ORIGINAL ARTICLE

Advanced malignant pleural mesothelioma: Experience in 42 patients

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KEY WORDS

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Abstract Malignant pleural mesothelioma is a rare, difficult to diagnose neoplasm with poor prognosis. To determine the prognostic factors for survival in patients with this disease at advanced stages (Stages III and IV), the medical files of 42 patients with this diagnosis were assessed, and factors known to be prognostic of poor survival were statistically analyzed. Age >60 years and serum albumin levels <3.5 g/dL were highly significant ($p < 0.001$). The presence of fever, dyspnea, weight loss >10%, and platelets >400,000/ μ L was highly significant ($p < 0.01$) and, finally, Eastern Cooperative Oncology Group performance status 3 or 4 and the presence of chest pain and cough were significant ($p < 0.05$). In contrast with reports in the literature, male gender, known exposure to asbestos, smoking, diabetes, leukocytosis, anemia, lactate dehydrogenase >500 IU/L in pleural fluid, presence of nodular pleural thickening on imaging studies, presence of pleural effusion >60%, mediastinal invasion, site of presentation, biphasic and sarcomatous lineage and forms of treatment showed no significant differences with regard to patient survival in our population. Mean survival was 8.1 months, with values ranging from 30 days to 1 year and 4 months. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION AND BACKGROUND

Malignant pleural mesothelioma (MPM) can be defined as a neoplasm deriving from mesothelial cells, specifically from the mesodermal surface of the embryonic coelomic cavity that later will give origin to the pleura, the pericardium, the peritoneum, and the tunica vaginalis of testicle¹. There is general consensus, based on numerous studies, that considers this tumor as being originated by the inflammatory and foreign body reaction that is produced by the deposit of fibers of asbestos², a group of double-chain, metamorphic, fibrous minerals that show great flexibility and heat resistance, and they have therefore been used in a large amount of products³⁻⁷.

The World Health Organization has declared all types of asbestos to be carcinogenic; since 2005, the European Union banned the use of all types of asbestos, with several countries having joined this initiative, for a total of just over 50^{3,5,8-10}.

Asbestos has been known to be a pleural mesothelioma causative agent since 1960; according to the United States Environmental Protection Agency, it comprises six types of minerals, all of them carcinogenic. Exposure to asbestos is known for entailing severe implications for health. Since 2005, the Rotterdam Convention includes all types of asbestos of the amphiboles group in Appendix III; however, the case of chrysotile has been more controversial and has not yet been included⁵⁻⁷.

In Mexico, where 21 out of every 100 households have metal, cardboard or asbestos roofing, and one out of every 100 has cardboard, asbestos, reed, bamboo, or palm walls; there are still no laws banning the use of asbestos, especially chrysotile. In this country, there are 500 confirmed cases of MPM every year since 2010, although there may be significant under-recording since in most cases it is confused with lung cancer¹¹⁻¹³.

Asbestos carcinogenic potential is related to the size, type and probably the amount of deposited fibers: Those <5 µm can be eliminated by macrophages or pulled to the trachea by the mucociliary epithelium, whereas longer fibers, which cannot be eliminated, accumulate and cause fibrosis, pleural plaque, pleural effusion, or mesothelioma¹⁴. With regard to the type of asbestos, amphiboles appear to be much more aggressive than chrysotile and, finally, the risk for developing MPM appears much higher in those people occupationally exposed to this mineral than in those who have suffered incidental exposure. The time elapsed from exposure to malignant pleural epithelioma clinical presentation is long, and there is usually a period of latency of up to 30 years^{3-8,14,15}.

Another demonstrated cause of MPM is erionite, which is the name by which three minerals of the tabular zeolites group are known: Calcium, potassium, and sodium erionite⁸. The unusually high rate of cases of MPM in Tuzköy, a municipality of the Turkish province of Nevşehir, is associated with these zeolites¹⁶. In the case of Mexico, in the village of Tierra Blanca de Abajo, San Miguel de Allende, Guanajuato, studies conducted at the Geosciences Center of the National Autonomous University of Mexico have also demonstrated the association of erionite and MPM¹⁷.

Other etiologic factors can be asbestos-free environmental pollution, the presence of viral oncogenes (simian va-

cuating DNA polyomavirus 40), chromosomal abnormalities or ionizing radiation^{2,14}. This neoplasm is more common in males at a 3.6 to 1 ratio¹⁵, and it affects people between the 5th and 6th decades of life².

Characteristic clinical presentation comprises four main manifestations: Chest pain, dyspnea, cough, and weight loss^{2,14}. Characteristic pain occurs in the chest, but it can also occur in the superior abdomen, scapular region, and shoulder due to diaphragmatic pleura implants; pain intensity is directly proportional to tumor extent and infiltration to the chest wall, it is dull, diffuse and it occurs in 80% of cases¹⁴. Dyspnea is observed in 60% of patients, and it is generally secondary to pleural effusion and/or pulmonary entrapment, which causes a decrease in functional pulmonary parenchyma and, consequently, a reduction of effective surface for gas exchange due to tumor invasion⁴. Weight loss is sustained and without appetite loss, with a reduction of up to 24% of body weight in 1 month, and it occurs to two-thirds of patients¹⁴. Characteristic cough is non-productive and in the decubitus position and is observed in 27-29% of patients^{14,18}. These symptoms and a history of risky exposure lead to suspect the diagnosis, and although confirmation should be by histopathology, some imaging studies are indispensable for staging and diagnostic-therapeutic approach.

