Original Article

Clinical characteristics and treatment outcomes in 132 patients with malignant mesothelioma

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ABSTRACT

Purpose: Our objective is to scrutinize clinical, laboratory, radiological characteristics, treatment regimens, and treatment outcomes of malignant mesothelioma (MM) cases in our hospital. **Materials and Methods:** We investigated, retrospectively, the clinical characteristics and treatment outcomes of all 132 MM patients at Dicle University Hospital between January 2006 and April 2010. **Results:** A total of 82 (62.1%) patients were male, and 50 (37.9%) female. Median age was 56.0 years. Mean survival time was 9.6±6.9 months. Mean survival time of patients who had received best supportive care was 7.5 months, chemotherapy 10.4 months, and multimodality treatment regimen 12.6 months. Patients in the multimodality treatment group survived longer than did those in the other two groups (P=0.042). A total of 76 patients received chemotherapy, of whom 17 (22.3%) were administered Cisplatin/Carboplatin and Gemcitabine, 58 (76.4%) Cisplatin/Carboplatin and Pemetrexed, and one (1.3%) Cisplatin + Docetaxel. Complete and partial response to treatment in patients receiving Cisplatin/Carboplatin and Gemcitabine was found 47.1% and Cisplatin/Carboplatin and Pemetrexed was found 50.0% (P>0.05). **Conclusions:** MM related to asbestos exposure is seen frequently in Turkey. Patients present with the typical clinical features of dyspnea, weight loss, and chest pain. Survival analysis shows that patients receiving multimodality treatment may be better.

KEY WORDS: Asbestos, chemotherapy, lung cancer, mesothelioma

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INTRODUCTION

Malignant mesothelioma (MM) is an aggressive tumor arising from pleural mesothelial cells. Less frequently, it may arise from other serous membranes such as the peritoneum, pericardium, and tunica vaginalis.[1] The two most important known etiologic factors in MM are asbestos and erionite, both mineral fibers. MM usually occurs as a result of environmental or occupational exposure to these fibers,[2] whose carcinogenic effect relates more to their physical than to their chemical structure. It has been shown that long, thin fibers (more than a 1:3 length/width ratio) are more carcinogenic.[3]

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Occupational asbestos exposure starts at the beginning of a worker's career and continues for 8 hours per day, 5 days per week, 46-48 weeks per year. In an asbestos-affected area, however, environmental exposure starts at birth and is continuous, though fiber concentration varies over long and short periods.[4]

Asbestos exposure in Turkey is generally environmental and asbestos-related diseases, especially MM, are frequent in some regions.[5,6] In Southeast Anatolia Region, environmental exposure occurs through tilling of asbestos-laden soil and use of asbestos for covering external and internal wall surfaces.[6-8] This region was included in a wide-area serial study of 176 patients that reported MM incidence as 2.28/million.[8]

The most common complaints of patients with MM are dyspnea and chest pain. Dyspnea occurs through an accumulation of pleural fluid or restriction caused by

thickened pleura. Pain is often expansive and obtuse on the lateral wall of the chest, generally chronic, persistent, and nonpleuretic.

Survival rates of MM are poor because there is no curative therapy. Mean survival has been reported as about 6-12 months in many patient series.[9,10] Treatments in use are surgery, chemotherapy, and radiotherapy. In recent years, multimodality treatment regimens have been reported as prolonging survival.[11]

We aimed to investigate clinical, laboratory, and radiological characteristics; treatment regimens; and treatment outcomes of MM cases in Diyarbakir Province, part of the Southeastern Anatolia Region. The inhabitants of this region frequently suffer from intensive environmental asbestos exposure.

MATERIALS AND METHODS

In this retrospective study, 132 patients with histopathological MM diagnosis were included. All patients were seen at Dicle University, Faculty of Medicine, Chest Diseases Department and Medical Oncology Department, during January 2006 to April 2010. Institutional Review Board approval was given.

The data obtained from patient files were recorded on standard forms, prepared in advance. Age, gender, hometown, residence, asbestos usage history, latent period between asbestos exposure and diagnosis, symptoms, symptom duration, diagnosis date, diagnostic method, localization, histopathological type, routine laboratory results, stage, karnofsky performance score (KPS), treatment regimen, pleurodesis, treatment response, date of death and survival times of patients were all recorded on the forms. Survival time is defined as the time between diagnosis and death, or end of the study time if the patient was then still alive.

