

Multicentric study on malignant pleural mesothelioma in Turkey: clinicopathologic and survival characteristics of 282 patients

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Received: 2 April 2012 / Accepted: 6 June 2012 / Published online: 22 June 2012
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Abstract Malignant pleural mesothelioma (MPM) is a relatively rare, but aggressive tumor that causes high mortality. The major risk factor involved in the etiology is environmental and occupational exposure to asbestos. The optimal modality of therapy is controversial. The present study retrospectively evaluated the data pertinent to 282 patients who were examined and treated in 11 different medical oncology centers in Turkey. There were 161 males (57.1 %) and 121 females (42.9 %), with a mean age of 56.38 ± 12.07 years. Surgery was used in 74 patients, 21 patients (28.4 %) received only chemotherapy and 28 patients (37.8 %) received chemoradiotherapy after surgery. The median survival in patients who were administered adjuvant therapy after surgery was 24 months, while

the median survival in patients who had only surgery was 6 months ($p = 0.029$). 106 patients were administered pemetrexed-platinum combination and 35 patients were administered gemcitabine-platinum combination as front-line chemotherapy. Median survival, 1- and 2-year survival rates in patients who received platinum analogues and pemetrexed or gemcitabine combinations were found statistically similar ($p = 0.15$). The median survival for all patients with MPM in our study was 18 months. The main factors influencing the overall survival were stage of the disease ($p = 0.020$), performance status ($p < 0.001$), asbestos exposure ($p = 0.030$) and mesothelioma histological subtypes ($p < 0.001$). Results of our study suggest that multi-modality treatment regimens consisting of

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surgery, radiotherapy and chemotherapy prolong overall survival. Survival rates in patients who received combining platinum analogues with pemetrexed or gemcitabine as front-line chemotherapy were found similar.

Keywords Malignant pleural mesothelioma · Asbestos exposure · Multi-modality treatment · Front-line chemotherapy · Prognostic factors

Introduction

Malignant mesothelioma is a tumor originating in the mesothelial surfaces of pleura, peritoneum, pericardium or tunica vaginalis. Malignant pleural mesothelioma (MPM) accounts for about 80 % of all cases diagnosed with malignant mesothelioma. MPM is an aggressive primary tumor of the pleura with an increasing incidence [1, 2]. The major risk factor involved in the etiology of MPM is environmental and occupational exposure to asbestos. History of exposure to asbestos has been shown in 70–80 % of the patients [3, 4]. Apart from asbestos exposure, exposure to erionite, a fibrous zeolite found in the Central Anatolia region in Turkey, has been demonstrated to play a considerable role in the etiology of MPM [5–7].

There is no standard treatment of the disease. Treatment alternatives cover a wide range from palliative therapy to multi-modality treatment regimens consisting of surgery, radiotherapy and chemotherapy [8–12]. Its median overall survival rate is 9–17 months and 5-year survival rate is less than 5 % [13, 14].

In the present study, we aimed to retrospectively examine the demographic and prognostic characteristics, outcome of the administered treatments, treatment responses and survival rates of 282 patients diagnosed with MPM.

Patients and methods

Patient population

The present study retrospectively examined the data pertinent to 282 MPM patients who were examined and treated in 11 different medical oncology centers in Turkey from July 2000 to February 2011. Clinical symptoms and signs, diagnostic and therapeutic methods, treatment responses and complications, prognostic characteristics and survival times of the patients were obtained from investigations of patient records. MPM diagnosis was given on the basis of the cytological analysis of pleural fluid, closed pleural biopsy or open biopsy.

Demographical data regarding the cases like age, sex, occupation, smoking, history of asbestos and erionite

exposure, place of residence, clinical properties like clinical symptoms, diagnostic method, histological type, tumor localization and stage as well as treatment methods, side effects of treatment and survival rates were all examined.

Staging was performed according to the staging system based on the tumor, node, metastasis (TNM) classification and suggested by International Mesothelioma Interest Group (IMIG) in 1995 [15]. Treatment toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0 grading system.

Statistical analyses

Prognostic factors such as stage, asbestos exposure, performance status, histological subtype were analyzed by the Kaplan–Meier method and statistically compared using log-rank test. Overall survival time was calculated as the time that elapsed between the time when the initial pathological diagnosis was given and the time when the patient died or was last contacted. Statistical tests resulting in *p* values of less than 0.05 were considered to be significant.

