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ORIGINAL ARTICLE

Multidisciplinary palliative treatment including isolated thoracic perfusion for progressive malignant pleural mesothelioma: a retrospective observational study

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Summary

Purpose: *To investigate the relative importance of isolated thoracic perfusion (ITP) in the multidisciplinary palliative treatment of progressive malignant pleural mesothelioma (MPM) patients.*

Methods: *Fifty-two MPM patients with progressive disease after systemic chemotherapy with cisplatin and pemetrexed were submitted to 112 ITP using mitomycin C (25 mg/m^2) and cisplatin (70 mg/m^2) between 2000 and 2017. Isolation of the chest was achieved by insertion of stop-flow balloon catheters via femoral or iliac access. Primary endpoints were adverse events, tumor response rate, progression-free survival (PFS) and overall survival (OS) from initial ITP.*

Results: *Median interval-time from MPM diagnosis was 9 months. There were no perfusion-related postoperative deaths. The main procedure-related complication was persistent leakage of lymphatic fluid from the incision in less than 10% of ITP. No severe perfusion-related toxicity was reported, with grade 3 haematological toxicity and platinum-induced neurotoxicity in less than 8% of the patients. Following initial ITP, overall tumor response rate was 25%, median PFS was 7 months (IQR 5-10.5), and median OS was 16 months (IQR 12.5-21). After the last ITP, 14 patients received further therapies, including targeted therapy with cetuximab or bevacizumab. Non-epithelioid histology, stage III, and ECOG performance status 3 pre-ITP were prognostic factors with a significant influence on OS. Median OS, calculated from the diagnosis of MPM, was 26.5 months (IQR 22.5-28).*

Conclusions: *ITP is safe, tolerable, and useful but its inclusion in the multidisciplinary palliative treatment of progressive MPM patients should be investigated in a larger multicentre controlled study.*

Key words: *chemotherapy, mesothelioma, perfusion, stop-flow, thorax*

Introduction

Mesothelioma is a disease arising from mesothelial cells, and malignant pleural mesothelioma (MPM) is the most prevalent type, accounting for 68-85% of all mesothelioma cases [1]. MPM, expected to increase over the next few years with a plateau incidence between 2015 and 2030, has a dismal prognosis with approximately 5000 patients dying in Europe each year [2].

Only early-stage (I) cases seem to benefit from radical surgery, and surgical treatments such as pleurectomy and decortication or extrapleural pneumonectomy (EPP) are rarely curative [3]. Stage

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III MPM represents the most common stage on clinical diagnosis. Consequently, the majority of patients are not submitted to surgery with curative intent and are treated with systemic chemotherapy, cisplatin and pemetrexed being the most used first-line drugs [2]. Unfortunately, more than 50% of patients are nonresponsive to systemic chemotherapy and are considered for palliative treatments with a multidisciplinary approach. The multidisciplinary approach is based on several therapies including surgery without curative intent, associated with two or three other treatments such as further systemic chemotherapy, radiotherapy, targeted therapy, gene therapy, immunotherapy and locoregional chemotherapy [4].

As for locoregional chemotherapy, hyperthermic intraoperative chemotherapy (HIOC) is administered in association with maximum surgical cytoreduction and, consequently, it is not possible to establish its specific efficacy in terms of response ratio, PFS and OS [5,6]. On the contrary, isolated thoracic perfusion (ITP) is administered without contemporary surgical excision and hyperthermia with the opportunity to assess its response ratio and PFS [7,8].

In the era of new targeted therapies and immunotherapies, the question is: does locoregional chemotherapy still matter in the treatment of progressive MPM? In an attempt to answer that question, a retrospective study has been done on a cohort of patients with MPM who had progressed following systemic chemotherapy and were submitted to ITP.

Methods

This retrospective observational study was performed at the University of L'Aquila, L'Aquila, Italy, after approval from the investigational review board [Ethics committee of "Azienda Sanitaria Locale n.1 Avezzano Sulmona L'Aquila, Regione Abruzzo, Italy; Chairperson: G. Piccioli; protocol number 10/CE/2018; date of approval: 19 July, 2018 (n.1419)] and following the consideration that all patients had unresectable disease with a predictable course. All patients were fully informed about the disease and the implications of the proposed palliative treatment, following the Declaration of Helsinki and the ethical standards of the committee on human experimentation at our institution, after which written informed consent was obtained from all.

