RESEARCH ARTICLE

Clinical Characteristics, Treatment and Survival Outcomes in Malignant Mesothelioma: Eighteen Years' Experience in Turkey

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Abstract

Background: Malignant mesothelioma (MM) is an insidious tumor with poor prognosis, arising from mesothelial surfaces such as pleura, peritoneum and pericardium. We here aimed to evaluate the demographic, clinical, and radiological features of patients with MM followed in our center as well as their survival. **Methods**: The study included 228 patients (131 male, 97 female) who were followed up in our institution between 1993 and 2010 with the diagnosis of MM. **Results**: The mean age was 59.1 years in men and 58.7 years in women and the sex ratio was 1.4:1 in favor of males. Environmental asbestos exposure was present in 86% of the patients for a mean duration of 40±20 years (range: 3-70). Pleural effusion and thoracic/abdominal pain were the most common presenting signs and symptoms (70.2% and 57.8%, respectively). One hundred-thirteen (66%) patients were treated with platinum-based combination chemotherapy (PBCT) plus supportive care (SC) and 67 (34%) patients received SC alone. The median follow-up time was 10.0 months. The median overall survival was significantly improved with PBCT plus SC compared to SC alone (11.4 vs. 5.1 months; p=0.005). The 6, 12, 18, and 24-month survival rates were significantly improved with PBCT plus SC compared to SC alone (72%, 43%, 19%, and 2% vs. 49%, 31%, 11%, and 1%). **Conclusion**: The survival of patients with MM improved in patients treated with PBCT. The survival advantage continued 12- and 24-month after the initial time of combination chemotherapy.

Keywords: Malignant mesothelioma - asbestos - chemotherapy - supportive care

Introduction

Malignant mesothelioma (MM) is an insidious tumor with poor prognosis, arising from mesothelial surfaces such as pleura, peritoneum, pericardium, and tunica vaginalis. In 80% of the cases, the disease originates from pleura; it is the most common malignant neoplasm of this tissue (Sterman et al., 2008). The disease is thought to ensue after 20-40 years of asbestos exposure. Although the data about the prevalence of the disease in most parts of the world are not sufficient, the incidence is expected to rise in the coming 20-30 years (Ismail-Khan et al., 2006; Bianchi and Bianchi, 2007). The districts of Sivas, Tokat, Yozgat, and Erzincan which are situated in the northeastern part of the Central Anatolia are among the richest regions in Turkey in terms of asbestos minerals (MTA, 2012). Sivas is a district with a population of nearly 700,000 where asbestos-contaminated soil has been used as stucco and roofing material, especially in the rural areas, for years (Figure 1).

This study aimed to determine demographic, clinical, and radiological features of the MM cases diagnosed in the district of Sivas between 1993 and 2010, and to discuss the treatment results in the context of relevant literature.
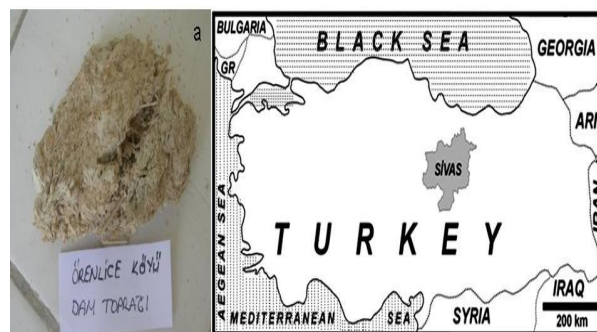

Figure 1. Sample of Asbestos-Contaminated Soil used as Stucco in the Village of Orenlice (a), The Localization of the District of Sivas on the Map of Turkey (b)

