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Effects of treatment regimens on survival in patients with malignant pleural mesothelioma

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Abstract. – BACKGROUND AND OBJECTIVE: In this study, we aimed to investigate the factors affecting the survival of patients with malignant pleural mesothelioma (MPM) according to their treatment regimens, including best supportive care (BSC), chemotherapy, surgical group and multimodality (MM) therapy.

PATIENTS: A retrospective analysis was performed on clinical data and treatment outcomes of 400 patients registered in our hospital with MPM between January 1989 and April 2010.

RESULTS: Mean age ($p < 0.001$), presence of asbestos exposure ($p = 0.0014$), presence of smoking history ($p < 0.001$), Karnofsky performance status ($p < 0.001$), histological subtype ($p = 0.034$) and stage ($p < 0.001$) variables were found to be significantly different among the four treatment regimens.

Mean survival time of all patients was 12.32 months. Mean survival time 10.5 months for the BSC group, 15.7 for the surgical group, 16.02 for the chemotherapy group, and 26.55 for the MM group. There were significant differences in mean survival time among the four treatment regimens. In addition, a significant difference was found in survival time between the two chemotherapy groups ($p = 0.032$). Mean survival time for cisplatin + gemcitabine was found to be 14.49 months and for cisplatin + pemetrexed, 18.34 months.

CONCLUSIONS: The MM group had better survival rates than the other groups. The new chemotherapy combination, cisplatin + pemetrexed, can be helpful in improving survival time.

Key Words:
Mesothelioma, Survival, Treatment, Prognosis.

Introduction

Malignant mesothelioma is a cancer originating in the pleura, pericardium, and peritoneum or tunica vaginalis; since the early 1960s, its relation to asbestos exposure has been very well recognized[1]. Asbestos exposure can be environmental or occupational. Moreover, erionite, a natural fibrous zeolite, which can be found in volcanic tuff, has been found to induce malignant pleural mesothelioma (MPM). MPM due to both asbestos and erionite environmental exposure is a relatively common cancer in Turkey[2].

MPM remains a fatal cancer despite improvements in treatment and still has increasing incidence associated with asbestos exposure[3]. Individual patients might respond to chemotherapy, radiotherapy or immunotherapy, and selected patients, especially in early stages, might benefit from radical surgery and multimodality (MM) treatment[4].

Although it is claimed that MM regimens prolong survival only slightly and for relatively few patients in whom it is possible to perform radical surgery[4,5], most patients have unresectable disease at presentation, and systemic therapy is the only treatment option for them[7].

The best treatment for MPM is trimodality therapy, consisting of extrapleural pneumonectomy (EPP), neoadjuvant or adjuvant chemotherapy, and adjuvant high-dose hemithoracic radiotherapy. Trimodality therapy has been reported to offer long-term survival in selected patients with MPM[8]. The MM treatment has achieved a median survival of 19 to 46 months, depending on the stage, histology, and completeness of the surgical resection[8-12].

In Turkey, few reports have been published about survival and MM treatment. Most of the studies published are about MPM epidemiology, and clinical and radiological features[13-15].

In this study, we aimed to investigate the characteristics of the several variables affecting the survival of patients with MPM according to their treatment schedules, including best supportive care (BSC), surgical treatment, chemotherapy, and MM treatment in a University Hospital setting.

Materials and Methods

Patients

Asbestos exposure is common in the southeast region of Turkey, and incidence of asbestos-related

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diseases is high there[13-15]. Most of our patients had been subjected to environmental exposure. The time period between the first asbestos exposure and diagnosis is described as the latent period.

A retrospective analysis was performed on clinical data and treatment outcomes of 400 patients registered in our Hospital with malignant pleural mesothelioma (MPM) between January 1989 and April 2010. Histology-proven MPM patients were included in the study. The local Ethical Committee approved the study protocol.

Because some patients did not allow thoracoscopy, Butchart et al staging system was used after histopathological diagnosis[16]. Thoracal and abdominal computed topographies (CT) were done, and cranial CT was done if necessary. These CT scans were evaluated by a radiological specialist.

Criteria were age (≤60 years or >60), gender, asbestos exposure (yes or no), primary site of disease (right, left, bilateral), histopathological subtype (epithelial or other), smoking history (yes or no), Karnofsky performance score (KPS) (≤60 or >60), presence of dyspnea, weight loss (more than 5% in last three months) and stage (stage I-II or stage III-IV).

The patients were classified into four groups according to their treatment schedule: the best supportive care (BSC) group, which consisted of patients with low performance status and who were not suitable for other treatment options (266 patients); the chemotherapy group (100 patients); the surgical group (18 patients); and the multimodality (MM) therapy group (16 patients).