Patient eligibility

The criteria for patient eligibility were the following: (i) diagnosis of MPM; (ii) increase of recurrence-size for at least three months following systemic chemotherapy; (iii) Eastern Cooperative Oncology Group (ECOG) performance status of 0-3; (iv) leukocytecount>2500cells/mm^3 and platelet count>50000 cells/mm^3; (v) serum creatinine level ≤1.2 mg/dL; (vi) patients with liver failure, deep venous thrombosis, severe atherosclerosis, or coagulopathy were not eligible for this study.

Patient characteristics

To avoid overlap of patients included in our previously published paper [8], this retrospective study

Table 1. Characteristics of 52 MPM patients in progression after standard treatments

Characteristics	*n*	*%*
Gender		
Female	2	3.85
Male	50	96.15
Age, years (Mean±SD)	52	(9±6.4)
Sites		
Right	22	42.3
Left	28	53.8
Multisite	2	3.8
Histology		
Epitheliod	38	73.1
Fibrous	5	9.6
Mixed	9	17.3
Stages		
II	10	19.2
III	42	82.8
Eastern Cooperative Oncology Group		
I	13	25
II	30	57.7
III	9	17.3
Symptoms		
No	12	23
Yes	40	77
pain	24	44.1
dyspnoea	21	40.4
cough	6	11.5
Previous treatments of MPM		
Surgery	52	100
Systemic chemotherapy	52	100
Cisplatin and pemetrexed	16	30.8
Pleural talk	3	5.8
Radiotherapy	1	1.9
EGFR overexpression		
Yes	4	7.7
No	48	92.3
VEGFR overexpression		
Yes	5	9.6
No	47	90.4
Median interval time from MPM diagnosis to initial ITP, Median (IQR, months)	9	(7-11)

SD: standard deviation, IQR: interquartile range, EGFR: epidermal growth factor receptor, VEGFR: vascular epidermal growth factor receptor

evaluated the period from 2000 to 2017, selecting 52 patients with MPM, in progression after previous treatments including systemic chemotherapy, submitted to 112 ITP with mitomycin C (25 mg/m^2) and cisplatin (70 mg/m^2). Patient demographics are displayed in Table 1. Approximately 31% of the patients were in progression after cisplatin and pemetrexed systemic chemotherapy. Based on the ECOG classification and symptoms such as pain, tiredness, lack of appetite and cough, the clinical profile of severity was between moderate and severe for all 52 patients. The median time interval from diagnosis of MPM to initial ITP was 9 months (IQR 7-11). ITP was repeated at approximately 8-weeks intervals. The rationale and timing of repetition in patients exhibiting a partial response or stable disease was based on a pilot study which indicated that progression was always observed in the presence of residual tumor [7]. Treatment was not repeated if complete response was achieved, if MPM had progressed >20% in dimension, if simultaneous distant relapses occurred, if the general condition of the patient worsened or if the patient withdrew his consent.

ITP procedure

During thoracic perfusion the target region includes the thorax and head for approximately 25 min (Figure 1). After systemic heparinisation (150 U/kg heparin), 3-lumen, 12-Fr. balloon catheters (PFM Medical AG, Cologne, Germany) were surgically inserted into the inferior vena cava via the saphenous vein and into the thoracic aorta via the femoral artery. The catheters were positioned at the diaphragm level using a guide wire under fluoroscopic guidance. After the second or third ITP, further procedures were performed via the iliac veins and arteries exposed via an abdominal extra-peritoneal approach. One of the three lumens of each catheter was used for inflating the balloons, and the other lumens for positioning the guide wire and for blood circulation during the chemofiltration phase. Both balloons were inflated simultaneously to avoid greater volume displacements. Two pneumatic cuffs were inflated at both roots of the arms (250 mm Hg) to complete isolation. Cytotoxic drugs (mitomycin C 25 mg/m^2) and cisplatin (70 mg/m^2) were administered as bolus injection within the first 3 min of the perfusion using the guidewire line of the arterial catheter. After deflating the balloons, catheters were used to activate an extracorporeal blood circulation to perform chemofiltration in order to reduce systemic toxic effects. Chemofiltration was controlled by a circulation device (Performer LRT; RanD, Medolla, Italy) containing a heating element and a chemofiltration module. The blood was withdrawn from the aorta with a flow of approximately 200 mL/min. The temperature at the outlet level of the heating element was 39°C. A polyamide haemofilter with a surface area of 2.1 m^2 (RanD, Medolla, Italy) was used for filtration. The duration of chemofiltration was approximately 50 min. At the end of the procedure, the catheters were pulled out and the vessels repaired. Protamine was injected at 200 IU/kg to reverse the anticoagulant effects of heparin.