On chest X-ray, the presence of pleural effusion, mediastinal ipsilateral shift or costal periosteal reaction can be observed; however, the most specific finding and, therefore, highly suspicious is diffuse pleural thickening with nodular images¹⁴. Contrasted axial computed tomography (CT) scan with fine sections is the imaging gold standard for MPM staging. It is useful to determine pleural alterations, tumor extent and mediastinal invasion. Findings include pleural effusion, pulmonary volume decrease, chest wall invasion, costal involvement, fatty planes obliteration, nodular pericardial thickening, and direct extension to soft tissues. It is important mentioning that the pulmonary parenchyma regularly does not show masses. With a sensitivity of 90%, it has the disadvantage that it is poorly sensitive to assess mediastinal lymph node involvement^{14,16,18}. Magnetic resonance imaging is slightly superior to CT to assess MPM morphology and extension to the chest wall and transdiaphragmatic extension, and the study contrasted with gadolinium assesses tumor perfusion, vascularization, and angio permeability. It is important to stress that this study does not reliably detect the presence of distant metastasis^{14,16}. Positron emission tomography can be used for pre-operative staging; however, its main role is in treatment response and relapse emergence assessment, as well as distant metastasis detection. Although its sensitivity and specificity are low (specificity: 92% and sensitivity: 75%), a standard uptake value >2.0 can be used as a cutoff point to detect N2 disease, and false positives can be observed in tuberculous pleuritis, empyema or in patients with previous history of pleurodesis^{18,19}.

Pleural fluid cytology is usually insufficient for diagnosis because, on the one hand, cellularity is not always obtained, and on the other, when it is obtained, cells can be mistaken with those originating from other malignancies such as adenocarcinoma or sarcoma. As an inconvenience, this method shows problems for diagnostic differentiation between benign and malignant mesothelial hyperplasia and is unable to demonstrate tumor invasiveness, which is considered essential for definitive diagnosis^{2,14}. Pleural fluid analysis

can be highly helpful when hyaluronic acid levels $>100 \mu\text{g}/\text{mL}$ are found, which is highly suspicious of MPM¹⁴.

Mesothelioma definitive diagnosis should be established by biopsy-obtained tissue histopathological analysis; the biopsy can be obtained by puncture or surgery.

“Blind” biopsy by needle puncture, i.e., without the use of real-time imaging techniques, provides rather unsatisfactory results, since it combines the small size of the sample obtained with this system with lack of control on extraction site exact localization, and it is therefore practically not used and, instead, CT-guided puncture is currently carried out with a diagnostic effectiveness rate of 75% when the sample is $>10 \text{ mm}$ ^{2,14}. On the other hand, diagnostic approach with surgically-obtained biopsy can be carried out with three main methods: Medical thoracoscopy, video-assisted thoracoscopic surgery, and thoracotomy¹⁴. Although medical thoracoscopy can be performed with analgesia and sedation in the bronchoscopy room, its diagnostic effectiveness in mesothelioma with sarcomatous component is suboptimal and, therefore, in these cases it is better to obtain samples with any of the other two aforementioned surgical methods, with video-assisted thoracoscopic surgery being the technique of choice, since in addition to being a minimally invasive procedure, it is associated with the capability to better stage the tumor, especially in the mediastinal area, and even to perform pleurectomy and decortication procedures, although it is not always available in all centers^{20,21}.

MPM histopathological diagnosis is usually difficult and even impossible with light microscopy examination, as it happens with the sarcomatous mesothelioma desmoplastic variety, which is indistinguishable from benign reactive pleural tissue. In all cases, special immunohistochemistry staining techniques are required for differentiation from neoplasms that appear very similar on microscopy^{1,22-25}. Differentiation between epithelioid-lineage MPM and adenocarcinoma (of the lung) involves the presence of epithelial markers for the former, especially calretinin, and absence of adenocarcinoma specific markers. A mesothelioma will never be positive for CD15, thyroid transcription factor-1 or estrogen receptor marker, with the former two being expressed in pulmonary adenocarcinoma and the latter in breast adenocarcinoma^{1,22-25}. With regard to malignant pleural sarcomatoid mesothelioma and squamous or transitional cell carcinoma, immunohistochemistry is based on sarcoma markers, especially p63, lack of expression, together with positivity for Wilms tumor antigen. It is important bearing in mind that the cytokeratin 5/6 marker, which is useful to differentiate mesothelioma from adenocarcinoma, is of no use for differentiation from squamous or transitional cell carcinoma, since both express it as well²⁶⁻²⁸. Reactive mesothelial tissue is nearly indistinguishable from MPM and immunohistochemistry techniques are, therefore, also necessary. Markers for desmin are used to differentiate them since they are positive in mesothelial reactivity. On the other hand, the insulin-like growth factor II RNA-binding protein is present in MPM and does not mark for reactive mesothelial tissue (Table 1)^{29,30}.

