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Prognostic factors in diffuse malignant pleural mesothelioma: effects of pretreatment clinical and laboratory characteristics

M. METINTAS*, S. METINTAS†, I. UCGUN*, A. R. GIBBS‡, E. HARMANCI*, F. ALATAS*, S. ERGINEL*, N. TEL§ AND O. PASAOGLU§

Departments of *Chest Diseases, †Public Health and §Pathology, Osmangazi University Medical Faculty, Eskisehir, Turkey and ‡Department of Histopathology, Llandough Hospital, Cardiff, U.K.

Abstract The aim of this study was to investigate the effects of various pretreatment clinical and laboratory characteristics on the survival of patients with diffuse malignant pleural mesothelioma (DMPM). One hundred histopathologically confirmed DMPM patients were evaluated. Fifty-nine were treated with chemoimmunotherapy, while 41 who had refused chemoimmunotherapy received supportive therapy alone. The following pretreatment characteristics were evaluated in both univariate and multivariate Cox regression analyses: age, gender, Karnofsky performance score (KPS), histology, asbestos exposure, presence of chest pain, dyspnoea, weight loss, symptom duration, smoking history, disease location, platelet count, haemoglobin, white blood cell (WBC) count, serum lactate dehydrogenase (LDH) and extent of disease (stage). Univariate analysis showed that patients with age $\geq$75 years, male gender, smoking history, advanced stages above stage I disease, KPS $<$70, WBC count $\geq$8450 and LDH level $\geq$500 IU l^{-1} have a worse prognosis. With multivariate Cox regression analyses, age $\geq$75 years, advanced stages above stage I disease, KPS $<$70 and LDH level $\geq$500 IU l^{-1} were found to be indicators of a poorer prognosis. In conclusion, in our study each of low performance status, older age, advanced stage disease, high LDH level and prognosis were found to be related.
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Keywords mesothelioma; prognosis; asbestos exposure; histopathology; treatment.

INTRODUCTION

Diffuse malignant pleural mesothelioma (DMPM) is a highly lethal neoplasm (1,2). It has continued to be an important health problem for communities that have occupational or environmental asbestos exposure (3–5). The incidence of this aggressive tumour is still increasing and is expected to go on doing so (6–8). In most published series of patients, the median survival for this disease is reported to be about 1 year (9–12). Although it is claimed that multi-modality regimens slightly prolong survival for relatively few patients in whom it is possible to perform radical surgery (13,14), most patients have unresectable disease at presentation and systemic therapy has been the only treatment option for them.

However, to date, the overall response rate is low and the median survival time is not long enough for chemotherapy schedules. Well defined studies indicate that mesothelioma may not be totally chemotherapy resistant, and some chemotherapeutics are moderately effective for responsive patients (15–18).

Studies are largely contradictory about prognostic factors for DMPM which would be helpful in planning appropriate treatment for these patients and evaluating the effects of treatment (19–21). Therefore, future investigations should be aimed at determining which patients will be responsive and identifying useful prognostic factors.

Our clinic is a department of the Medical Faculty of Osmangazi University in Eskisehir, Turkey. The Eskisehir district is located in central Anatolia. Many patients with DMPM or other asbestos-related chest diseases are admitted to our clinic in each year. Although there is no occupational asbestos exposure in the Eskisehir district, environmental asbestos exposure due to the use of asbestos-contaminated white-soil was very widespread in our rural region until the 1980s (7).

In this study we aimed to investigate the effects of various pretreatment clinical and laboratory characteristics on the survival of patients with DMPM.

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Correspondence should be addressed to: Dr Muzaffer Metintas, Omeraga mahallesi Adsiz sokak No:11, 26220 Eskisehir, Turkey. Fax: +90 222 2394714; E-mail: metintas@ada.net.tr

MATERIALS AND METHODS

Patients

One hundred consecutive patients with histologically-proven DMPM, from January 1991 to December 1999, were evaluated in this study. Histopathological examination of biopsy samples from all patients has been performed in the Pathology Department of our Faculty. Of the samples, 29 were also examined by Dr A.R. Gibbs from Llandough Hospital in U.K. Samples were stained with haematoxylin–eosin, alcian blue and mucicarmine histochemical stain. Immunohistological confirmation of carcinoembryonic antigen and Leu-M1 was obtained for these 29 patients, and carcinoembryonic antigen, vimentin and keratin in the others. After the histopathological diagnosis, all patients were staged according to the International Union Against Cancer staging system by using thoracic, abdominal and brain computer tomographic scans, bone scan with TC^{99} and other related tests (22,23).