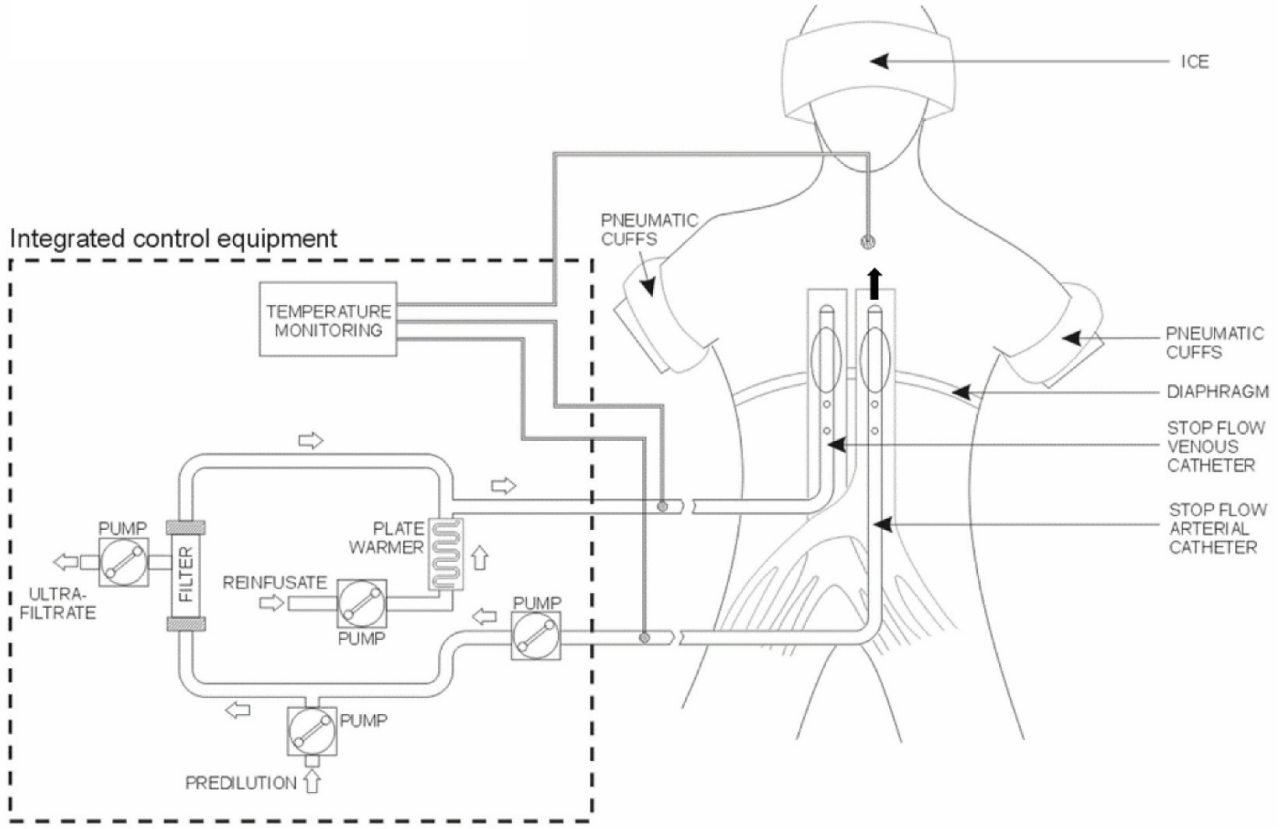

Figure 1. Scheme of isolated thoracic perfusion with chemofiltration.

Anaesthesia and haemodynamics

All 91 ITPs were performed under general anaesthesia, as previously described [11]. ITP did not require a routine pulmonary artery catheterisation, except in high cardiac risk patients. Central venous catheterisation, however, should be regarded as the minimum level of monitoring such procedures. During ITP, a temporary increase (approximately 25%) of the mean arterial pressure (mean value 120 mmHg) has been observed in the thoracic area, and a mean value of 40 mmHg was measured in the abdominal compartment [10,11].