Staging systems proposed in previous decades tend to classify advanced state tumors more in detail and are usually based on researchers' personal experiences. The oldest MPM staging method was proposed by Erick Butchart in 1976 with the scale that bears his name¹⁸. Subsequently, in Har-

vard University Brigham and Women's Hospital, David Sugarbaker developed a new scale using clinical and radiologic approaches. Subsequently, the International Mesothelioma Interest Group introduced a staging system in 1995 that was accepted in 2002 by the International Union Against Cancer (Union Internationale Contre le Cancer)^{2,18} and the American Joint Committee on Cancer. The new staging system takes the T (tumor), N (lymph node), and M (metastasis) factors into consideration. This is a complex classification system originally designed for patients assessed in surgery. Due to the diffuse presentation of the tumor, even with currently available imaging techniques, there are often difficulties to classify the T and N factors^{19,31}.

Treatment is controversial with survival periods ranging from 16 to 24 months on average. During the 1st years of this century, each one of the specialized centers offered diverse options and different algorithms with options including chemotherapy, radiotherapy, immunotherapy, or combinations thereof for medical approach and pleurectomy/decortication, extrapleural pneumonectomy as surgical alternatives, but still without an international management standard. In 2009, the European Respiratory Society and the European Society of Thoracic Surgeons in 2010 determined that radical surgery can only be performed in the setting of clinical trials, with the use of decortication and pleurectomy being reserved to effusion palliation, whereas chemo- and radiotherapy should be adjusted to each patient's characteristics. In 2013, the European Society of Medical Oncology and, in 2015, the National Comprehensive Cancer Network, based on the results of the scarce clinical trials, suggested that MPM Stages I to III with N1 and without contraindication for surgery can (with or without pre-operative chemotherapy) undergo extrapleural pneumonectomy, lymph node resection of at least three stations and diaphragm and pericardium ipsilateral resection. Patients with N0 might undergo pleurectomy and decortication. For Stages III with N2 or mixed histology, oncologic surgery procedures should only be performed within the setting of clinical trials or at centers with experience in this tumor. Finally, if tumor complete resection is not possible, the surgical procedure should be aborted, and palliation will consist in safe debulking and, if appropriate, pleurodesis^{20,21}. Patients with clinical Stage IV of the sarcomatous histological type, both clinically inoperable or in the post-operative period, may benefit from chemotherapy, with radiotherapy being left only as adjuvant treatment in the post-operative period of a successful resection surgery^{20,21}. Supportive and palliative measures as sole intervention are generally recommended at Stage IV, when patient conditions are poor or when no treatment is willingly accepted^{20,21}.

Objectives

In this work, we present the experience of 7 years in the management of MPM; we will analyze factors reported as being of poor prognosis for patient survival at any stage, and we will contrast them with observations in our group of patients at advanced stages.

Hypothesis

Survival in patients with Stages III and IV MPM will be affected by the same risk factors reported worldwide.

Table 1. Mesothelioma differential immunohistochemistry

Epithelioid mesothelioma versus Adenocarcinoma					
Antibody	Target	Epithelioid mesothelioma		Adenocarcinoma	
		Staining	Positivity (%)	Staining	Positivity (%)
Mesothelioma					
Calretinin	Nucleus	+	80-100	-	≈5
	Cytoplasm	+	80-100	-	5-10
Cytokeratin 5/6	Cytoplasm	+	60-100	-	2-10
Wilms tumor antigen 1	Nucleus	+	43-93	-	0
Epithelial membrane antigen	Membrane	+	60-100	-	≈5
	Cytoplasm	-	10-15	+	70-100
Podoplanin	Membrane	+	80-100	-	7
Lung adenocarcinoma					
Monoclonal carcinoembryonic antigen	Cytoplasm	-	≈ 0	+	50-90
CD 15	Membrane	-	0	+	50-70
Ber-EP4	Membrane	-	20	+	95-100
Thyroid transcription factor 1	Cytoplasm	-	0	+	70-85
Lewis blood group 8 ^y	Focal	-	7	+	90-100
B72.3	Cytoplasm	-	< 1	+	70-85
Breast carcinoma					
RE	Nucleus	-	0	+	≈70
Sarcomatoid mesothelioma versus Squamous cell and transitional cell carcinoma					
Antibody	Target	Sarcomatoid mesothelioma		Squamous cell and transitional cell carcinoma	
		Staining	Positivity (%)	Staining	Positivity (%)
Mesothelioma					
Calretinin	Nucleus	+	80-100	-	≈5
	Cytoplasm	+	80-100	-	5-40
Cytokeratin 5/6	Cytoplasm	+	60-100	+	100
Wilms tumor antigen 1	Nucleus	+	43-93	-	0
Squamous cell carcinoma					
P63	Nucleus	-	0	+	≈100
Ber-EP4	Cytoplasm	-	20	+	80-100
MOC 31	Membrane	-	2-10	+	97-100
Mesothelioma versus Reactive mesothelial reaction					
Antibody		Mesothelial proliferation		Mesothelioma	
		Staining	Positivity (%)	Staining	Positivity (%)
Desmin		+	85	-	10
Epithelial membrane antigen		-	20	+ (Epit)	80 (Epit)
P53		-	0	+, - (Sarc)	45 (Sarc)
Glucose transporter-1		-	3	+	67
Insulin-like growth factor-II RNA binding protein		-	0	+	73
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MATERIALS AND METHODS