The period between the first complaint and diagnosis was registered as symptom duration, and that between first asbestos exposure and diagnosis as latent period. The primary incurred serous membranes were classified as pleura, peritoneum, pericardium and others (eg, tunica vaginalis). Diagnostic methods were classified as either Closed Pleural Biopsy with Ramel Needle and Surgical Biopsy. Hemotoxylin and eosin staining was used as standard in histopathological evaluation. Histological investigation was used on surgical and/or necropsy material and proven MM patients were included. Histochemical or immunohistochemical staining were used if necessary. Diagnosis and subtype assessment were carried out with differential immunohistochemical staining in some cases in whom, hemotoxylin and eosin staining could not be done. Staging studies were made after histopathological diagnosis and included thorax, abdominal and cerebral tomography, and Technetium (Tc)-99 bone scintigraphy. One chest physician and two radiology physicians evaluated radiological data. Because some patients did not accept thoracoscopy, the Butchart staging system was used, as it is applicable to all patients.[12]

Treatment regimens were divided into three groups: Best supportive care (BSC), chemotherapy, and multimodality treatment. The multimodality treatment regimen was administered as adjuvant chemoradiotherapy after extrapleural pneumonectomy.[13]

A modified response evaluation criteria in solid tumors (RECIST) technique was used to evaluate the treatment response of patients undergoing chemotherapy.[14] Baseline values were calculated by taking total long diameters of measurable lesions, adding them and comparing the result with baseline values after chemotherapy. Results were recorded as follows:

- Complete response (CR): Disappearance of all target lesions with no evidence of tumor elsewhere
- Partial response (PR): Reduction of at least 30% in the total tumor measurement (sum of six unidimensional measurements, acquired in two positions at three separate levels on transverse cuts of CT scan)
- Progressive disease (PD): Increase of at least 20% in the total tumor measurement
- Stable response (SR): Disease meeting the criteria of neither PR nor PD.

Statistical analysis

SPSS 11 computer programs were used for statistical analysis of patients' data.

The Kolmogorov-Smirnov one-sample test was used to determine whether measurable variables of patients were matched to normal distribution. The Mann–Whitney *U* test was used to compare measurable nonparametric variables. The treatment efficiency rate was compared with Chi-square test at 95% confidence interval (CI); kaplan–meier (KM) survival analyses were used for survival comparisons. Survival times were calculated with KM, median, and 95% CI. In statistical analysis, difference of $P<0.05$ was accepted as meaningful. The period from date of diagnosis to date of death or to April 2010 (if the patient survived until that date) was accepted as survival time.

RESULTS

The median age of patients was 56.0 years; 82 (62.1%) patients were male and 50 (37.9%), female.

Environmental asbestos exposure was determined in 76.5% of patients, with the mean duration of exposure being 33.2±11.8 (0-63) years. Ten (7.6%) patients were suffering from ongoing exposure. The mean latent period was 45.5±12.3 (25-85) years.

At diagnosis, 101 (76.5%) patients had dyspnea; 98 (74.2%),

weight loss; and 91 (68.9%), chest pain. The mean duration of symptoms was 6.7±6.4 (1-52) months. A total of 70 (53.1%) patients were smokers. In 119 (90.2%) patients disease was originated pleura; 68.1% of them with the epithelial subtype, as identified in the histopathological examination [Table 1].

Symptom duration for each histopathological subtype was determined as 7.5±7.3 months for the epithelial subtype, and 4.8±2.9 months for non-epithelial subtypes. The difference was significant (P=0.013). Seventy-three patients resided in three different towns in our region [32 (24.2%) in Ergani, 23 (17.4%) in Cermik, 18 (13.6%) in Siverek], all of which wer involved in intensive usage of environmental asbestos. A total of 93 (70.4%) patients were diagnosed by means of a closed pleural biopsy and 39 (29.6%) by surgical pleural biopsy.

The mean erythrocyte sedimentation rate value was 60.1±22.3 mm/h. The mean number of white blood cells was 10,340±9,226 K/μL. The mean number of platelets was 385,000±186,000 K/μL. Mean serum lactate dehydrogenase level was 337±186 U/L. There was leukocytosis in 26% of the patients, thrombocytosis in 31%, and anemia in 46%. The mean KPS of patients was calculated as 56.9±11.9. KPS was <60% in 63 (47.7%) patients and ≥60% in 69 (52.3%). Ninety patients (68.1%) were stage 1-2 and 42 patients (31.9%) were stage 3-4. For treatment regimens, 56 (42.4%) patients had the best supportive care, 61 (46.3%) had chemotherapy and 15 (11.3%) had multimodality treatment.