In the surgical group, decortication of visceral and parietal pleura was performed with BSC. This group of patients was not eligible for other treatment options. All chemotherapy was given at our Chemotherapy Unit between 1990 and 2005 as cisplatin (75 mg/m^2 1 day) + gemcitabine (1250 mg/m^2 1 and 8 day schedules) (45 patients) and after 2005 as cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2) (55 patients).

In the MM group, surgical resection consisted of extrapleural pneumonectomy (EPP) with resection of the lung, parietal pleura, hemipericardium and diaphragm. A systematic hilar and mediastinal lymphadenectomy was conducted. The diaphragm and pericardium were reconstructed using mesh. Adjuvant radiotherapy was delivered to the hemithorax, the thoracotomy incision, and at the sites of chest drains. The chemotherapy protocol for the entire MM group was cisplatin (75 mg/m^2) + pemetrexed (500 mg/m^2).

Statistical Analysis

Mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogorov-Smirnov test. For the purpose of analysis, one-way ANOVA test was used as appropriate. Pearson's Chi-Square (χ^2) test was used to evaluate associations between the categorical variables. Logistic Regression (LR) analysis was performed in order to determine the risk variables of MPM. Odd's ratios were also calculated by LR. All variables were included in the backward stepwise procedure. Kaplan-Meier survival curves were used to find the survival time of BSC, chemotherapy, surgical and MM therapy groups. Survival curves for the cisplatin + gemcitabine and for the cisplatin + pemetrexed therapy groups were also determined. The differences among survival curves were found by using Log Rank Analysis (Mantel-Cox). Two-sided p values were considered statistically significant at $p < 0.05$. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The mean age of patients (n=400) was 50.57 ± 11.22 (19-85) years. There were 236 male patients (59%) and 164 (41%) female patients. Eighty-six percent of patients had environmental asbestos exposure, and mean duration of asbestos exposure was found to be 32.46 ± 14.87 years. The mean latent period of patients with a history of exposure was 45.2 ± 12.2 years.

Mean Karnofsky performance score (KPS) was 62.83 (50-80). Of the 400 patients in this study, 285 (71.2%) were diagnosed by non-invasive pleural biopsy and 115 (28.8%) were diagnosed by surgical pleural biopsy. The average sedimentation value of patients was 69.7 ± 21.9 mm/hour.

Average survival time of all patients after diagnosis was calculated to be 12.3 ± 8.6 (1-53) months. Median follow up was 13 months.

As determined by univariate analysis in the 400 patients, poor prognosis was associated with the presence of smoking history ($p < 0.007$; 9.0 versus 10.5 months), a poor KPS ($p < 0.001$; 7.0 versus 15.0 months), a nonepithelial histology subtype ($p < 0.018$; 8.0 versus 11.0 months), and stage III-IV disease ($p < 0.000$; 7.0 versus 14.0 months).

Characteristics of the patients according to their treatment groups are presented in Table I. The mean

Table I. Characteristics of the patients according to their treatment schedule.

No	BSC group N (%) 266 (66.5)	CT group N (%) 100 (25)	Surgical group N (%) 18 (4.5)	MM group N (%) 16 (4)	Test value
Mean age, years	56.6 ± 10.5	51.6 ± 11.3	50.0 ± 12.6	49.7 ± 8.71	F = 6.77; $p < .001$
Male : Female	163:103	50:50	12:6	11:5	$\chi^2 = 4.45$ $p = .217$
Asbestos exposure	240 (90.2)	76 (76)	15 (83.3)	13 (81.2)	$\chi^2 = 10.55$ $p = .014$
Smoking history	105 (39.5)	59 (59)	14 (77.3)	11 (68.7)	$\chi^2 = 18.18$ $p < .001$
Weight loss	110 (41.3)	45 (45)	10 (55.5)	9 (56.2)	$\chi^2 = 0.679$ $p = .878$
Dyspnea	195 (73.3)	66 (66)	13 (72.2)	10 (62.5)	$\chi^2 = 0.443$ $p = .931$
KPS	108 (40.6)	75 (75)	14 (77.7)	11 (68.7)	$\chi^2 = 30.23$ $p < .001$
Primary site of disease					
Left	82 (30.8)	30 (30)	6 (33.3)	7 (43.7)	$\chi^2 = 4.676$ $p = .586$
Right	169 (63.6)	59 (659)	11 (61.2)	9 (56.3)	
Bilateral	15 (5.6)	9 (9)	1 (5.5)	0 (0.0)	
Histological subtype					
Epithelial	190 (71.5)	35 (35)	7 (38.8)	9 (56.2)	$\chi^2 = 18.12$ $p = .034$
Sarcomatous	14 (5.2)	15 (15)	1 (5.5)	0 (0.0)	
Mixed	46 (17.3)	20 (20)	7 (38.8)	0 (0.0)	
Unidentified	16 (6)	30 (30)	3 (16.9)	7 (43.8)	
Stage					
I-II	123 (46.2)	81 (81)	15 (83.3)	15 (93.7)	$\chi^2 = 39.69$ $p < .001$
III-IV	143 (53.8)	19 (19)	3 (16.7)	1 (6.3)	