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Materials and Methods

The study was approved by the clinical research ethics committee of the Cumhuriyet University and included 228 patients who were followed up in our institution between 1993 and 2010 with the diagnosis of MM. The demographical, clinical and radiological characteristics of the patients were recorded alongside the diagnostic and treatment modalities they received. Radiological features were assessed according to direct chest radiography and thoracic computerized tomography reports. The level of environmental exposure to asbestosis was expressed as the duration of living in houses where asbestos-contaminated soil was used as stucco, which was recorded in patients' files. Of these patients, 197 (86.4%) who were treated in our institution were divided into two groups according to provided treatment as those who received platinum-based combination chemotherapy (PBCT) plus supportive care (SC) and those who received SC alone. The patients in the latter group consisted of those who were not administered chemotherapy due to Karnofsky performance scale below 50 and those who did not consent to chemotherapy. Supportive care included use of steroids, analgesic drugs, bronchodilators, palliative radiotherapy, and nutritional support.

The survival analysis excluded the patients with malignant peritoneal mesothelioma. The survival rates of the patients after 6, 12, 18, and 24 months of diagnosis were calculated. The median lifetime after diagnosis was analyzed for the patients whose dates of death could be accessed in patients' files and provincial Population Registry Directorate records.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 14.0. All P values are two-tailed and are considered statistically significant if they are less than 0.05. Descriptive statistics, including frequencies, means, medians, and Standard deviations (SD), were calculated where appropriate. Student's t test was conducted for parametric data. For all patients, the overall survival was estimated using the Kaplan-Meier method.

Results

Between 1993 and 2010, yearly 13 patients in average were diagnosed as MM in our institution. Of 228 patients in total, 131 (57%) were men and 97 (43%) women. The male to female sex ratio of the patients was 1.4:1. The mean age was 59.11±12.9 years in men and 58.73±12.5 years in women, and these were statistically not different (p=0.78). When classified according to age groups, the highest percentage of patients (29%) was covered in the range of 60-69 years (Figure 2).

More than 80% of the patients were farmers or housewives and lived in rural areas. Environmental asbestos exposure was present in 196 patients (86%) for an average duration of 40±20 years (range: 3-70). The patients presented most frequently with chest pain (57.8%) and dyspnea (46.5%). The interval between the start of complaints and the diagnosis time was 4.0±4.0 months in average. Nine patients (3.9%) underwent
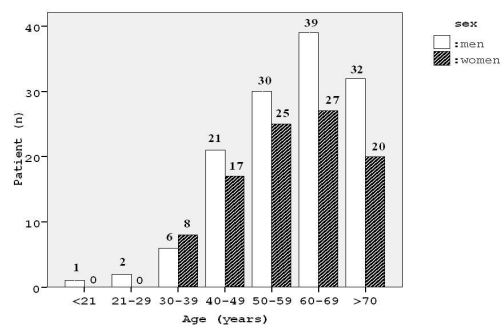

Figure 2. Age Distribution, in Decades, of 228 Patients with Malignant Mesothelioma

Table 1. Demographical, Exposure and Clinical Data of the Patients (n=228)

		n (%)
Symptoms:	Thoracic/abdominal pain	132 (57.8)
	Breathlessness	106 (46.5)
	Weight loss	52 (22.8)
	Cough	50 (21.9)
	Unspecified	22 (9.6)
Environmental asbestos exposure		
	Yes	196 (86.0)
	No	10 (4.4)
	Uncertain	22 (9.6)
Anatomical disease site:	Pleural	211 (92.6)
	Peritoneal	9 (3.9)
	Unspecified	8 (3.5)
Radiological signs in thoracic imaging		
	Pleural effusion	160 (70.2)
	Pleural thickening /nodulation	103 (45.2)
	Atelectasis/volume loss	52 (22.8)
	Pleural mass	40 (17.5)
	Unknown	22 (9.6)
Diagnostic procedure:	Blind CPNB*	119 (52.2)
	Thoracotomy	26 (11.4)
	CT guided CPNB*	22 (9.6)
	Thoracoscopy	7 (3.1)
	Pleural fluid cytology	6 (2.7)
	Excisional biopsy of the chest wall mass	5 (2.2)
	Laparotomy/laparoscopy	9 (3.9)
	Clinical and radiological diagnosis	12 (5.3)
	Unknown	22 (9.6)

*Closed pleural needle biopsy

laparoscopy/laparotomy to be diagnosed as malign peritoneal mesothelioma. All patients with pleural effusion underwent firstly thoracentesis for pleural fluid cytology. Malign pleural mesothelioma (MPM) was diagnosed in 119 patients (56.4%), out of 211, through blind closed pleural needle biopsy (CPNB) with Abram's needle (Table 1).