Adverse events and response

Adverse events were assessed using the NCI Common Toxicity Criteria (CTC v 4.03). Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors, v 1.1 (RECIST 1.1) [12]. Responses of patients treated before 2009 were retrospectively re-classified. Evaluation of tumor response was made by computerized tomography scan, while positron emission tomography (PET) was added based on the investigators' assessment. Objective responses were confirmed three months later.

Pain controlled by <50% of pre-ITP analgesic therapy 30 days after perfusion, was considered objective pain relief. Follow-up was scheduled every three months up to disease progression or death.

Post-ITP therapy

The final 14 patients received further therapies. Systemic chemotherapy was administered in 5 patients, radiotherapy in 1 patient, targeted therapy in 9 patients based on new biopsies and biomolecular analyses. Four patients received cetuximab (250 mg/m^2), and 5 patients received bevacizumab (5 mg/kg).

Statistics

Statistical analyses included descriptive statistics estimated with 95% confidence intervals (95%CI). Survival was estimated by using the Kaplan-Meier product limit method. Survival was stratified according to the clinical variables that potentially could affect it. A table of patients at risk was prepared for each variable when comparing survival rates, and log-rank test was used to assess the significance of the differences between the groups. Hazard ratios (HR) were estimated by using a proportional hazard Cox regression model. The assumption of proportional hazards was tested by using the Schoenfeld test. The statistical analyses were performed by using STATA software, version 14 (StataCorp, College Station, Texas). Means±standard deviations (SD) were also used.

Results

After a median time of 9 months from MPM diagnosis, 52 patients underwent 112 ITPs. The median number of ITPs per patient was 2 (mean±SD, 2.15±0.80). The median hospital stay for one ITP was 6 days (mean±SD, 6.88±2.33).

Procedure-related complications

There were no haemodynamic or vascular complications during the 112 perfusions and no perfusion-related postoperative death occurred. One technical complication (balloon catheter rupture) was registered. Femoral or iliac cannulation was always possible. The complications registered (Table 2) were seroma (10 episodes), persistent leakage of lymphatic fluid from incision (7 episodes), inguinal haematoma (3 episodes), wound dehiscence (5 episodes), lymphangiitis (1 episode), and wound infection (1 episode).

ITP with chemofiltration-related toxicity

No severe perfusion-related haematologic toxicity was registered (Table 2). Among the 52 patients who underwent 112 perfusions, the number of patients with grade 1, grade 2, and grade 3 toxicities was 15 (28.84%), 9 (17.30%), and 3 (5.76%), respectively. Granulocyte colony-stimulating factor was administered in patients with G3 neutropenia. Treatment was discontinued due to severe hematologic toxicity (G3-4) in 2 patients (3.84%). Other toxicities were: G2 alopecia in 8 patients (15.4%), and G1-2 nausea and vomiting in 17 patients (32.7%). G1 platinum-induced neurotoxicity was registered in 1 patient (1.9%). G2 dyspnoea and fatigue were registered in 11 patients (21.15%).

ITP tumor and pain responses

Overall tumor response rate following initial ITP was 25%; 2 CR (3.8%), 11 PR (21.1%), with 39

Table 2. Procedure-related complications and toxicity after 112 ITP in 52 MPM patients

Complications	*Grade / no. of ITP (%)*
Seroma	1 / 10 (8.92)
Persistent leakage of fluid from the incision	2 / 7 (6.25)
Wound infection	1 / 1 (0.89)
Inguinal hematoma	1 / 3 (2.68)
Wound dehiscence	2 / 5 (4.46)
Lymphangiitis	2 / 1 (0.89)
Toxicity	*Grade / no. of patients (%)*
Bone marrow hypocellularity	1 / 15 (28.84)
	2 / 9 (17.30)
	3 / 3 (5.76)
Alopecia	1 / 8 (15.38)
Nausea and vomiting	1 / 17 (32.69)
Platinum-induced neurotoxicity	1 / 1 (1.92)
Dyspnea and fatigue	2 / 11 (21.15)

SD (75%). No partial responses were registered in subsequent ITP treatments. Ten patients with thoracic pain showed considerable pain decrease and analgesic requirement within 36 to 48 h from the initial ITP treatment. One month after initial ITP, 3 patients achieved partial pain relief with reduction of the mean Tramadol dosage per day from 400 mg to 200 mg, 1 patient had a complete pain relief, and 7 patients achieved a moderate improvement in their general conditions (ECOG PS 3 decreased to ECOG PS 2).