Of the patients, 59 were put on a chemoimmunotherapy programme consisting of cisplatin, mitomycin C and recombinant interferon-α 2a or carboplatin, mitomycin C and ifosfamid, while 41 were given supportive therapy alone (24).

The following pretreatment characteristics were evaluated for prognostic importance: age ($\geq$75 years or $<$75 years), gender, Karnofsky performance score (KPS) ($\geq$70 or $<$70), asbestos exposure (yes or no), presence of chest pain, presence of dyspnoea, weight loss (more than 5%), symptom duration ($\geq$3 months or $<$3), smoking history, primary location of disease (right, left), platelet count ($>400\,000\ \mu l^{-1}$ or $\leq 400\,000$), haemoglobin, white blood cell (WBC) count, serum lactate dehydrogenase (LDH), extent of disease (stage), histopathologic subtype. Histopathologic subtype could not be determined in 23 patients, who were excluded in the analysis of the prognostic importance of histopathology. Since laboratory normal range was not suitable for LDH, we chose a level of over 500 IU l^{-1} as the cut-off level, to be consistent with published literature (20). Since the accepted norms for WBC and haemoglobin levels vary, we firstly determined the median values for each in the study group and used those as cut-off levels for prognostic evaluation ($8450\ \mu l^{-1}$ for WBC and 12·65 g dl^{-1} for haemoglobin (21).

Statistical analysis

Duration of survival and median and mean event times, with 95% confidence interval (CI), were estimated according to the Kaplan–Meier method. The duration of survival was defined as the period between the time of diagnosis and the time of death, or last contact if the patient had not died at the time of analysis. Comparisons for all survival were made using two-tailed log-rank tests. The proportional hazards regression model with stratification for the clinical trial was used for both univariate and multivariate analyses. Univariate analyses examined the prognostic importance of all factors mentioned above. The cox proportional hazards model was used to examine variables. A two-sided test was used at 0·05 level of significance. A step-down/step-wise variable selection procedure was used to fit the multivariate model. Only parameters which had P-values $\leq$0·10 in univariate analysis were taken in the final model for multivariate analysis (19).

The importance of a prognostic factor was assessed by the P-value of the Wald χ^2 statistic, the relative risk (RR; risk in patients in a given category as compared with the reference one), and its 95% CI. Statistical analyses were performed using SPSS statistical software.

RESULTS

The patients' characteristics are given in Table I. Of the 100 patients, 81 had environmental asbestos exposure. Of the total, six patients were alive at the time of the analysis.

The overall median survival time of the patients was 8·0 $\pm$ 0·9 months. The median survival time was 9·0

TABLE I. Characteristics of the patients

Patients characteristics	
Patient number	100
Mean age (range)	57·0 (26–90) years
Male: female	49 : 51
Asbestos exposure	81 (81%)
Mean asbestos exposure duration (range)	26·7 (0–80) years
Stage	
I	31 (31%)
II	20 (20%)
III	32 (32%)
IV	17 (17%)
Histopathologic subtype	
Epithelial	48 (48%)
Mixed	18 (18%)
Sarcomatous	11 (11%)
Unidentified	23 (23%)
Mean Karnofsky performance status (range)	70·5 (50–90)
Smoking history	42 (42%)
Men smoking	38/49 (78%)
Women smoking	4/51 (8%)
Mean symptom duration (range)	5·0 (0·3–72) months
Symptoms at diagnosis	
Weight loss	53 (53%)
Chest pain	78 (78%)
Dyspnoea	80 (80%)
Number of patients treated with chemotherapy	59