PBCT and SC were administered to 130 patients (66%). SC alone was provided to 67 patients (34%) who did not accept chemotherapy and/or whose Karnofsky performance scale was below 50 (Figure 3). In the PBCT plus SC group, 9 patients underwent decortication procedure. In total, 42 patients from both groups underwent pleurodesis.

The median follow-up time was 10.0 months and the median survival was again 10.0 months. There was no difference between male and female patients in terms of survival time (p=0.252). The median overall survival was significantly improved with PBCT plus SC compared to SC alone (11.4 vs. 5.1 months; p=0.005). The survival rates were significantly improved in the PBCT plus SC

Figure 3. The Distribution of the Patients with Regard to Treatment Modalities

Figure 4. Kaplan-Meier Survival Curves for Malignant Mesothelioma Patients Receiving Platinum-Based Combination Chemotherapy Plus Supportive Care and Patients Receiving Supportive Care Alone

Table 2. The Survival Rates According to Used Treatment

	Months				
	6th	12th	18th	24th	p
PBCS plus SC (%)	72	43	19	2	0.005
SC (%)	49	31	11	1	

group (Table 2 and Figure 4). The 6, 12, 18, and 24-month survival were significantly improved with PBCT plus SC compared to SC alone (72%, 43%, 19%, and 2% vs. 49%, 31%, 11%, and 1%).

Discussion

Malignant mesothelioma is primarily a disease of adults and usually presents in the fifth to seventh decades, and 70-80% of cases occur in men. Those diagnosed between the ages of 20-40 years usually have a history of childhood exposure (Moore et al., 2008). In the MM cases related to environmental asbestos exposure, it was reported that exposure started at childhood, gender ratio was nearly 1, and the disease appeared at 5th or 6th decade (Pasetto et al., 2005). A study from Turkey reported that male to female ratio was 1.3:1 (Senyigit et al., 2000). Metintas et al. (1999) compared the relative risk of women versus men for MPM due to environmental amphibole asbestos exposure. The relative risk was higher

for women than for men: 159.8 per 100,000 vs. 114.8 per 100,000, respectively. In our series, the patients were diagnosed more frequently at seventh decade and the mean age during diagnosis was 59 years, in accordance with relevant literature.

Inhalational exposure has been clearly established as the predominant cause of malignant mesothelioma in humans (Metintas et al., 2010). Approximately 70 percent of cases of pleural mesothelioma are associated with documented asbestos exposure. The latency period from asbestos exposure to the development of mesothelioma ranges from approximately 20-50 years (Sterman et al., 2008). In a study involving 2544 patients with MM, the mean latency period was found to be 43 years for occupational asbestos exposure and 48 years for environmental exposure (Marinaccio et al., 2007). Bianchi et al. (2001) observed the latency periods being between 14 years and 75 years, with a mean of 48.8 years and a median of 51 years. Skammeritz et al. (2011) reported that the median (interquartile range) of latency was 42 (12.5) years in a series of MM from an occupational clinic. In our study, 86% of the patients stated to dwell in houses where asbestos-contaminated soil was used, for a mean duration of forty years. It can be suggested that the disease affected both genders almost equally in Sivas because the exposure of women to environmental asbestos was comparable to that of men.

The initial clinical presentation for most patients with MPM is progressive dyspnea and/or dull chest wall pain. Dyspnea is usually the result of a large pleural effusion, and the nonpleuritic chest pain is generally caused by significant chest wall invasion. There also may be dry cough, weight loss, fever, fatigue, or night sweats (Ismail-Khan et al., 2006; Sterman et al., 2008). The median interval from the development of symptoms to definitive diagnosis ranges from 2-8 months (Renshaw et al., 1997).