A cross-sectional, retrospective study of patients diagnosed with MPM in the time period comprised from April 2008 to

December 2015 was conducted at the Hospital Juárez de México. We assessed those variables that, according to the literature, were considered predictors in a retrospective longitudinal study.

Population

A total of 76 medical records were found with the MPM registry diagnosis, out of which 49 (64.5%) corresponded to males and 27 (35.5%) to females; of the 76 subjects, 7 had diagnosis registration mistakes, and 13 had no histopathology report or staging or obtaining them was not possible to, which left 56 patient files with MPM accurate diagnosis. Of these, 8 had incomplete medical records, and other 6 had no follow-up or were not deemed adequate for the study, which left 42 medical files that met the inclusion criteria, out of which 29 (69.1%) corresponded to males and the remaining 13 (30.9%), to females. The files were reviewed, and data were collected in case report forms. This material was analyzed by means of the Statistical Package for the Social Sciences 24.0 software. Variables were grouped in demographic, history, clinical presentation, laboratory, and imaging studies, diagnosis and treatment aspects, adding up to a total of 27. The Kaplan-Meier method was used for survival analysis, and univariate analysis for each one of these aspects determined their statistical significance, considered as such at a $p < 0.05$ (Figs. 1 and 2).

RESULTS

Survival

Mean survival in our population was 8.1 months, with a minimum of 30 and a maximum of 1 year and 4 months; the Shapiro-Wilk test, with $W > p$ ($0.96 > 0.16$) demonstrated that data followed a normal distribution.

Demographic variables

A total of 37 patients came from the Megalopolis of Central Mexico (Mexico City, State of Mexico, Hidalgo, Morelos, Puebla, and Tlaxcala), 2 from Chiapas and Veracruz, and the remaining 3 from Querétaro; none of our cases came from Guanajuato. Mean age of our patients was 62.4 years, with a minimum value of 38 and a maximum of 85 years. Data distribution was corroborated to be normal with a W-value of 0.98 and a p value of 0.64 in the Shapiro-Wilk test. As a prognostic factor for survival, a cutoff point of 60 years was set, with a distribution of 59.2% above, and the remaining 40.8% below this value. Patients older than 59 years had a mean survival of 6 months versus 11.4 months for those younger than 60 years. The percentage of patients alive at 1 year in the older age group was 0%.

With a $p < 0.0001$, age was the most significant prognostic factor in our study. With an incidence of 2.23:1 in favor of the male gender, gender did not show differences in terms of mean survival, with 8.2 months for either gender, although, at 1 year, 21.4% of males remained alive in contrast with 8.3% of females; there were no statistically significant differences with regard to patient prognosis.

History

Only 12 patients (28.57%) acknowledged having a past history of exposure to asbestos, and survival in this group of patients was not also very different to that in those who did

Figure 1. Kaplan-Meier survival curve for age ($p < 0.001$).

Figure 2. Kaplan-Meier survival curve for serum albumin levels ($p < 0.001$).

not acknowledge exposure to asbestos (7.8 vs. 8.5); in our group, it was not a significant factor that affected survival. History of tobacco consumption was found in 17 patients (40.5%), with a mean of 13.3 packs/year (min 3, max 23). Using a cutoff point of >10 packs/year for all 42 patients, smoking was analyzed as a poor prognosis factor, and with a difference slightly higher than 1 month for survival being found in favor of patients with no history of smoking or with <10 packs per year, this factor was not significantly different in our population's patient survival. The incidence of diabetes mellitus in our population was 28.6%; however, there was no significant difference in survival of patients with or without this disease.

Clinical presentation

The Eastern Cooperative Oncology Group (ECOG)-developed performance status (PS) grade at diagnosis was different for each one of the performance grades, with the longest survival period being reached by Grade 1 with 11.3 months (min 3.5, max 16) and the shortest shown by Grade 3 with 5.9 months (min 1, max 13). Overall, those patients who were unable to be entirely responsible for their self-care (Grades 3 and 4) had a significantly poorer prognosis than those who at least were able to do it (Grades 0-2), with the survival of 6.5 and 10.2 months, respectively. In the classification of chest pain being present for the purposes of the study, we included the patients in whom this symptom occurred located in the hemithorax for at least 3 or more hours on a daily basis and ranged from blunt to impairing pain;

in more serious cases, pain was impairing and constantly present and only partially relieved by potent analgesics. Patients with chest pain accounted for 78.6% of our population and had a 7.3-month survival versus 11.3 months in those patients who did not experience pain. Pain was shown to be a symptom that significantly affected the prognosis.