Results

Patient characteristics

Characteristics of the patients and the tumor are presented in Table 1. The study registered a total of 282 patients, of whom 121 (42.9 %) were females and 161 (57.1 %) were males. The ages of the patients ranged between 28 and 87.5 years, with a mean age of 56.38 ± 12.07 years. Environmental exposure to asbestos was found in 138 (48.9 %) patients and exposure to erionite was found in 11 (4 %) patients. Asbestos and erionite exposure started in childhood. Of the patients, 37 had not been exposed to asbestos and asbestos exposure had not been asked to 107 patients. None of our patients had occupational asbestos exposure. The patients lived in Eastern, South Eastern and Central Anatolia regions of Turkey where natural asbestos and erionite deposits are found. The 11 patients exposed to erionite lived in Nevsehir city.

Of the patients, 26.24 % were in the age range between 60 and 69; 29.43 % were in the age range between 50 and 59; 19.86 % in the 40–49 age range; 28 patients (9.9 %) were under 40; and 41 patients (14.6 %) were over 70 years. Our youngest case was 28 years old. There was no difference between males and females in terms of the distribution of age.

Clinical presentation

The most common presenting complaints among the patients were shortness of breath in 156 (55.3 %), weight

Table 1 Demographic data regarding the patients and the tumor

Characteristics	<i>n</i>	%
Age (years)		
Median	56.38 ± 12.07	
Range	28–87.5	
Gender		
Male	161	57.1
Female	121	42.9
ECOG score		
0	65	23
1	129	45.7
2	76	27
Histological subtype		
Epitheloid	150	53.2
Biphasic	26	9.2
Sarcomatoid	8	2.8
Stage		
I	8	2.8
II	60	21.4
III	123	43.6
IV	91	32.2
Localization		
Right hemithorax	161	57.1
Left hemithorax	121	42.9
Asbestos exposure		
Present	138	48.9
Absent	37	13.1
Erionite exposure		
Present	11	4
Absent	271	96
Smoking		
Present	107	37.9
Absent	127	45
Weight loss (10 % or greater weight loss in the last 6 months)		
Present	83	9.4
Absent	192	68.1

ECOG The Eastern Cooperative Oncology Group performance status

loss in 83 (29.3 %), chest pain in 71 (25.2 %) and coughing in 42 (14.9 %). Other common signs and symptoms included malaise, night sweats and mass on the chest wall. The duration of symptoms was shorter than 3 months in 145 patients (50.4 %). In only 49 patients (17.4 %), the symptoms had lasted for more than 6 months.

Tumor characteristics

The tumor was located in the right hemithorax in 161 patients (57.1 %) and in the left hemithorax in 121 patients (42.9 %). The histological subtype of the tumor was epithelial in 150 patients (53.2 %), sarcomatoid in 8 patients

(2.8 %) and biphasic in 26 patients (9.2 %), but histological subtype was either not determined or not recorded in 98 patients (34.8 %). The patients were staged according to the criteria of the IMIG. Eight patients (2.8 %) were identified as stage I, 60 (21.4 %) as stage II, 123 (43.6 %) as stage III and 91 patients (32.2 %) as stage IV. At the time of diagnosis, 46 patients (16.1 %) had distant organ metastasis (Table 1). Metastatic sites were liver (*n* = 11), contralateral lungs (*n* = 11), bone (*n* = 8), ipsilateral lung (*n* = 8) and other sites (*n* = 8).

Treatment modalities

Different treatment modalities were administered in the patients. A majority of the patients had locally advanced or metastatic disease at the time of diagnosis. Surgery was used in 74 patients (decortications/pleurectomy), 21 patients (28.4 %) received only chemotherapy after surgery and 28 patients (37.8 %) received chemoradiotherapy after surgery. As the chemotherapy regimen, 29 patients (49.2 %) were administered pemetrexed-cisplatin, 14 patients (23.7 %) were administered gemcitabine-cisplatin and the other patients received cisplatin-adriamycin and single-agent gemcitabine. Twenty-five patients (33.8 %) did not receive chemotherapy after surgery.

Out of the 208 patients who did not undergo surgery, 157 (75.4 %) were administered front-line chemotherapy. As the chemotherapy regimen, 106 patients were administered pemetrexed-platinum combination (pemetrexed-cisplatin to 95 patients and pemetrexed-carboplatin to 11 patients) and 35 patients were administered gemcitabine-platinum combination (gemcitabine-cisplatin to 30 patients and gemcitabine-carboplatin to 5 patients). The rest of the patients received double- or triple-agent chemotherapy regimens containing cisplatin-based agents other than those cited above or single-agent pemetrexed or gemcitabine. For the patients who received pemetrexed-platinum regimen, a median of 6 cycles of chemotherapy was administered and 50 patients (47.2 %) were able to receive all 6 cycles as planned. For the patients who received gemcitabine-platinum regimen, a median of 6 cycles of chemotherapy was administered and 19 patients (54.3 %) were able to receive all 6 cycles. Median survival was found 16 months in the pemetrexed-platinum regimen and 26 months in the gemcitabine-platinum regimen. There was no statistically significant difference between the patients who received pemetrexed-platinum and gemcitabine-platinum regimens in terms of the median overall survival (*p* = 0.15, Figure 2).