Table 2. Univariate analysis of patient characteristics influencing survival

Variable	O/N*	%	Survival†	95% CI	P
Age (years)					
<75	86/92	0.93	8.50	5·37–11·63	0·02
≥75	8/8	1·00	2·00	0·00–4·13	
Sex					
Male	46/49	0·94	6·70	5·56–7·84	0·09
Female	48/51	0·94	11·50	7·62–15·38	
Asbestos exposure					
Absent	17/19	0·89	6·70	4·99–8·41	0·92
Present	77/81	0·95	8·50	4·97–12·03	
Smoking					
Ever	39/42	0·95	6·30	5·03–7·57	0·10
Never	55/58	0·93	11·0	7·27–14·73	
Stage					
I	27/31	0·87	16·0	8·90–23·10	
II	20/20	1·00	6·30	4·11–8·49	0·00
III	30/32	0·94	6·30	4·82–7·78	
IV	17/17	1·00	5·00	3·66–6·34	
Histopathological type					
Epithelial	45/48	0·94	9·00	4·83–13·17	
Mixed	18/18	1·00	6·70	2·54–10·86	0·16
Sarcomatous	11/11	1·00	7·00	2·31–11·69	
Karnofsky					
≥70	65/70	0·93	11·00	7·42–14·58	0·0002
<70	29/30	0·97	5·00	3·66–6·34	
Primary site of tumour					
Right	57/59	0·97	8·00	6·07–9·93	0·53
Left	37/41	0·90	11·00	5·37–16·63	

*Observed death number/total patient number.
†Median survival (months).

months for the patients treated with chemotherapy and 8·0 months for the patients had supportive care alone; there was no signifigance between these groups (log rank = 1·28; $P = 0·26$). Univariate analyses of patient characteristics and various aspects influencing survival at presentation are shown in Tables 2 and 3.

Age ≥75 years, male gender, smoking, advanced stage above stage I disease, KPS <70, WBC count ≥8450 and LDH level ≥500 IU l^{-1}, with P-values ≤0·05 in univariate analysis taken in the final model for multivariate analysis (Table 4).

In the multivariate analysis model, age ≥75 years, advanced stage above stage I disease, KPS <70 and LDH level ≥500 IU l^{-1} were found to be indicators of a poorer prognosis.

The survival curves of the patients for age, stage, KPS and LDH values of the patients are shown in Figs 1–4, respectively.

DISCUSSION

In the present study, we investigated the effects of various pretreatment characteristics on the survival of patients with DMPM. Most of our patients had environmental asbestos exposure due to the use of asbestos-contaminated white-soil (7). There are some differences not only in terms of the nature of the exposure between those with environmental and those with occupational exposure but also in the individual characteristics of the patients. The male to female ratio of our patients was nearly 1:1. This ratio reflects the environmental exposure to asbestos in rural areas, as women and men live in the same rural environment and conditions. Mean lengths of exposure were the same for both sexes (7). On the other hand, the mean age of our patients was 57 years. In another study from Turkey, the environmental asbestos exposure series for Selçuk, the average age was 50 years, with a quarter of the patients below 40 years of age (4). The mean ages of the patients are around 60–65 years in patients with occupational exposure (25,26). The younger mean age in our series may be due to the beginning of asbestos exposure at birth.

DMPM arises from the pleura and/or peritoneum, with a poor prognosis, and until recently there has been no treatment schedule to slow its course (3,5,9–12,14,20,27,28). Most patients with DMPM have had

Table 3. Univariate analysis of other various patient characteristics influencing survival

Variable	O/N*	%	Survival†	95% CI	P
Chest pain					
Ever	73/78	0·94	8·00	6·02–9·98	0·87
Never	21/22	0·95	8·50	3·67–13·33	
Dyspnoea					
Ever	76/80	0·95	8·00	6·17–9·83	0·52
Never	18/20	0·90	8·50	4·12–12·88	
Weight loss					
Ever	50/53	0·94	8·0	6·28–9·72	0·2-8
Never	44/47	0·94	10	5·20–14·80	
Platelet count					
≤ 400 000	67/72	0·93	8·50	5·48–11·52	0·44
> 400 000	27/28	0·96	6·00	3·41–8·59	
WBC count					
< 8450	45/49	0·92	11·00	6·43–15·57	0·07
≥ 8450	49/51	0·96	7·00	5·06–8·94	
Haemoglobin					
< 12·65	48/49	0·98	9·00	4·60–13·40	0·73
≥ 12·65	46/51	0·90	7·00	4·50–9·50	
LDH level ≥500 IU l^{-1}					
Yes	22/22	1·00	3·50	0·00–7·41	0·02

unresectable disease at presentation and systemic therapy has been the only treatment option for them (13–17,20,22–38). Chemotherapy regimen cannot be considered as the standard of DMPM treatment (9,16,17,20–22,27,31,32). Although to date the overall response rate has been low and the median survival time is not long enough to justify chemotherapy schedules, some studies indicate that mesothelioma may not be totally chemotherapy-resistant and that some chemotherapeutics are moderately effective and tolerable, especially for responsive patients (16,20,24,27,32). In view of this, future investigations should be aimed at determining which patients will be responsive and which patients will have a chance of good prognosis.