The daily presence of episodes of temperature higher than 38.4°C lasting at least 1 h was documented in 8 patients (22.2%), with other causes for this sign being able to be ruled out, and, in 6 patients (75% of the group with fever), it followed an almost exclusively nocturnal pattern; in all 8 patients it was accompanied by chills and sweating. 28 patients did not experience fever and, in 6 patients, the presence or absence of this sign was not objectively documented. Absence of this sign practically doubled survival (8.5 vs. 4.3 months) and was a significant prognostic factor.

More than 90% of patients experienced dyspnea, and its absence, as in the case of fever, doubled survival, with a mean of 7.5 months for the group free of the symptom, and 14.8 for the group that did experience it.

Dry, persistent cough, which commonly required treatment with antitussives since diagnosis, was also a significant factor for poor prognosis; this factor was present in 83.3% of patients.

Weight loss occurred in 40 patients (95%), with average weight loss being 13.9% within the month before diagnosis. Overall, 35 patients had a weight loss higher than or equal to 10%, with mean weight loss of 15.0% versus 4.2% in the remaining 7 patients. With a difference of nearly 5 months in survival, weight loss was considered to be a factor significantly associated with poor prognosis.

Laboratory tests

White blood cell (WBC) count at diagnosis, or in case of any demonstrated infectious process, once the infectious process subsided, was $10.65 \times 10^3/\mu\text{L}$ on average, with 14 patients (33.3%) showing leukocytosis with a mean of $16.48 \times 10^3/\mu\text{L}$ (min: $10.4 \times 10^3/\mu\text{L}$ and max: $21.4 \times 10^3/\mu\text{L}$), and this being a factor significantly associated with worse prognosis for survival.

Mean platelet count was $308 \times 10^3/\mu\text{L}$, with 5 patients (11.9%) showing thrombocytopenia (mean: $110 \times 10^3/\mu\text{L}$), 25 patients (59.5%) with normal platelet count (mean: $259 \times 10^3/\mu\text{L}$), and 12 patients (28.6%) with thrombocytosis (mean: $493 \times 10^3/\mu\text{L}$, min: $441 \times 10^3/\mu\text{L}$, and max: $535 \times 10^3/\mu\text{L}$), with the latter group showing a significant difference in terms of survival (5 vs. 9.4 months) in the groups with thrombocytopenia or normal counts. Therefore, in our population, thrombocytosis was a factor of poor prognosis for survival. In no case could the cause of these platelet anomalies be identified.

Mean hemoglobin in our population at diagnosis was 11.3 g/dL (min 8.8 g/dL and max 13.7 g/dL). There were 34 patients with levels <13 g/dL (mean 10.9 g/dL), while 8 patients have normal hemoglobin values, with a mean of 13.25 g/dL. There were no differences between both these groups in terms of survival; therefore, hemoglobin levels did not affect prognosis in our population.

Pleural fluid lactate dehydrogenase (LDH) levels in our population ranged from 265 IU/L to 1954 IU/L, with a mean

of 1009 IU/L. With a cutoff point set at >500 IU/L, mean value in patients with low levels was 312.5 IU/L, whereas the group with high levels had a mean of 1407 IU/L, with survival differences of around 2.5 months; there was no significant difference regarding its prognostic value.

Normal albumin values were significantly associated with more than 2-fold survival levels than in case of hypoalbuminemia (9.8 vs. 4.5 months); mean serum albumin in our population was 3.7 g/dL (min 1.7 g/dL and max 5.7 g/dL), with a mean of 2.6 g/dL for the group with low albumin and 4.2 g/dL for the group with adequate albumin levels.

Imaging studies

Except for three patients, pleural thickening with nodular pattern was a consistent finding on chest CT, and in the vast majority on plain X-ray, without a relationship between its presence and prognosis being able to be established. Pleural effusion occurred in 37 patients (88%); however, it was massive (>60% of at least one hemithorax) in 13 patients (30.9%); pleurodesis was necessary in 20 patients (47.6%) and was carried out with povidone-iodine at bedside or transoperative in a biopsy procedure. Survival results were identical in the groups with and without massive effusion with 8.2 months. Mediastinal invasion was established in 39 patients (92.8%), but no prognostic difference could be established. There were also no significant differences with regard to the side of MPM involvement, although there was clear trend for development on the right side, which occurred in 65.8% of the patients with unilateral MPM.

Diagnosis

Plain X-ray and chest CT scan studies were performed in 100% of cases.

The diagnosis was histologically confirmed by means of open biopsy in 18 patients (42.9%) or CT-guided biopsy in the remaining 24 (57.1%). Of note, in 4 cases (9.5%) open biopsy occurred after a report of insufficient material for diagnosis with CT-guided biopsy, with the main indicators to decide this procedure being pleural thickness, site of location and patient general status. In our patient universe, nobody presented with clinical Stage I or II, and the prognostic impact was, therefore, studied in patients at both MPM most advanced stages: 7 patients (16.7%) at clinical Stage III with an 8.1-month mean survival showed no significant differences in comparison with 35 patients (83.3%) at clinical Stage IV with an 8.2-month survival.

