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ORIGINAL ARTICLE

Clinical characteristics, treatment and survival outcomes in malignant pleural mesothelioma: An institutional experience in Turkey

Mehmet Kucukoner[1], Mehmet Ali Kaplan[1], Ali Inal[1], Zuhat Urakci[1], Ozlem Abakay[2], Abdullah Cetin Tanrikulu[2], Abdurrahman Abakay[2], Hatice Selim Sen[2], Gul Turkcu[3], Abdurrahman Senyigit[2],Huseyin Buyukbayram[3], Abdurrahman Isikdogan[1]

[1]Department of Medical Oncology, [2]Department of Chest Diseases, [3]Department of Pathology, Dicle University, Diyarbakir, Turkey

Summary

Purpose: *To compare treatment modalities and investigate potential prognostic factors for survival in patients with malignant pleural mesothelioma (MPM).*

Methods: *The present study has investigated the data of 150 patients with MPM who were examined and treated in our center from 2005 to 2012.*

Results: *The study included 87 male (58%) and 63 female (42%) patients. Surgical resection (pleurectomy/decortications (P/D), and extrapleural pneumonectomy (EPP)) was performed in 32 (36.7%) patients; 87 patients (58%) received chemotherapy alone and 16 (10.7%) had surgery, chemotherapy and radiotherapy (trimodal treatment). The median progression free and overall survival (PFS and OS) for all patients were 10.6 and 14.8 months, respectively. No statistically significant difference was observed between the patients who received pemetrexed/cisplatin (N=54) and gemcitabine/cisplatin (N=28) in terms of PFS and OS (p=0.145, p=0.244, respectively). Also, no statistically significant difference was registered between operated and non operated patients (PFS and OS, p=0.416, p=0.095, respectively). There was no difference in both PFS and OS rates between patients who had P/D or EPP (p=0.87, p=0.652, respectively). Log rank analysis: Eastern Cooperative Oncology Group performance status (ECOG PS)(p=0.018), histology (p<0.001), stage (p<0.001) and leukocytosis (p=0.005) were found to be significant prognostic factors of OS. At multivariate analysis, ECOG PS (p=0.016) and stage (p<0.001) were independent prognostic factors for OS.*

Conclusion: *Median OS was approximately 1 year. ECOG PS, histological type, stage and presence of leukocytosis were prognostic factors that affected both PFS and OS. EPP or P/D surgical options did not provide difference in terms of survival. Survival rates in patients who received a combination of platinum analogues with pemetrexed or gemcitabine as front-line chemotherapy were similar.*

Key words: *malignant pleural mesothelioma, prognosis, treatment*

Introduction

MPM is an aggressive malignancy with high mortality and is originated from mesothelial cells (eg, pleura, peritoneum, pericardium) [1,2]. Epidemiologic studies have established that exposure to asbestos fibers is the primary cause of MPM [3]. Exposure to erionite and tremolite has been demonstrated to play a considerable role in Turkey, where the incidence of MPM is high [4]. Epithelial variants are the most frequent type and have a better prognosis than biphasic and sarcomatoid MPMs [5].

Although new approaches exist for cancer treatments today, treatment for MPM still causes disappointment [6-8]. MPM has no standard treatment, and surgery, chemotherapy and radiotherapy are used individually or in combination [7]. Also the type of surgery remains extraordinarily controversial as there is a lack of randomized controlled clinical trials [7,9,10]. It has generally been accepted that the combination of peme-

Correspondence to: Mehmet Kucukoner, MD. Dicle University, 21280, Diyarbakir, Turkey. Tel: + 90 4122488001, Fax: + 90 4122488001, E- mail:drmehmetonko@hotmail.com
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trexed/cisplatin (P/C) should be considered as the first choice of chemotherapy for MPM [11]. The most commonly used second-line chemotherapy have been gemcitabine/cisplatin (G/C) combination [12,13] However, there is a lack of prospective studies comparing these two regimens of chemotherapy.