Identification of the patient's prognostic characteristics may be useful in planning future studies and understanding and interpreting their results. Various patient characteristics have been examined in a number of studies to determine whether they have any potential effect on the prognosis of patients with DMPM (20). In most of these studies, cases of stage I disease with epithelial histology and good performance status were commonly presented to have a good prognosis. However, in recent studies, additional parameters such as older age (20,33), LDH ≥500 IU l^{-1}, platelets > 400 000 μl^{-1}, chest pain (20), male gender (21) and high WBC count (21) were reported to have a significantly poorer prognosis.

Any regression model is based on a particular, assumed relationship between the dependent variable and the explanatory covariates. It is important to examine the validity of this assumed relationship. Most regression models allow the model assumption to be examined.

In the current study, we determined by using univariate analyses, that age ≥75, male gender, smoking, advanced stages above stage I disease, KPS < 70, WBC count > 8450 and LDH level ≥500 IU l^{-1} are linked to the worse prognosis. In multivariate Cox regression analyses, age ≥75, advanced stages above stage I disease, KPS < 70 and LDH level ≥500 IU l^{-1} were determined as indicators of a poorer prognosis independently.

The factors related to a poor prognosis in malignant mesothelioma put forward in most publications to date are the following: low performance status, advanced age, advanced stage of disease. In one study, a mixed histopathology was reported to have a worse survey than others (19). However, in another study it was found that mesotheliomas with mixed type histology were associated with longer survival time than the sarcomatous types (2). In three other studies, it was determined that the prognosis of epithelial type mesotheliomas was better than the others (1,20,34). Authors in that study

Table 4. Multivariate stepwise model

Varaiable	Risk ratio	95% CI	*P*
Age (years)			
<75	1		
≥75	2·513	1·173–5·384	0·018
Stage			
I	1		
II,III,IV	1·936	1·145–3·273	0·014
Gender			
Female	1		
Male	1·476	0·808–2·695	0·205
Karnofsky score			
≥70	1		
<70	2·587	1·490–4·492	0·001
WBC count			
<8450	1		
≥8450	1·380	0·880–2·162	0·161
LDH level ≥500 IU l^{-1}			
No	1		
Yes	1·703	1·025–2·830	0·040
Smoking			
Never	1		
Ever	1·402	0·779–2·522	0·260

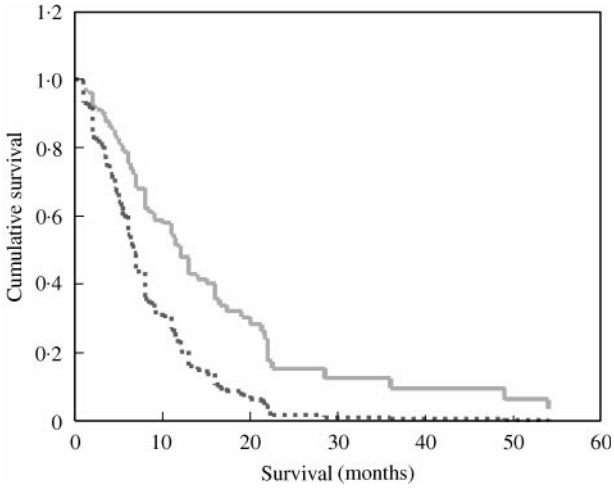

Fig. 1. Survival curves for age of patients. Age <75 years (—) and age ≥75 years (- - - -).