Survival

The median OS of the 52 patients, calculated from the diagnosis of MPM, was 26.5 months (IQR 22.5-28). These patients had undergone surgery, systemic chemotherapy and radiotherapy, with a median interval time of 9 months from diagnosis to initial ITP treatment (IQR 7-11). Following initial ITP treatment, the median time-to-death of these 52 patients was 16 months (IQR 12.5-21), which was associated with 71.1% survival at one year, 9.61% survival at two years and 5.8% survival at three years.

Following initial ITP, histology, stages and pretreatment ECOG PS influenced survival (Figure 2A, B, C), whereas gender, age, thoracic sites of disease, previous chemotherapy with cisplatin and pemetrexed, symptoms, number of ITP treatments, and further therapy after the last ITP did not (Table 3).

PFS, calculated from the initial ITP treatment, exhibited a median of 7 months (IQR 5-10.5) in

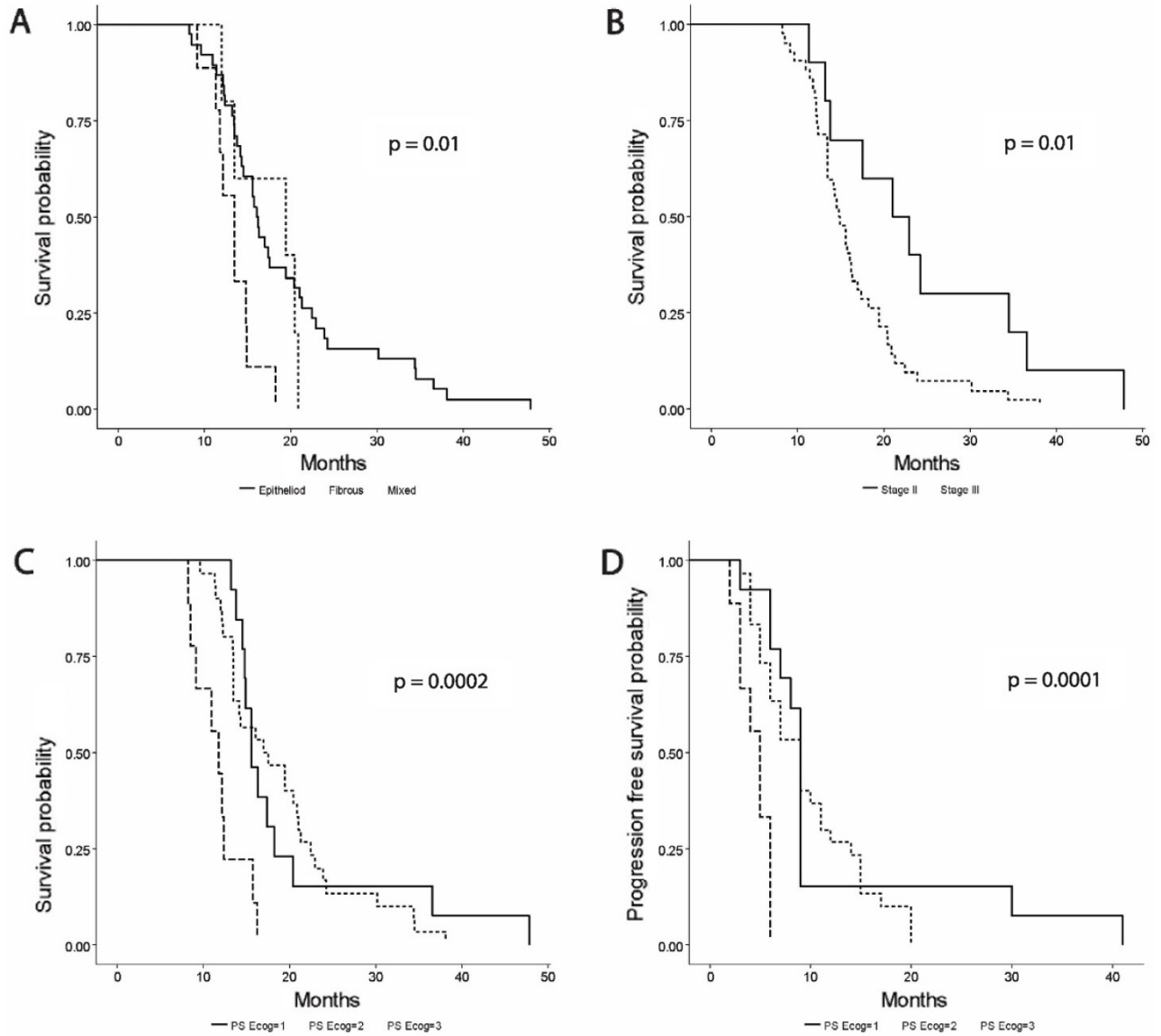

Figure 2. Kaplan Meier curves in 52 progressive MPM patients submitted to ITP. **A:** survival according to epitheliod, fibrous, and mixed histology. **B:** survival according to stages II and III. **C:** survival according to performance status ECOG 1,2, and 3. **D:** progression-free survival according to ECOG PS 1,2 and 3.

the 52 patients, and it was significantly influenced only by pre-treatment ECOG PS (Figure 2 D), with a median PFS of 5 months for ECOG PS 3 patients (Log-Rank x^2=19.3, p=0.001).

Follow-up

No patients were lost to follow-up. All patients died of MPM. Interruptions after the initial ITP treatment were due to consent withdrawal in 6 cases, to hematological toxicity in 2 cases, and cisplatin-induced neurotoxicity in 1 case. After the last ITP, 14 patients received further therapies, 9 of them were submitted to targeted therapy, interrupted for grade 2 dermatological toxicity in 3 patients. In 4 patients the site of progression was abdomen with inferior vena cava stenosis and ascites.

Discussion

This study showed that a multidisciplinary treatment including ITP proved safe and effective for advanced MPM patients in progression after standard therapies, providing a median OS of 26.5

Table 3. Survival from initial ITP with mitomycin C and cisplatin in 52 patients with MPM previously in progression after surgery, systemic chemotherapy and radiotherapy. Stratification according to age, gender, sites, histology, stages, ECOG PS, symptoms, previous systemic chemotherapy with cisplatin and pemetrexed, number of ITP and post-ITP therapy