Chemotherapy adverse events

As ours was a retrospective study, not all toxicity data, particularly data regarding low-grade toxicity, might have been

reached. The most common adverse effect was myelosuppression. The most frequently observed non-hematological toxicities included nausea, vomiting, malaise, diarrhea and neuropathy. There was no mortality associated with chemotherapy toxicity.

Patient survival

The median survival duration of the patients in the study was 18 months. One-year, 3- and 5-year survival rates were 69, 28 and 13 %, respectively. Survival rates were similar in males and females. There was no difference between the survival rates of the patients under and over 60 years of age. Factors that affected overall survival were stage of the disease ($p = 0.020$), performance status ($p < 0.001$), asbestos exposure ($p = 0.030$) and mesothelioma histological subtypes ($p < 0.001$; Table 2).

Discussion

Malignant pleural mesothelioma is a rare, but aggressive tumor that causes high mortality. Two major factors that are known in its etiology are exposure to asbestos and erionite fibers. The disease develops as a result of the inhalation of these fibers [16]. Asbestos deposits are greater in some rural residential areas in the Eastern and South-eastern Anatolia Regions of Turkey. The soil contaminated with asbestos has been used in the whitewashing of houses for many years in these areas. [17–20]. MPM due to environmental exposure rather than occupational exposure is more common in Turkey [21, 22]. The incidence of MPM associated with erionite, which plays a key role in the etiology of MPM apart from asbestos, is very high around Nevsehir city in the Central Anatolia region of our country [6, 7, 23]. Erionite is found in the volcanic rocks used as building blocks in this area. Exposure to minerals starts with birth, and therefore, even people who have emigrated at early ages are afflicted by the disease [5, 18, 24]. In our study, most of the cases with a history of environmental exposure reside in Eastern and Southeastern Anatolia regions. The 11 patients who had a history of erionite exposure were from the residential areas of Central

Anatolia. The fact that our cases did not work in the areas where asbestos is used suggests that environmental factors are at play in the development of MPM.

That MPM patients are generally at advanced ages suggests that the development of MPM takes a fairly long latent period. The mean period between the first exposure and the development of the disease is 25 to 40 years, with some studies indicating a period between 10 and 65 years [25–28]. The mean age of our patients is 56.38 years (28–87.5 year) which is consistent with literature.

Malignant pleural mesothelioma is more common in males, with the male/female ratio of occupational asbestos exposure standing at 1/3–1/12, and the incidence of the disease increases with age. That is because MPM associated with occupational exposure to MPM is more common among males. However, among the patients who have a history of environmental asbestos exposure, the ratio of males to females is closer, as was the case in our study [16, 29, 30]. The male to female ratio among our patients was 1.33. The reason for this is the fact that both sexes live in the same environmental conditions [10, 31, 32].

Clinical symptoms of the disease depend on the local progression of the tumor. The most common presenting clinical symptoms and signs include shortness of breath, chest pain and ipsilateral pleural effusion. Some constitutional symptoms like weight loss, malaise, cough and fever are also observed, but to a lesser extent [33–36]. The most common symptoms in our patients were shortness of breath at a rate of 55.3 %, weight loss at a rate of 29.3 % and chest pain at a rate of 25.2 %. Our clinical findings were consistent with those of other researchers.

In 161 patients (57.1 %), pleural mesothelioma originated in the right side pleural surface and this finding was also similar to the findings of other studies [37, 38]. Despite the lack of any definitive explanation as to why pleural mesothelioma is more common in the right side, one hypothesis is that the right main bronchus is separated from the trachea by a narrower angle [13].

The diagnosis of MPM can be challenging and compulsion to confirm histologically [39]. The diagnostic value of the cytological analysis of the pleural fluid ranges between 7 and 32 % [40, 41]. The diagnostic value of closed pleural biopsy has been reported higher [42]. It is known that the combination of closed pleural biopsy and cytology has a greater diagnostic value [43]. Video-assisted thoracoscopic surgery (VATS), on the other hand, provides an accurate diagnosis over 90 % of the time thanks to its ability to provide a better image of the pleural cavity [44]. In our study, diagnosis was given by pleural biopsy in 168 patients (59.6 %), VATS in 61 patients (21.6 %) and cytological analysis in 33 patients (11.7 %).