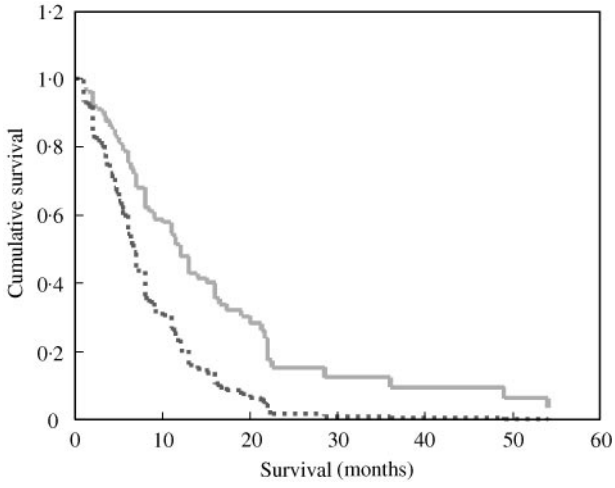

Fig. 2. Survival curves for stages of patients. Stage I (—) and stages II, III, IV (- - -).

claimed that this result could be due to the low incidence of sarcomatous type cases in their study or to international differences in subtype classification (19). In our study, patients with the epithelial type had a 9-month median survival, sarcomatous 7 months, and mixed 6·7 months. There were no significant differences between the three types of tumour.

In our study, as in the majority of other studies, a relation was found between each of older age, performance status, advanced stages above stage I disease and LDH level ≥500 IU l^{-1}, and prognosis both in univariate and multivariate analyses. An overview of the relevant publications provides grounds for making a generalization concerning these relations.

We determined a relation between male gender, smoking history and poor prognosis in univariate analysis but not multivariate. Possibly, since in our patients smoking rate was much higher in males than females (78% *vs*.

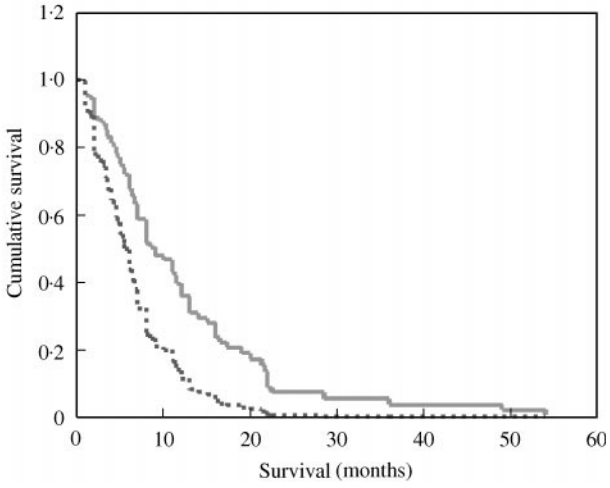

Fig. 3. Survival curves for Karnosky performance score of patients. Karnosky ≥ 70 (—) and Karnofsky < 70 (- - - - -).

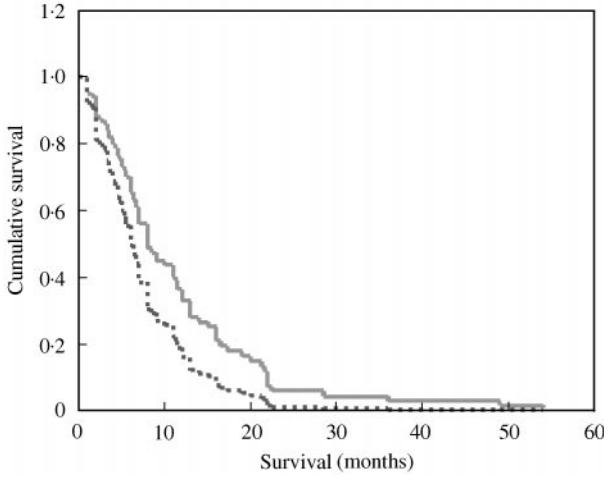

Fig. 4. Survival curves for LDH values of patients. LDH $< 500\ \text{IU}\,\text{l}^{-1}$ (—) and LDH $> 500\ \text{IU}\,\text{l}^{-1}$ (- - - -).

8%), smoking-related co-diseases such as chronic obstructive lung disease (COPD) and atherosclerotic heart disease might have an effect on the survival of smokers and therefore on the the survival of male patients.

There is insufficient knowledge to date about whether or not there is a relationship between patients' responsiveness to chemotherapy and the prognostic characteristics so far studied and determined. For this reason, as we have stated above, in order to evaluate such an important point as the ability to determine beforehand which patients will respond to chemotherapy there is an urgent need for studies investigating prognosis and the related parameters, as well as the relations between these parameters and responsiveness, in both patients responsive and non-responsive to chemotherapy.

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