Variables (number of patients)	n	*MST (months)*	*Log rank*	*p value*	*Cox HR*
Age, years			0.72 (ns)	0.39	
<50	15	16			
≥50	37	16			
Gender			(ns)		
Female	2	16			
Male	50	13.5			
Sites			2.41 (ns)	0.12	
Right	22	17			
Left	28	14			
Multisite	2	22.5			
Histology			7.85	0.01	[1.60, 1.08 – 2.38]
Epitheliod	38	16			
Fibrous	5	20			
Mixed	9	14			
Stage			5.53	0.01	[2.28, 1.08 – 4.43]
II	10	22			
III	42	15			
Eastern Cooperative Oncology Group (ECOG)			17.28	0.001	[1.91, 1.11 – 3.29]
I	13	16			
II	30	17.5			
III	9	12			
Symptoms			1.07 (ns)	0.30	
No	12	16			
Yes	40	14.5			
Previous cisplatin and pemetrexed systemic chemotherapy			3.41 (ns)	0.06	
No	36	16			
Yes	16	16			
Number of ITP			1.06 (ns)	0.30	
< 3	39	14			
≥ 3	13	20			
Post-ITP therapy	38	15.5			
Systemic chemotherapy/RT	5	21	3.50 (ns)	0.17	
Targeted therapy	9	16			

MST: median survival time, HR: hazard ratio, ns: not significant

months. In subjects non-responsive to systemic chemotherapy, ITP achieved a 25% of tumor response and a median PFS of 7 months. From the initial ITP, a median OS survival of 16 months has been registered in our 52 MPM patients and these results are in line with data reported in a recently published phase II study on progressive MPM patients treated with the same procedure (median PFS 9 months, median OS 12 months) [9]. One month after initial ITP, approximately 20% of patients showed a pain response which is a substantial benefit in the palliative treatment of patients excluded from curative therapy. Non-epithelioid histology, stage III, and ECOG PS 3 pre-ITP resulted in negative prognostic factors with a significant influence on OS. The prognostic data detected in our study are in line with a recently published experience regarding 128 of 323 MPM patients not in progression after systemic chemotherapy and submitted to extrapleural pneumonectomy (EPP) [4]. Our analysis provided information about a patient category comparable to those 195 subjects in progression after systemic chemotherapy and unsuitable to EPP not evaluated by the group of Zurich [4].

The cisplatin and mitomycin C drug regimen used in this cohort of patients has been chosen based on a previous pilot study [7] and in consideration of two reasons: (i) MPM is an extremely hypoxic tumor [13-15]; (ii) mitomycin C is ten times more toxic to tumor cells under hypoxic conditions [16].