During the study, 93 (70.4%) patients died. Mean survival time for all patients was calculated as 9.6±6.9 (1-41) months, and was significantly longer in the multimodality treatment group compared to that in the other groups (P=0.042) [Table 2]. In all, 76 patients underwent chemotherapy in the chemotherapy and multimodality treatment groups. No significant difference was found among the three treatment groups as far as age, gender, stage, and asbestos exposure were concerned (P<0.005). Drug regimens were: Cisplatin + Gemcitabine or Gemcitabine + Carboplatin in 17 (22.3%) patients, Pemetrexed + Cisplatin or Carboplatin + Pemetrexed in 58 (76.4%) patients, and Cisplatin + Docetaxel in one (1.3%) patient.

On average, patients received chemotherapy 4.3±1.9 times. Complete response rate was 11.8% in Cisplatin + Gemcitabine or Gemcitabine + carboplatin group. Complete response rate was determined as 10.40% in the Cisplatin + Pemetrexed or Carboplatin + Pemetrexed group [Table 3]. Complete and partial response to treatment in patients receiving Cisplatin/Carboplatin and Gemcitabine was found 47.1% and Cisplatin/Carboplatin and Pemetrexed was found 50.0% (P>0.05).

A total of 31 patients underwent pleurodesis independently of their treatment options. Talc was used as a chemical agent in all pleurodesis procedures.

Table 1: Demographic features patients with malignant mesothelioma

Feature	*N* (%)
Total number of patients	132 (100)
Asbestos exposure	101 (76.5)
Symptoms	
Dyspnea	101 (76.5)
Weight loss	98 (74.2)
Chest pain	91 (68.9)
Smoking history	70 (53.1)
Presence of pleural fluid	128 (96.9)
Primary involvement	
Pleura	119 (90.2)
Peritoneum	12 (9.1)
Pericardium	1 (0.7)
Histopathological subtype	
Epithelial	90 (68.1)
Sarcomatous	5 (3.8)
Mix	5 (3.8)
Undefined	32 (24.3)
Stage	
Stage 1-2	90 (68.1)
Stage 3-4	42 (31.9)

Table 2: Mean survival time of patients for particular treatment types

Treatment types	Mean survival time (month)	% 95 Confidence interval		*P*
		Lower bound	Upper bound	
Best supportive care	7.5	6.03	9.47	P<0.05
Chemotherapy	10.4	8.42	12.38	
Multimodality	12.6	7.60	17.78	
Total	9.6	8.28	10.99	

Table 3: Treatment response of patients who had received chemotherapy regimen

	CG1 or CG2 *N* (%)	CP1 or CP2 *N* (%)	Cisplatin+ Docetaksel n (%)
Indication			
Palliative	8 (66.6)	45 (77.5)	1 (100)
Adjuvant	4 (33.4)	13 (22.5)	-
Response of treatment			
Complete response	2 (11.8)	6 (10.4)	-
Partial response	6 (35.3)	23 (39.6)	-
Stable response	7 (41.1)	26 (44.8)	1 (100)
Progression	2 (11.8)	3 (5.2)	-
Total	17 (100)	58 (100)	1 (100)

CG1: Cisplatin+Gemcitabine, CG2: Carboplatin+Gemcitabine. CP1: Cisplatin+Pemetrexed, CP2: Carboplatin+ Pemetrexed

DISCUSSION

The etiological relationship of mesothelioma with asbestos was first identified in 1960, and the first studies into the disease in Turkey was undertaken in the early 1970s.[15] MM is a rare tumor in the normal population, only 10-22/100,000 in a year for societies in which asbestos or mineral fiber contact has never been reported is between.[16]

In our region, the incidence of MM is reported as 2.28/million.[8] Of local MM patients, 60-65% reported asbestos exposure, usually as environmental (plaster,

whitewash, the processing of asbestos in the soil in order to sell).[8,17] In our study, 76.5% of the patients reported asbestos exposure, with 9.9% still exposed at the time of diagnosis. MM was detected at earlier ages in our region (at a mean age of 52.4 years[6] in an earlier study) because environmental asbestos exposure starts from birth.[6,8] Our finding is in accord with the literature.

