion

In conclusion we find that subtype of histology appears to be significantly associated with survival. Patients with epithelioid histology may have a better prognosis than patients with non-epithelioid subtype. Our results show no significant difference in overall survival in patients who received different cisplatin-based doublet-regimes, but due to an uneven distribution of histological subtypes between the groups, this result has to be interpreted with caution. MPM is still a disease with a poor prognosis, and the survival rates in this retrospective study are comparable to other published data.

The therapeutic ceiling for conventional chemotherapy in terms of survival improvement in patients with inoperable MPM seems to be reached, but further improvements in feasibility and ways of administration of the different doublet regimens could be obtained through the initiation of randomized trials.

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