ITP has proven feasible, safe and tolerable, according to results in terms of procedure-related complications and toxicity. No serious adverse events were reported in the overall patient population enrolled; G-3 haematological toxicity and platinum-induced neurotoxicity were registered in less than 8% of patients; this was due, in our opinion, to the use of chemofiltration, confirming the data previously observed [8].

After the last ITP, a subgroup of our patients received a targeted therapy, although these drugs are not formally incorporated into standard clinical care [17]; the median OS in this subgroup of patients was 27 months, but the univariate analysis showed that a post-ITP therapy including cetuximab or bevacizumab did not significantly influence OS. Although cetuximab demonstrated therapeutic efficacy on blocking cell growth in MPM cell lines and mouse models [18] and bevacizumab administration has been supported by high VEGF levels in the tissue specimens of patients with MPM and as free circulating molecules [19], to date the use of tyrosine kinase inhibitors against EGFR and VEGF does not correlate with clinical outcomes according to the results of phase II [20] and phase III trials [21].

Multidisciplinary protocols that combined systemic chemotherapy and/or radiotherapy with aggressive surgery have been proposed, but improvement on OS has been obtained in only a highly selected group of patients submitted to EPP with epithelial histology, no nodal involvement, and clear resection margins, at the cost of substantial morbidity and mortality [22]. Unfortunately, more than 50% of the patients at time of diagnosis were not suitable for EPP due to advanced stage or other concurrent illnesses and surgery may be required only to establish the diagnosis, or to perform cytoreduction and palliate symptoms [23]. Specialized centers have reported very interesting survival rates with the use of loco-regional chemotherapy, but it is difficult to translate the observed therapeutic benefits to the broader population [24]. When hyperthermic intraoperative chemotherapy (HIOC) in association with maximum surgical cytoreduction has provided a significantly prolonged OS of 35.3 months has been reported by a North-American group [6]; this result has not been confirmed by a German group using the same procedure and referring an OS of 18 months [6].

The most relevant aspect of this study is that our patients were heavily pre-treated and in progression after systemic chemotherapy. Approximately 31% were non-responsive to cisplatin and pemetrexed, to date being considered the gold standard first-line therapy. In this subgroup of patients, a median OS of 27 months has been registered and this result deserves to be confirmed in a larger phase III study. The combination of platinum-antifolate, compared to cisplatin-alone therapy, increased the median OS from 10 months to approximately 13 months [25]. The recent randomized phase III MAPS trial, comparing pemetrexed/cisplatin with or without bevacizumab, showed a significantly increased median OS from 16.1 months in the no bevacizumab arm to 18.8 months in the bevacizumab arm [21].

Potential limitations of this study are: (i) the small sample size influencing the possibility of multivariate analysis; (ii) the lack of a control group not submitted to ITP; (iii) the complexity of the procedure performed only in specialized centers. The observed ITP response rate and survival, however, should not be neglected, considering that treatments which are proven effective for other cancer types, such as tyrosine kinase inhibitors and new immunotherapy drugs do not show clinical benefit for progressive MPM patients. The efficacy of loco-regional chemotherapy with mitomycin C and cisplatin could be related to the mechanisms

that MPM cells exploit to survive within their hostile, inflammatory and hypoxic microenvironment. In conclusion, the data emerged from this retrospective observational study seem to suggest that the inclusion of ITP in the multidisciplinary palliative treatment of progressive MPM patients should be investigated in a larger multicentre controlled study.

Conflict of interests

The authors declare no conflict of interests.