This study was performed to assess the clinicopathologic disease characteristics and to determine prognostic factors which might impact the survival of patients with MPM. Furthermore, outcomes with the administered treatments (surgery and chemotherapy) were investigated in terms of survival advantages to each other.

Methods

Patient population

One hundred and fifty patients with MPM who have been referred to the Medical Oncology clinic of Dicle University Hospital were included into our study. MPM diagnosis was realized by open pleural biopsy, closed needle biopsy, computed tomography (CT)-guided biopsy ,thoracoscopic biopsy and video-assisted thoracoscopic surgery (VATS). Data about the age, gender, smoking history, exposure to asbestos, complaint for referral, ECOG PS, histopathological type, stage, surgical treatment, chemotherapy, radiotherapy, and their responses to treatment, and treatment toxicities were obtained from clinical records. On admission of patients for diagnosis, leukocyte count, hemoglobin level, platelet count, and lactate dehydrogenase (LDH) level were recorded. Laboratory reference ranges of our center were: number of leukocytes 4,300-10,400 /mL, the upper limit of normal of LDH 250 ml / dL, platelet count 120,000-450,000 /mL, normal range of hemoglobin 12-16 g/dL. Performance status was evaluated by using ECOG scale [14]. Patient staging was performed by the International Mesothelioma Interest Group (IMIG) TNM staging [15].

Treatment assessment

P/D, EPP, and talc pleurodesis methods were applied to surgically and medically operable patients. P/C combination which has been approved in our country as first-line treatment was administered as first chemotherapy option. G/C combination has also been applied for its efficiency in the patients before P/C approval. Chemotherapy was applied to patients whose ECOG PS score was ≤ 2, hematologic reserve was sufficient, renal and hepatic functions were normal. Pemetrexed 500 mg/m2 and cisplatin 75 mg/m^2 were administered on day 1 every 21 days; gemcitabine 1000 mg/m^2 (days 1 and 8) and cisplatin 75 mg/m^2 were administered on day 1 every 21 days. RECIST criteria were used to assess tumor response [16]. Radiotherapy (50-60 Gy) was applied as trimodal treatment (with surgery and chemotherapy); palliative treatment was applied as 20-40 Gy or 21 Gy on drainage and biopsy areas. Toxicity evaluation was performed by using the National Cancer Institute Toxicity Criteria, version 2.0 17.

Statistics

All analyses were conducted using the SPSS (SPSS Inc., Chicago, IL, USA) software package. Possible prognostic factors for survival such as histological subtype, stage, PS, treatment regime were analyzed by the Kaplan–Meier method and statistically compared using the log-rank test. OS time was calculated as the time between initial pathological diagnosis and the time of patient's death or last contact. PFS was calculated as the period from treatment onset to progression or death due to any cause. Statistical tests resulting in p values <0.05 were considered to be significant. Factors with p values <0.05 in the univariate analysis entered multivariate Cox regression analysis.

Results

Eighty seven patients were male (58%) and 63 (42%) female with median age 55 years (range 32-85). When the patient referral symptoms were investigated, 61 patients (40.7%) had dyspnea, 27 (18%) had dyspnea and chest pain, and 15 (10%) had chest pain. Ninety-two (61.3%) patients had asbestos contact history while no such history was present in the remaining 58 (39.7%) patients or such contact was unknown. Seventy (46.7%) patients had smoking history and 63 (42%) had not smoked; In the remaining 17 patients smoking history was unknown. Among 70 patients with smoking history 60 (85.7%) were male and 10 (14.3%) female (p<0.001) (Table 1). Curative surgery was performed in 32 (21.3%) patients, pleurodesis was applied in 29 (19.3%) while surgical procedure was not performed in 89 (59.3%). Among 87 patients in whom chemotherapy was administered, P/C was applied in 54 (62.1%) patients, G/C in 28 (32.2%) and raltitrexed/cisplatin in 5 (5.7%) patients as first-line therapy. Fifty-four (36%) patients had neither chemotherapy nor radiotherapy. The median number of chemotherapy courses was 5 (range 1-6) in patients who had received P/C and 5 (range 2-6) in patients who had received G/C. Sixteen (10.7%) patients had trimodal treatment including surgery, chemotherapy and radiotherapy. The most frequently observed non-hematological toxicities were nausea and vomiting (14/17% patients had grade 3 and 4 nausea and vomiting). Twelve (15%) patients had grade 3 and 4 leukopenia. P/C was better tolerated