Exposure is higher for men in industrialized countries because most of them work in the asbestos industry, or in industries that use asbestos. Because men and women share the same lifestyle in rural areas, the share of the risk is equal too, and the male/female ratio is approximately one in related patient series.[4,5,18] Although the men mine and carry asbestos in our region, the disease affects women just as seriously because they process asbestos with water and get exposed via inhalation. Some studies in our region have found male/female ratios as close as 1.3:1.[17] In our study, this ratio is 1.6:1.

Environmental asbestos exposure starts at birth in rural areas, and our country series shows a latent period of 50-55 years, longer than the workplace series, but with a younger diagnosis age.[4,5] The mean latent period was determined as 45 years in our study – lower, we believe, because of more intensive exposure to asbestos than in other regions.

At 46-52%, the epithelial subtype was reported as the most frequent subtype in the series, with the mixed subtype (21-26%) in second place.[8,17-19] We also found that epithelial was the subtype most frequently detected.

Although the period between symptom onset and diagnosis varies from a few weeks to eight months, it is generally about 3 weeks.[5,20] In our study, the average symptom duration was 6.7 months and was longer for patients with the epithelial histopathological subtype, suggesting that this subtype exhibits a more moderate clinical course.

MM has a poor prognosis no matter what treatment regimen is attempted. Earlier studies determined average survival time as 6-12 months.[10,11,21] Mean survival time was found to be 9.6 months in our study.

One study reported treatment results of 274 patients with pleural MM over 17 years (16 patients per year) and another, from our region, has reported treatment results of 45 MM patients over four years (11 patients per year).[7,22] In our study, we researched 132 patients over three years, a shorter time than the others, but the fact that there was an average of 44 patients a year may imply a greater frequency in this region.

Average survival time in MM patients has been reported at approximately 7 months in the best supportive care group,[21] 12 months[21,23,24] in the chemotherapy group, and 16-21 months[22,24] in the multimodality treatment group. In our study, mean survival time was determined as 7.7 months for the best supportive care group, and 10.4 months for the chemotherapy group.

The longest average survival 12.6 months in the multimodality treated group, longer than the other two groups. In our study, while the average survival time was consistent with literature data in both the best supportive care and chemotherapy groups, it was shorter than previous studies had found for the multimodality treatment group.

Recently, platinum-based combination therapies have come into use for the treatment of MM. Gemcitabine, Vinorelbine, Pemetrexed, and Raltitreksed are among the new agents used in combination chemotherapy.[7] Treatment response rates (sum of complete and partial responses) to the different chemotherapy regimens are reported as: Cisplatin + Gemcitabine 48%,[25] Cisplatin + Pemetrexed 41%,[26] and Cisplatin + Raltitreksed 23.6%.[23] In our study, patients received Cisplatin + Gemcitabine or Carboplatin + Gemcitabine, Cisplatin + Pemetrexed or Carboplatin + Pemetrexed or Cisplatin+ Docetaxel, and treatment response rates were confirmed as 47.1%, 50.0%, and 0%, respectively. In one study, patients received Cisplatin + Pemetrexed, and this regimen increased treatment response.[26] In our study, patients receiving a Cisplatin + Pemetrexed regimen showed the best response in the chemotherapy group, but we studied only a limited number of patients who received chemotherapy, so the reliability of this data may be low. Therefore, we suggest that it would be useful to carry out treatment response evaluation in a larger series.

Multimodality treatment regimen might be useful in cases at an early stage, as it offers a significantly longer survival time than other treatment regimens.