With regard to histological lineage, malignant epithelioid pleural mesothelioma was the most common with 23 patients (54.8%), followed by sarcomatoid histology in 10 patients (23.8%) and mixed histology in 9 (21.4%). Neither the epithelial nor the sarcomatoid type showed survival differences in our population, with a survival mean of 8 and 7 months for the epithelial and sarcomatoid lineages, respectively (Table 2).

Antitumor treatment

Surgical antitumor treatment was contraindicated in all Stage IV patients. Among the 7 Stage III patients (all T3 N2 M0), surgical treatment was also contraindicated in those

Table 2. Lineage and staging for treatment in study patients

Staging					ECOG performance status		Histology			
							Epithelioid	Sarcomatous	Mixed	
T	N	M	Stage	Patients (%)	0-2	3-4	Sarcomatous	n (% of stage)	n (% of stage)	
3	2	0	III	7 (16.7)	4 (57.1)	3 (42.9)	2 (28.36)	3 (42.9)	2 (28.6)	
2	0	1	IV	1 (2.4)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	
	1	1		2 (4.8)	2 (100)	0 (0)	0 (0)	1 (50)	1 (50)	
	2	1		2 (4.8)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)	
3	2	1	IV	6 (14.3)	3 (50)	3 (50)	4 (66.7)	2 (33.3)	0 (0)	
	3	0		5 (11.9)	2 (40)	3 (60)	2 (40)	1 (20)	2 (40)	
		1		7 (16.7)	2 (28.6)	5 (71.4)	3 (42.9)	1 (14.3)	3 (42.9)	
4	2	0	IV	6 (14.3)	2 (33.3)	4 (66.7)	5 (83.3)	1 (16.7)	0 (0)	
		1		3 (7.1)	1 (33.3)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	
		3		0	2 (4.8)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)
				1	1 (2.4)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)
Total stage					Total ECOG PS		Total lineage			
I	II		III	IV	PS 0-2	PS 3-4	Epithelioid	Sarcomatous	Mixed	
0 (0)	0 (0)		7 (16.7)	35 (83.3)	19 (45.2)	23 (54.8)	23 (54.8)	10 (23.8)	9 (21.4)	
ECOG: Eastern Cooperative Oncology Group.										

ECOG: Eastern Cooperative Oncology Group.

with sarcomatous mesothelioma. Of the 4 patients with epithelioid or mixed mesothelioma, the N2 lymph node stage present in all of them contraindicated antitumor surgical treatment with pleurectomy and decortication, and the possibility of extrapleural pneumonectomy was therefore contemplated, with the procedure being contraindicated in the 2 patients with mixed mesothelioma owing to poor spirometric results.

Both patients with stage T3 N2 M0 epithelioid mesothelioma underwent surgical exploration with the purpose to perform extrapleural pneumonectomy, with initial exploration revealing complete resection was impossible, and the procedure was therefore aborted, and pleurodesis and debulking were performed in as much as it was safe.

As a logical consequence, if antitumor radiotherapy is considered as post-operative adjuvant treatment after any of both procedures that are specific for this entity, no patient was candidate to antitumor radiotherapy.

Of the 35 patients at Stage IV, 20 underwent palliative care owing to an ECOG PS of 3 or 4; the remaining 15, with ECOG PS of 0 to 2, were assessed for observation or chemotherapy initiation, with this treatment being administered in 8 cases. As for patients with sarcomatous lineage at Stage III (3 patients) or mixed histology (2 patients with medical contra indication for surgery), none underwent antitumor chemotherapy, either because they were maintained under observation (2 patients) or because they were maintained on palliative care (3 patients). Both patients who underwent surgical exploration received chemotherapy. The chemotherapeutic regimen administered in all cases was based on a combination of pemetrexed and platinum salts.

Symptom and palliative treatment

In those patients who experienced pleural effusion-associated dyspnea, drainage and/or pleurodesis with povidone-iodine was practiced, either at the moment of the open biopsy procedure or after diagnosis by placing the pleural drainage catheter at bedside. In addition, dyspnea that was not associated pleural effusion was managed with supplemental oxygen with nasal cannulas or different variants of masks. For the treatment of cough, when it was dyspnea or cyanosis-producing, benzonatate was resorted to; however, dextromethorphan, codeine, and dexamethasone were also used. Chest pain usually responded to combined analgesics; however, at more advanced stages, fentanyl-releasing patches were used, or when it was associated with dyspnea, morphine. Food supplements failed to stop weight loss; however, they caused for it to be less pronounced. Nausea, either secondary to the neoplastic process or to chemotherapy, was managed with metoclopramide and ondansetron. No patient received palliative radiotherapy. Patients who required pleurodesis (30.9%) due to pleural effusion, in spite of not having a significant increase in survival, did refer clinical and the quality of life improvement.

Treatment-related prognostic factors

Most importantly, no type of treatment was superior to another with regard to patient survival. Upfront chemotherapy not associated with surgery yielded a 7.5-month survival; with palliative treatment, it was 8.8 months, and with observation, 7.4 months.