Our series showed that the most common presenting symptoms were chest pain and breathlessness and that the interval between the initiation of symptoms and the time of diagnosis was 4 months in average. The most frequent radiological features of MPM were pleural effusion and pleural thickening or nodularity. To sum up, the demographical, clinical and radiological characteristics in our series were similar to those in literature (Yilmaz et al., 1998; Wang et al., 2004).

Closed pleural needle biopsy (CPNB) has been considered as a safe and effective manner of diagnosing malignant mesothelioma of the pleura (Beauchamp, 1992). Blind Abram's needle biopsy obtaining pleural tissue was diagnostic in approximately 50% of patients presenting with malignant effusion and can be performed safely by all grades of medical staff with due attention to technique and supervision. The data support that closed pleural biopsy is still of value as a diagnostic procedure, and should be carried out prior to invasive procedures such as thoracoscopy or open pleural biopsy (Al-Shimemeri et al., 2003; Chakrabarti et al., 2006).

Blind CPNB was the diagnostic procedure in 119 (56%) of our 211 patients with MPM. Being simple, inexpensive and easily performed, this procedure is still essential and its value can be augmented when it
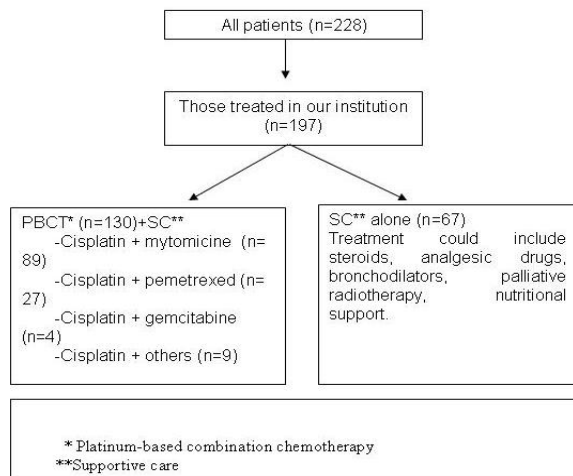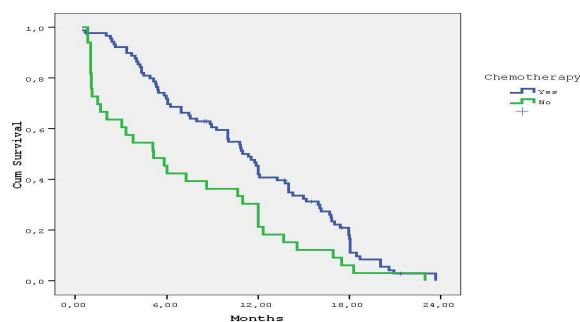
is guided with computerized tomography or ultrasound (Koegelenberg and Diacon, 2011). Adams et al. (2001) showed that pleural fluid cytology and non-image-guided Abrams or Cope biopsies had sensitivities of approximately 30% for detecting malignant mesothelioma while this rate reached up to 86% with image-guided CPNB. Recent reviews suggested that blind biopsy technique was no longer recommended for the diagnosis of malignant pleural disease (Rahman and Gleeson, 2008; Wallters and Maskell, 2011).

Treatment of MPM with more than palliative intent remains inadequate at all stages of presentation. Generally, surgery as a single modality has failed to improve survival. However, it was reported that multimodal treatment including radiotherapy, chemotherapy, and extrapleural pneumonectomy had survival benefits especially in early-stage cases (Sugarbaker et al., 1999; Rusch et al., 2001; Scherpereel et al., 2010). In advanced disease, chemotherapy remains the main therapeutic modality whereas either surgical intervention or local radiation therapy may also be useful for the local control of pain or symptoms often associated with pleural fluid accumulation (Pistolessi et al., 2004; van Thiel et al., 2011).