REFERENCES

1. O'Reilly KM, McLaughin AM, Beckett WS, Sime PJ. Asbestos related lung disease. Am Fam Physician 2007;75:683-8.
2. Gibbs AR. Role of asbestos and other fibres in the development of diffuse malignant mesothelioma. Thorax 1990;45:649-54.
3. Aisner J. Current approach to malignant mesothelioma of the pleura. Chest 1995;107:332-44.
4. Metintas M, Ozdemir N, Hillerdal G, Uçgun I, Metintas S, Baykul C, *et al*. Environmental asbestos exposure and malignant pleural mesothelioma. Respir Med 1999;93:349-55.
5. Selçuk ZT, Cöplü L, Emri S, Kalyoncu AF, Sahin AA, Bariş YI. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey. Analysis of 135 cases. Chest 1992;102:790-76.
6. Tanrikulu AC, Senyigit A, Dagli CE, Babayigit C, Abakay A. Environmental malignant pleural mesothelioma in SoutheastTurkey. Saudi Med J 2006;27:1605-7.
7. Cil T, Isikdogan A, Onat S, Zincircioglu B, Ulku R, Özekinci S, *et al*. Single center experience of mesothelioma patients in southeast region of Turkey. UHOD 2009;19:153-8.
8. Senyiğit A, Babayiğit C, Gökirmak M, Topçu F, Asan E, Coşkunsel M, *et al*. Incidence of malignant pleural mesothelioma due to environmental asbestos fiber exposure in the southeast of Turkey. Respiration 2000;67:610-4.
9. Montanaro F, Rosato R, Gangemi M, Rosato R, Ricceri F, Merler E, *et al*. Survival of pleural malignant mesothelioma in Italy: A population-based study. Int J Cancer 2009;124:201-7.
10. Borasio P, Berruti A, Billé A, Lausi P, Levra MG, Giardino R, *et al*.

Malignant pleural mesothelioma: Clinicopathologic and survival characteristics in a consecutive series of 394 patients. Eur J Cardiothorac Surg 2008;33:307-13.
11. Batirel HF, Metintas M, Caglar HB, Yildizeli B, Lacin T, Bostanci K, *et al*. Trimodality treatment of malignant pleural mesothelioma. J Thorac Oncol 2008;3:499-504.
12. Butchart EG, Ashcroft T, Barnsley WC, Holden MP. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. Thorax 1976;31:15-24.
13. Sugarbaker DJ, Norberto JJ. Multimodality management of malignant pleural mesothelioma. Chest 1998;113:61S -5.
14. Ceresoli GL, Chiti A, Zucali PA, Cappuzzo F, De Vincenzo F, Cavina R, *et al*. Assessment of tumor response in malignant pleural mesothelioma. Cancer Treat Rev 2007;33:533-41.
15. Yazicioglu S, Ilçayto R, Balci K, Sayli BS, Yorulmaz B. Pleural calcification, pleural mesotheliomas and bronchial cancers caused by tremolite dust. Thorax 1980;35:564-9.
16. Hillerdal G. Mesothelioma: Cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56:505-13.
17. Senyiğit A, Bayram H, Babayiğit C, Topçu F, Nazaroğlu H, Bilici A, *et al*. Malignant pleural mesothelioma caused by environmental exposure to asbestos in the Southeast of Turkey: CT findings in 117 patients. Respiration 2000;67:615-22.
18. van Gelder T, Hoogsteden HC, Vandenbroucke JP, van der Kwast TH, Planteydt HT. The influence of the diagnostic technique on the histopathological diagnosis in malignant mesothelioma. Virchows Archiv A Pathol Anat Histopathol 1991;418:315-7.
19. Craighead JE, Kane AB. The pathogensis of malignant and nonmalignant serosal lesions in body cavities consequent to asbestos exposure. In: Jauren MC, Bignon J. editors. Mesothelial cell and mesothelioma, 1st ed. New York: Marcel Dekker; 1994.p.79-101.
20. Chapman A, Mulrennan S, Ladd B, Muers MF. Population based epidemiology and prognosis of mesothelioma in Leeds, UK. Thorax 2008;63:435-9.
21. Muers MF, Stephens RJ, Fisher P, Darlison L, Higgs CM, Lowry E, *et al*. Active symptom control with or without chemotherapy in the malignant pleural mesothelioma (MS01): A multicentre randomized trial. Lancet 2008;371:1685-94.
22. Ak G, Metintas S, Metintas M, Yildirim H, Erginel S, Kurt E, *et al*. Prognostic factors according to the treatment schedule in malignant pleural mesothelioma. J Thorac Oncol 2009;4:1425-30.
23. van Meerbeeck JP, Gaafar R, Manegold C, Van Klaveren RJ, Van Marck EA, Vincent M, *et al*. 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.
24. Schipper PH, Nichols FC, Thomse KM, Deschamps C, Cassivi SD, Allen MS, *et al*. Malignant pleural mesothelioma: Surgical management in 285 patients. Ann Thorac Surg 2008;85:257-64.
25. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, *et al*. Cisplatin and gemcitabine treatment for malignant mesothelioma: A phase II study. J Clin Oncol 1999;17:25-30.
26. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, *et al*. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.

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