Mortality

Our patients' survival was 8.1 months, with a range of 1 to 16 months. Factors affecting survival in our population, in order of importance, were age and serum albumin ($p < 0.001$) (Figures 1-2); platelet count, presence of fever,

weight loss and dyspnea ($p < 0.01$), and WBCs, ECOG PS, chest pain, and cough ($p < 0.05$) (Table 3).

Factors that had no weight with regard to prognosis in our population were gender, exposure to asbestos, smoking, diabetes, hemoglobin levels, pleural fluid LDH, the presence of pleural nodules or mediastinal invasion, bila-

Table 3. Study variables statistical analysis

Study variables	n (%)	x (min-max)	SD	Alive 6 months	Alive 12 months	p
Age	42	62.4 (38-85)	1.4			
>60 years	25 (59.52)	6 (1-12)	3.4	52%	0%	0.0001
<60 years	17 (40.48)	11.4 (5-16)	3.1	88.2%	41.2%	
Gender						
Male	29 (69.05)	8.2 (1-16)	4.5	64.3%	21.4%	0.6291
Female	13 (30.95)	8.2 (1-13)	3.5	83.3%	8.3%	
Exposure to asbestos						
Present	12 (28.57)	7.8 (1-16)	5.4	58.3%	33.3%	0.453
Absent	30 (71.43)	8.3 (1-14)	3.7	70%	10%	
Smoking						
>10 packs/year	12 (28.57)	7.3 (1-15)	4.9	63.6%	27.3%	0.9361
<10 packs/year	30 (71.43)	8.5 (1-16)	3.9	69%	10.3%	
Diabetes						
Present	12 (28.57)	7.4 (1-15)	4.6	58.3%	25%	0.7959
Absent	30 (71.43)	8.5 (1-16)	4.1	70%	13.3%	
ECOG PS						
3-4	23 (54.76)	6.5 (1-13)	4.2	47.8%	8.7%	0.0145
0-2	19 (45.24)	10.2 (5-16)	3.3	89.5%	26.3%	
Chest pain						
Present	33 (78.57)	7.3 (1-15)	4	57.6%	9.1%	0.0327
Absent	9 (21.43)	11.3 (7-16)	3.3	100%	44.4%	
Fever						
Present	8 (22.22)	4.3 (1-9)	3.2	37.5%	0%	0.0052
Absent	28 (77.78)	8.5 (1-15)	3.8	67.9%	17.9%	
Dyspnea						
Present	38 (90.48)	7.5 (1-13)	3.8	63.2%	7.9%	0.006
Absent	4 (9.52)	14.8 (14-16)	1	100%	100%	
Cough						
Present	36 (85.71)	7.5 (1-14)	4	61.1%	13.9%	0.0425
Absent	6 (14.29)	12.2 (8-16)	3	100%	33.3%	
Weight loss						
>10% weight	35 (83.33)	7.4 (1-13)	3.9	64.3%	0%	0.0059
<10% weight	7 (16.67)	12 (6-16)	3.8	100%	66.7%	
WBC						
>10,000/ μ L	14 (33.33)	6 (1-12)	3.6	50%	0%	0.0134
<10,000/ μ L	28 (66.67)	9.3 (1-16)	4.1	75%	25%	
Platelets						
>400,000/ μ L	12 (28.57)	5 (1-10)	3.3	41.7%	0%	0.0012

(Continue)

Table 3. Study variables statistical analysis (*Continued*)