*Variance analysis and chi-square test were used for statistical analysis.

age of patients ($p < 0.001$), asbestos exposure ($p = 0.014$), smoking history ($p < 0.001$), KPS ($p < 0.001$), histological subtype ($p = 0.034$) and stage variables ($p < 0.001$) were found to be significantly different among the four treatment types (Table I).

However, the male:female ratio and differences among weight loss, dyspnea and primary site of disease were not statistically significant ($p > 0.05$).

A binary logistic regression (LR) model was used to find the risk variables of MPM for all patients. Low KPS ($p = 0.007$), treatment types ($p < 0.001$) and asbestos exposure ($p < 0.001$) risk variables were significant in the LR model (Table II). The Odd's coefficients and confidence interval (95%) of the risk variables were 4.700 (1.534-14.39), 0.403 (0.267-0.607), and 1.65 (1.30-2.1), respectively. We found the overall five-year survival rate to be 1.25%.

The survival curves for treatment types were found using the Kaplan-Meier method and are presented in Figure 1. Chemotherapy was applied to patients 4.1 ± 1.8 times averagely. Chemotherapy was completed on 50.0% of patients in the multimodality (MM) group and 53.0% in the chemotherapy group. Mean survival time of all patients was 12.32 ± 0.50 months. Mean survival time was 10.5 ± 0.49 months for the best supportive care (BSC) group (n=266), 15.7 ± 2.24 for the surgical group (n=18), 16.02 ± 1.14 for the chemotherapy group (n=100), and 26.55 ± 6.6 for the MM group (n=16). Significant differences were found regarding survival time among the four treatment types.

The survival curves for the chemotherapy group were found using the Kaplan-Meier method and are presented in Figure 2. Mean survival time was 14.49 ± 1.2 months for cisplatin + gemcitabine (n=45) and 18.34 ± 1.48 months for cisplatin + pemetrexed (n=55). A significant difference was found regarding survival time between the two chemotherapy groups (p=0.032). All MM therapy was implemented between 2005 and 2010 (Table IV).

Table II. The outcomes of binary logistic regression model for all of the patients.

Variables	Odds ratio	95% CI	p
Karnofsky	4.7000	1.534 – 14.39	.007
Treatment types	.403	.267 – .607	< .001
Asbestos exposure	1.648	1.303 – 2.086	< .001

Table III. Overall mean survival time for treatment types with MPM patients in our and several studies.

	This study	Ak et al.[33]	Bolukbas et al.[27]	Metintas et al.[28]	Muers et al.[29]	Flores et al.[20]	Sugarbaker et al[16]	Vogelzang et al.[34]
Number of patients	400	235	102	161	409	945	183	456
Treatment types	Survival (months)	Survival (months)	Survival (months)	Survival (months)	Survival (months)	Survival (months)	Survival (months)	Survival (months)
BSC	10.5	7.0	∅	8.0	7.6	∅	∅	∅
CT	16.0	11.5	∅	11.3	9.5	∅	∅	12.1
Surgical	15.7	∅	∅	∅	∅	10	∅	∅
MM	26.5	21.0	30	∅	∅	20	19	∅

+ = significant; – = not significant; ∅ = Not studied.

Discussion

In spite of improvement in treatment regimens, malignant pleural mesothelioma (MPM) is still a poor prognosis; survival time of patients is 6-12 months[7,17-21]. In our study, mean survival time was 12 months.

In several studies, poor prognostic factors associated with MPM were detected to be older age[13,18,22], male gender[17,18,23], advanced stage[13,24], nonepithelioid histology[17-20,22,23], thrombocytosis[17,22], higher serum LDH level[13,22], higher WBC count[17,23], lower hemoglobin level[4], and poor performance status[13,17,20,22,23]. In our study, worse survival rates were observed in patients with lower KPS and asbestos exposure.

The median survival is 8 months in patients receiving best supportive care (BSC), about 9.5-12 months in those receiving chemotherapy, and about 10 months in those receiving surgery, whereas the survival of patients with multimodality (MM) treatment is 19-30 months (Table III). As expected, patients who had BSC treatment had the shortest survival times (less than 12 months), as they were generally older, and had advanced-stage MPM and low KPS. We determined that the median survival time was 10.5, 16, 15.7 and 26.5 months in BSC, chemotherapy, surgical and MM groups respectively. In our Hospital, before MM treatment, only decortications were done in MPM patients if possible. This group had better survival than the BSC group, possibly due to this protocol.