In a study by Law et al. (1984), there was no prognostic difference between the patients who were treated (chemoteraphy and radioteraphy) and who were not. Ruth et al. (2003) reported that the median survival was less than a year in non-treated patients. In a review evaluating diverse treatment approaches, the median survival was 6-18 months in patients who received different therapies such as pleurodesis, pleurectomy, radiotherapy, single agent or combination chemotherapy, and best supportive care; most of the patients were lost within one year (Hughes, 2005).

In a phase III trial involving 456 patients, pemetrexed and cisplatin combination was found to provide longer survival compared with cisplatin alone (respectively 12.1 months versus 9.3 months in the control arm, p=0.020) (Vogelzang et al., 2003). Another randomized trial involving 406 MM patients from 76 centers compared active symptom control (ASC) approach (treatment could include steroids, analgesic drugs, bronchodilators, palliative radiotherapy), ASC plus four cycles of combined mitomycin, vinblastine and cisplatin (MVP), and ASC plus vinorelbine in terms of survival benefit. No statistically significant improvement in overall survival was observed when combining both chemotherapy arms (mean survival time 8.5 months) compared with the ASC arm (mean survival time 7.6 months) (p=0.32). There was also no significant improvement of symptom control except for chest pain and sweating which were reduced with the cisplatin regimen (Muers et al., 2008). In a study including 81 patients treated with a platinum analog plus gemcitabine (n=40) or pemetrexed (n=41), the median survival was 10 months (95% confidence interval, 7.7-12.3), with 1- and 2-year survival rates of 0.42 and 0.21, respectively. Survival did not appear to be influenced by the chemotherapy agent used (Lee et al., 2009).

In this study, the survival rates of the patients receiving PBCT plus SC were 72%, 43%, 19%, and 2% respectively for 6th, 12th, 18th, and 24th months. The same parameters were 49%, 31%, 11%, and 1% respectively in the patients receiving SC alone. Also, the median survival prolonged with PBCT. The survival advantage continued 12- and 24-month after the initiation of combination chemotherapy. The retrospective nature of the study, the lack of differentiation with regard to histological phenotypes, and a possible selection bias due to recruitment of the patients with lower performance scale (with probably advanced disease) to SC alone group render this conclusion disputable. Another limitation of this study was the low number of patients receiving PBCT plus SC, which was insufficient for intragroup comparison of chemotherapeutics combined with cisplatin in terms of survival.

Today, it is suggested that platinum analogues, doxorubicin, and some antimetabolites can be used as single agents and that a modest benefit can be obtained from monotherapy. As combination therapy, pemetrexed and cisplatin or, alternatively, pemetrexed and carboplatin can be used. Furthermore, if extrapleural pneumonectomy is planned, platinum-based neoadjuvant or adjuvant combination chemotherapy should be considered (Stahel et al., 2010).

The current chemotherapy protocol employed in our institution includes the combination of pemetrexed and cisplatin. However, the number of cases sufficient enough to discuss the efficacy of this protocol and to compare with other chemotherapy regimens is not reached yet.

A variety of prognostic factors have been evaluated, including histological type, gender, age, weight loss, chest pain, and performance status, among others. A study analyzing the influence of pre-treatment clinical features of 337 patients on prognosis found that chest pain, dyspnea, platelet count >400,000/microL, weight loss, serum lactate dehydrogenase level >500 IU/L, pleural involvement, low hemoglobin level, high leukocytes count, and increasing age over 75 years led to worse prognosis (Herndon et al., 1998). In our series, the patients with weight loss appeared to have shorter median survival time than those without weight loss (7.5 and 10.9 months, respectively); however, this outcome was not statistically significant. Due to lack of laboratory parameters, other factors regarding prognosis could not be assessed (O'Byrne et al., 2004; Kumar and Kratzke, 2005).

In conclusion, the eighteen-year experience of our center showed that platinum-based combination chemotherapy did improve survival of our patients at the 24th month analysis excluding histology types and stage status.

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