Malignant pleural mesothelioma has 3 histological subtypes. The most common subtype is the epithelial type

Table 2 Prognostic factors that affect overall survival

Prognostic factors	Good	Poor	<i>p</i>
ECOG score	0, 1, 2	3, 4	<0.001
Stage	I, II	III, IV	0.020
Histologic subtype	Epithelial	Sarcomatoid	<0.001
Asbestos exposure	Present	Absent	0.030

ECOG The Eastern Cooperative Oncology Group performance status

(55–60 %), followed by the biphasic type (25–30 %) and sarcomatous type (10–15 %) in frequency [45, 46]. Epithelial histological subtype has a better prognosis than other subtypes. Of our patients, 53.2 % had epithelial subtype and, in congruence with the literature data, the prognosis of these patients was better than that of the patients with the sarcomatous type.

Although new treatment strategies have been developed, the survival and prognosis of MPM patients is poor in general. Mean survival rates range between 6 and 17 months, with the mean less than 12 months and 5-year survival rates below 5 % [13, 14]. Median survival for all patients in our study was 18 months and the rate of 5-year survival was 13 %.

No clear consensus has been reached over the treatment of MPM patients. The fact that none of the treatments is useful in and of itself has brought the multi-modality treatment method to the fore. Multi-modality treatment consists of surgery and adjuvant treatment alternatives including radiotherapy and systemic and/or intrapleural chemotherapy. The best outcomes are obtained by multi-modality treatments in selected patients. The administration of such treatments has brought about an improvement, though modest, in the survival of patients [44, 47, 48]. Clinical stage II–III patients who do not have comorbid diseases and whose performance status is good are candidates for multi-modality treatments. However, since most MPM patients have late-diagnosed, unresectable and locally advanced disease or comorbid diseases, radical surgical interventions cannot be conducted [8, 49]. In our study, 74 patients (26.2 %) were operated on. As the surgical operation, EPP was performed in 8 patients and decortication in 66 patients. The comparison between patients who were operated on and those who were not did not reveal any statistical difference in their median overall survival rates ($p = 0.85$, Fig. 1). There are no randomized, controlled studies showing the efficacy of only surgery in treatment [50].

Most of the patients who have curative surgery are administered adjuvant chemotherapy and/or radiotherapy [51]. In a 183-patient series published in 1999, Sugarbaker et al. reported 2-year survival to be 38 % and 5-year survival to be 15 % in the multi-modal treatment approach consisting of pleuropneumonectomy and adjuvant chemoradiotherapy [52]. In a study where stage II and III pleural mesothelioma patients who had decortication or pleurectomy following neoadjuvant intrapleural IL-2 were administered adjuvant gemcitabine-cisplatin chemotherapy and radiotherapy together with long-term IL-2, mean survival time was reported to be 28 months [53]. In our study, the median survival in patients who were administered adjuvant therapy after surgery was 24 months, while the median survival in patients who had only surgery was 6 months ($p = 0.029$; Fig. 2).

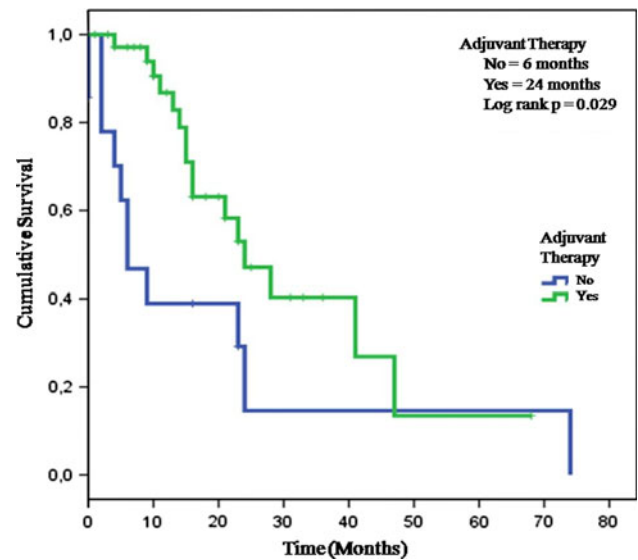


Fig. 1 Overall survival curves of the patients who did and did not receive adjuvant therapy after surgery