Study variables	n (%)	x (min-max)	SD	Alive 6 months	Alive 12 months	p
<400,000/ μ L	30 (71.43)	9.4 (1-16)	3.9	76.7%	23.3%	
Hemoglobin						
<13 mg/dL	34 (80.95%)	7.7 (1-16)	4.1	64.7%	11.8%	0.2979
>13 mg/dL	8 (19.05)	10 (3-15)	4.2	75%	37.5%	
Pleural fluid LDH						
>500 IU/L	28 (66.67)	7.3 (1-15)	4.1	64.3%	14.3%	0.1283
<500 IU/L	14 (33.33)	9.9 (3-16)	3.9	71.4%	21.4%	
Serum albumin						
<3.5 g/dL	13 (30.95)	4.5 (1-9)	3.1	30.8%	0%	0.0001
>3.5 g/dL	29 (69.05)	9.8 (3-16)	3.5	82.8%	24.1%	
Pleural nodulation						
Present	39 (92.86)	7.8 (1-16)	4.1	64.1%	12.8%	0.2176
Absent	3 (7.14)	12.7 (11-14)	1.5	100%	66.7%	
Pleural effusion						
>60%	13 (30.95)	8.2 (1-14)	4	69.2%	15.4%	0.8432
<60%	29 (69.05)	8.2 (1-16)	4.3	65.5%	17.2%	
Mediastinal invasion						
Present	39 (92.86)	8.2 (1-16)	4.1	69.2%	15.4%	0.9971
Absent	3 (7.14)	7.3 (3-14)	5.9	33.3%	33.3%	
Bilaterality						
Bilateral	4 (9.52)	10 (1-14)	6.1	75%	50%	0.3377
Unilateral	38 (90.48)	8 (1-16)	4	65.8%	13.2%	
Involved hemithorax						
Right	25 (65.79)	7.6 (1-16)	4.1	60%	8%	0.5827
Left	13 (34.21)	8.8 (3-15)	3.8	76.9%	23.1%	
Stage						
IV	35 (83.33)	8.2 (1-16)	4.5	62.9%	20%	0.4702
III	7 (16.67)	8.1 (6-12)	2	85.7%	0%	
Non-epithelial lineage						
Non-epithelial	19 (45.24)	8.4 (1-16)	4.9	63.2%	21.1%	0.3316
Epithelial	23 (54.76)	8 (1-13)	3.7	69.6%	13%	
Sarcomatous lineage						
Sarcomatous	10 (23.81)	7 (1-15)	5.2	50%	20%	0.7862
Non-sarcomatous	32 (76.19)	8.5 (1-16)	3.8	71.9%	15.6%	
CT versus others						
CT alone	8 (20)	7.5 (5-12)	2.3	62.5%	0%	0.2548
Non-CT	32 (80)	8.4 (1-16)	4.7	65.6%	21.9%	
PAL versus others						
PAL	23 (54.76)	8.8 (1-16)	4.9	65.2%	30.4%	0.0937
Non-palliative	19 (45.24)	7.4 (1-12)	3.2	68.4%	0%	
CT versus OB						
CT	8 (47.06)	7.5 (5-12)	2.3	62.5%	0%	0.8139
OB	9 (52.94)	7.4 (1-12)	4.2	55.6%	0%	

SD: Standard deviation; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; WBC: White blood cell; LDH: Lactate dehydrogenase; CT: Computed tomography; PAL: Palliative.

terality or side, stage, lineage, and the different treatment modalities.

DISCUSSION

We present the experience on the treatment of MPM with a series of a similar number of subjects to those reported by other authors; however, our population was characterized for including predominantly American Indian ethnicity patients at Stages III and IV.

Gender and mean age distribution in our group was similar to those reported in the literature. Although age older than 60 years was a significant risk factor, male gender was not a poor prognosis factor in our study.

Another situation that draws the attention in our study is the small number of patients who referred having worked with or been exposed to asbestos, which differs from all existing literature. However, the causes can be multifactorial, and the considerably elevated latency time, lack of knowledge about substances handled at work, and the marked use of asbestos in structures as widely spread as asbestos sheets on household roofs might contribute to explain this apparent lack of exposure.

Smoking and diabetes, consistent with other studies, neither seem to influence on MPM patients' survival. Mesothelioma synchronicity or lung cancer could not be determined in our population since no patient had both these conditions.

In other studies, the ECOG PS scale has been shown to be an index with prognostic value, with Grades 0, 1, and 2 being associated with higher survival, which is consistent with data obtained in our population.

Clinical presentation in our patients was similar to that described in previous publications; however, dyspnea and cough were present in 9 and 8 out of every 10 patients, respectively, which are figures much higher than those reported in the literature and that cannot be explained by the presence of infection, clinical stage, or comorbidities at diagnosis. Weight loss at diagnosis was also different in our population since 80% of patients lost 10% of their weight in 3 months versus 25% reported in the literature. Fever showed similar figures to those reported in the literature. The patient clinical presentation was fundamental to prognosis, and all clinical presentations were significantly related to patient prognosis.

Laboratory tests results were essentially shown, as in other studies, to be of prognostic importance; however, the fact that hemoglobin and pleural fluid LDH levels were not related to survival draws the attention; probably this was due to the number of individuals in one of the groups resulting from the division according to the cutoff point, or else to the disease advanced stage. One last factor that has not been prognostic, or has not been investigated in patients with MPM, is serum albumin, which, in our population, was a significant factor.

The involved hemithorax or the presence of bilateral involvement, massive pleural effusion and mediastinal invasion had no impact on survival as it could be expected, probably owing to the advanced stage of the disease in our patients, which rendered these factors being present in most patients, which in turn lowered the power for statistical comparison of the resulting groups, in addition to the lack of contrast with patients at earlier stages of disease.

As a finding that differs from reports in other studies, in our population, the type of MPM and the type of treatment had no impact on survival. This unusual situation might be due to the fact that all patients were at advanced Stages III and IV.

Patient survival was lower than that generally reported for MPM; however, it was consistent with the survival expected for Stages III and IV and, therefore, we believe that survival in our group of patients was adequate to that expected for advanced stages.

CONCLUSIONS

MPM is an aggressive condition that in our setting is lately diagnosed, with poor treatment response and adverse prognosis, especially at advanced stages, with the highest survival observed in these cases being 16 months. The three most influential factors on patient prognosis are age older than 60 years, patient clinical presentation, and presence of abnormalities in laboratory tests. At more advanced stages, lineage and type of treatment had no impact on patient survival in our population, which warrants the conduction of studies with larger samples and with earlier stages to corroborate this observation.

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