References

1. Segura-Gonzalez M, Urias-Rocha J, Castelan-Pedraza J. Malignant mesothelioma of the tunica vaginalis: a rare neoplasm–case report and literature review. Clin Genitourin Cancer 2015;13:401-5.
2. Bakker E, Guazzelli A, Krstic-Demonacos M, Lisanti M, Sotgia F, Mutti L. Current and prospective pharmacotherapies for the treatment of pleural mesothelioma, Expert Opin Orphan Drugs 2017;5:455-65.
3. Lee YC. Surgical resection of mesothelioma: an evidence-free practice. Lancet 2014;384:1080-1.
4. Opitz I, Friess M, Kestenholz P et al. A new prognostic score supporting treatment allocation for multimodality therapy for malignant pleural mesothelioma. A review of 12 years' experience. J Thorac Oncol 2015;10:1634-41.
5. Sugarbaker DJ, Ritu R, Yeap BJ et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-63.
6. Ried M, Potzger T, Braune N et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. Eur J Cardiothorac Surg 2013;43:801-7.
7. Guadagni S, Clementi M, Valenti M et al. Thoracic stop-flow perfusion in the treatment of refractory malignant pleural mesothelioma: a phase I-II evaluation/trial. In vivo 2006;20:751-6.
8. Aigner KR, Selak E, Gailhofer S. Isolated thoracic perfusion with chemofiltration for progressive malignant pleural mesothelioma. OncoTargets Ther 2017;10:3049-3057.
9. Guadagni S, Fiorentini G, Clementi M et al. Does locoregional chemotherapy still matter in the treatment of advanced pelvic melanoma? Int J Mol Sci 2017;18:2382. doi:10.3390/ijms18112382.
10. Varrassi G, Guadagni S, Ciccozzi A et al. Hemodynamic variations during thoracic and abdominal stop-flow regional chemotherapy. Eur J Surg Oncol 2004;30:377-83.
11. Guadagni S, Clementi M, Valenti M et al. Hypoxic abdominal stop-flow perfusion in the treatment of advanced pancreatic cancer: a phase II evaluation/trial. Eur J Surg Oncol 2007;33:72-8.
12. Eisenhauer EA, Therasse P, Bogaerts J et al. New response valuation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
13. Graziani I, Eliasz S, De Marco MA et al. Opposite effects of Notch-1 and Notch-2 on mesothelioma cell survival under hypoxia are exerted through the Akt pathway. Cancer Res 2008;68:9678-85.
14. Ivanov S, Liao SY, Ivanova A et al. Expression of hypoxia-inducible cell-surface transmembrane carbonic anhydrases in human cancer. Am J Pathol 2001;158:905-19.
15. Francis RJ, Segard T, Morandeau L et al. Characterization of hypoxia in malignant pleural mesothelioma with FMISO PET-CT. Lung Cancer 2015;90:55-60.
16. Rockwell S. Effect of some proliferative and environmental factors on the toxicity of mitomycin C to tumor cells in vitro. Int J Cancer 1986;38:229-35.
17. Remon J, Requart N, Corral J, Lianes P. Malignant pleural mesothelioma: new hope in the horizon with novel therapeutic strategies. Cancer Treat Rev 2015;41:27-34.
18. Kurai J, Chikumi H, Hashimoto K et al. Therapeutic antitumor efficacy of anti-epidermal growth factor receptor antibody, cetuximab, against malignant pleural mesothelioma. Int J Oncol 2012;41:1610-8.
19. Fujimoto N, Gemba K, Kishimoto T. Clinical significance of serum vascular endothelial growth factor in malignant pleural mesothelioma. J Thorac Oncol 2011;6:971-2.
20. Buikhuisen WA, Scharpfenecker M, Griffioen AW, Korse CM, van Tinteren H, Baas P. A randomized phase II study adding Axitinib to Pemetrexed-Cisplatin in patients with malignant pleural mesothelioma: a single-center trial combining clinical and translational outcomes. J Thorac Oncol 2016;11:758-68.
21. Zalcman G, Mazieres J, Margery J et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, openlabel, phase 3 trial. Lancet 2016;387:1405-14.
22. Rusch V, Baldini EH, Bueno R et al. The role of surgical cytoreduction in the treatment of malignant pleural mesothelioma: meeting summary of the International Mesothelioma Interest Group Congress, September 11–14, 2012, Boston, MA. J Thorac Cardiovasc Surg 2013;145:909-10.

23. Hountis P, Chounti M, Matthaios D, Romanidis K, Moraitis S. Surgical treatment for malignant mesothelioma: extrapleural pneumonectomy, pleurectomy/decortication or extended pleurectomy ? JBUON 2015;20:376-80.

24. Papaspyros S, Papaspyros S. Surgical management of malignant pleural mesothelioma: impact of surgery on survival and quality of life-relation to chemotherapy, radiotherapy, and alternative therapies. ISRN Surg 2014;817203. http://dx.doi.org/10.1155/2014/817203.

25. van Meerbeeck JP, Gaafar R, Manegold C et al. European Organisation for Research and Treatment of Cancer Lung Cancer Group; National Cancer Institute of Canada. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. J Clin Oncol 2005;23: 6881-9.