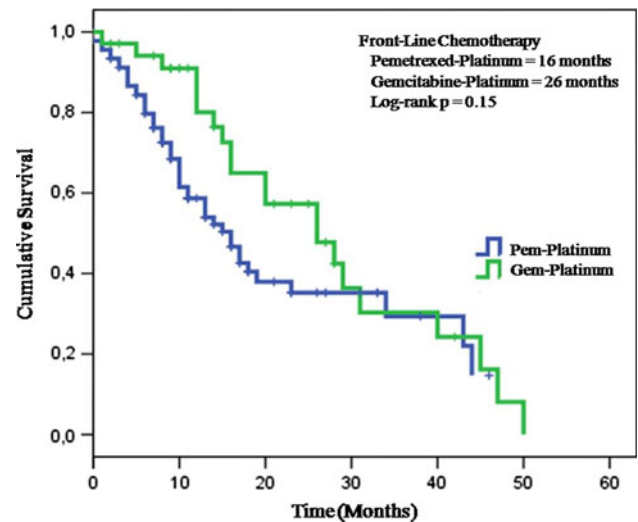


Fig. 2 Overall survival curves of the patients who were administered pemetrexed-platinum and gemcitabine-platinum as front-line chemotherapy

Chemotherapy is used in several settings, such as in multi-modality treatment and, chemotherapy can be used as a neoadjuvant treatment in order to reduce the tumor volume or for adjuvant treatment to reduce local and distant recurrences, and it is used for palliative purposes [50, 54]. Many chemotherapeutic agents have been used either as a single agent or as part of a combined chemotherapy regimen in MPM patients. Platinum analogues, doxorubicin, gemcitabine, methotrexate, raltitrexed and pemetrexed are all single agents with proven efficacy, and according to the results of a systemic review of studies published from 1965 to 2001, the highest response rates were obtained with

combined chemotherapy regimens [54]. The most frequently employed chemotherapy protocol is the cisplatin-based regimens [55, 56]. The efficacy and response rates of cisplatin and carboplatin are similar in MPM patients [57].

Recent studies indicate that response and survival rates obtained with platinum analogues and pemetrexed or gemcitabine combination regimens are pretty good. A phase III trial randomized 456 chemotherapy-naïve patients receive cisplatin plus pemetrexed or cisplatin alone. Results of the study showed that median overall survival was 12.1 months in the combined regimen. When compared to the single-agent cisplatin, combined regimen improved median survival, time to progression, response rate, pulmonary functions and symptom control [58]. On the basis of the results of this 2003 study, pemetrexed-cisplatin combination regimen is accepted as the standard in the treatment of MPM. However, gemcitabine-cisplatin combination from phase II studies is used in the clinical practice due to the significant results obtained in response and survival rates. This combination regimen leads to response rates between 12 and 48 % and median overall survival times of 9.4–17.3 months [59–61]. The efficacy of a gemcitabine-carboplatin combination regimen has also been reported [62]. In a retrospective Canadian study, Lee et al. presented comparing platinum plus pemetrexed ($n = 34$) with platinum plus gemcitabine ($n = 38$) and reported no difference in median survival, 1- and 2-year survival rates [63]. In our study, the survival rates of the patients who received front-line chemotherapy were found 26 months in the patients who were administered gemcitabine-platinum ($n = 35$) and 16 months in the patients who were administered pemetrexed-platinum ($n = 106$; $p = 0.15$). An evaluation of survival rates demonstrated that 1- and 2-year survival rates were 90 and 57 %, respectively, in the patients who received gemcitabine-platinum and 59 and 36 %, respectively, in the patients who received pemetrexed-platinum and there was no statistically difference between the treatment groups ($p = 0.15$).

Previous studies reported that the factors which affected prognosis were age, sex, performance status, serum lactate dehydrogenase level, thrombocyte count, stage, histologic subtype and surgical resection [64–67]. In our study, good performance status ($p < 0.001$), early stage ($p = 0.020$), epitheloid histology ($p < 0.001$) and presence of asbestos exposure ($p = 0.030$) positively contributed to survival.

Conclusion

Malignant pleural mesothelioma is an important disease due to its high incidence in some regions of the world. The fact that none of our patients had MPM-associated occupational history indicates that environmental exposure is dominant in the development of the disease.

Results of our study suggest that multi-modality treatment prolongs overall survival. Survival rates in patients who received platinum analogues and pemetrexed or gemcitabine combinations as front-line chemotherapy were found similar.

Additionally, we believe that novel treatment modalities such as systemic and intrapleural chemotherapeutic agents and targeted agents may contribute to the treatment of the disease. In order to obtain more satisfying results and determine the optimal therapeutic alternative in MPM treatment, multicenter phase III prospective randomized trials phase is needed.

Acknowledgments This manuscript was not supported by any financial help or other relationships.

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