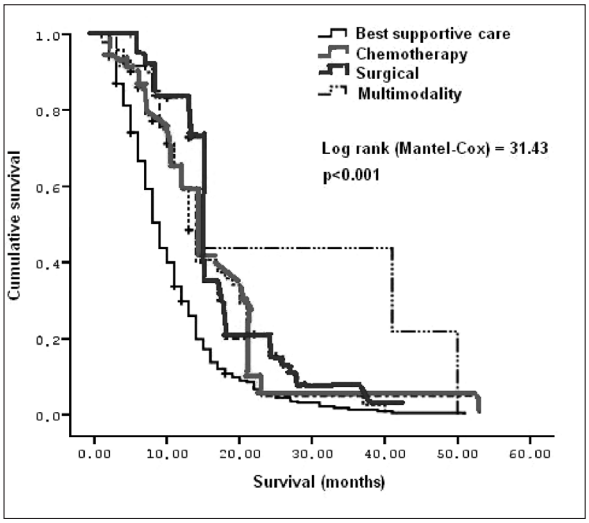

Figure 1. Kaplan-Meier survival curves for the best supportive care, the chemotherapy, the surgical and the multimodality therapy group.

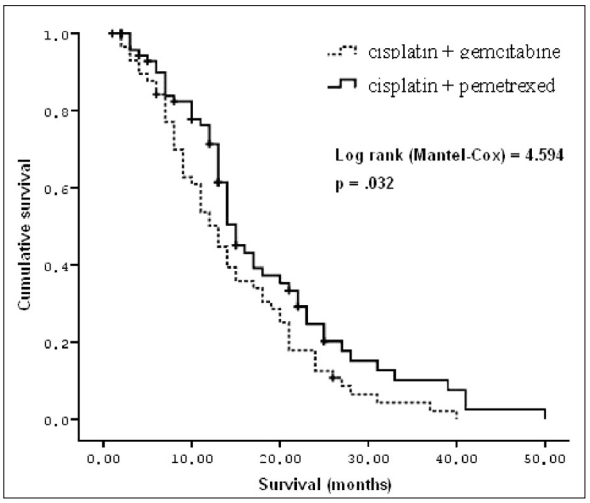

Figure 2. Kaplan-Meier survival curves for the cisplatin + gemcitabine and the cisplatin + pemetrexed therapy group.

Patients who received MM treatment were younger, their KPS was higher, and they were at earlier stages in the disease when compared with the other treatment groups. Patients in the MM treatment group also had better survival times than other treatment groups, potentially due to lower patient age, better performance status and lower clinical stage. In an earlier study conducted in Turkey, MPM patients receiving MM therapy, who had stage I-II, epithelial types and earlier ages, had better survival rates than other groups[25]. Thus, age, histopathological type of MPM, KPS and stage are very important prognostic factors for planning the treatment after the diagnosis.

The chemotherapy group had better survival than the BSC group. Patients who received cisplatin + pemetrexed after 2005 had a mean survival of 18.34 months. We determined that better survival in the chemotherapy group is associated with this new combination. In a study comparing cisplatin + pemetrexed with cisplatin alone in patients with MPM, mean survival in the cisplatin + pemetrexed group was found to be 12.1 months, while it was 9.3 months for cisplatin, and this difference was statistically significant[26]. We presented survival series in Table III, but in these series, we generally used older chemotherapeutic agents.

The main limitation for this study is that this was not a randomized trial; therefore, patient characteristics, especially comorbidities, varied.

Conclusions

Malignant pleural mesothelioma (MPM) is remains a fatal prognosis. We investigated the various pretreatment clinical and laboratory characteristics affecting the survival of patients with MPM according to their treatment schedules. The MM treatment group had better survival rates than the other groups. However, the new chemotherapy combination cisplatin + pemetrexed can be helpful for improving survival time of MPM. Henceforth, priority should be given to studies which will determine clinical and biochemical markers that may help to identify patients who will benefit from these treatment options.

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Table IV. Distribution of treatment groups of patients for 5 year intervals.

Years	BSC		CT		Surgical		MM	
	n	%	n	%	n	%	n	%
1989-1994	113	42.5	10	10.0	3	16.7	0	0
1995-1999	77	28.9	13	3.0	2	11.1	0	0
2000-2004	33	2.4	26	26.0	3	16.7	0	0
2005-2010	43	6.2	51	51.0	10	55.5	16	100
Total	**266**	**100**	**100**	**100**	**18**	**100**	**16**	**100**

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