Table 1. Patient, disease characteristics and univariate survival analysis

Characteristics	*N (%)*	*Progression free survival*		*Overall survival*	
		Median (months)	*p-value*	*Median (months)*	*p-value*
Sex					
Female	63 (42.0)	10.6	0.895	15.6	0.986
Male	87 (58.0)	10.6		12.5	
ECOG PS					
1	107 (71.3)	11.4		16.0	
2	34 (22.7)	6.9	0.023	7.1	0.018
3	9 (6.0)	8.5		8.5	
Histological type					
Epithelioid	86 (57.3)	12.6		20.1	
Biphasic	16 (10.7)	9.7	0.008	9.7	<0.001
Sarcomatoid	10 (6.7)	5.5		4.5	
Unknown	38 (25.3)	8.6		8.7	
Chemotherapy					
Pemetrexed/Cisplatin	54 (65.9)	10.5	0.145	16.2	0.681
Gemcitabine/Cisplatin	28 (34.1)	12.6		16.2	
Stage					
1	13 (8.7)	29.7		29.7	
2	31 (20.7)	22.3	<0.001	25.7	<0.001
3	60 (40.0)	11.8		15.3	
4	46 (30.7)	7.2		7.7	
Operation					
Yes	32 (26.4)	14.4	0.416	18.4	0.095
No	89 (73.6)	9.5		10.7	
Operation type					
P/D	23 (15.3)	14.4	0.875	21.6	0.652
EPP	9 (6)	12.6		18.4	
Leukocyte count					
>10200	27 (28.8)	8.6	0.019	8.6	0.005
<10200	67 (71.2)	14.4		18.9	
Total	150 (100)				

P/D: pleurectomy/decortication, EEP: extrapleural pneumonectomy

Table 2. Drug-related grade 3 or 4 toxicities

Toxicities	*Pemetrexed/ cisplatin (N=54)*	*Gemcitabine/ Cisplatin (N=28)*
	Grade 3-4, N (%)	*Grade 3-4, N (%)*
Hematological		
Absolute neutrophil count	8 (15)	5 (18)
Hemoglobin	10 (5)	3 (10)
Thrombocytopenia	2 (4)	2 (7)
Gastrointestinal		
Nausea/vomiting	9 (16)	5 (17)
Other		
Neuropathy	4 (8)	3 (10)

than G/C (Table 2).

As of November 2012, 126 (84%) of 150 patients had disease progression and 124 (82.7%) of them died. In survival analysis PFS was 10.6 months (95% CI: 8.6 – 12.6); OS was 14.8 months (95% CI: 11.5- 18.2). The median survival was 9.9 months in non-treated patients and 15.6 months in patients who received any treatment (p=0.003). Univariate survival analysis is summarized in Table 1. It appeared that ECOG PS impacted significantly survival (p=0.018). Epithelioid type had the best survival rates for both PFS and OS (12.6 and 20.1 months). There were significant differences between the stage and survival in terms of both PFS and OS (Figures 1,2). There was no significant difference between P/C and G/C combination chemotherapy in terms of survival (Figure 3). The median survival in patients who received trimodal treatment was 24 months. However, this did not differ statistically compared to other treatments (p=0.09). Surgical methods (P/D or EPP) showed no difference in terms of survival (Figure 4). Of the 32 patients who had undergone surgery, 13 had stage III and 12 stage II. Survival analysis was applied for each type of surgery in relation to stage. In stage II and III, there was no statistical difference in terms of OS and PFS between surgery types (p=0.994 and p=0.806 for stage II; p=0.829 and p=0.726 for stage III). In stage I-II and III-IV, there was statistically significant dif-

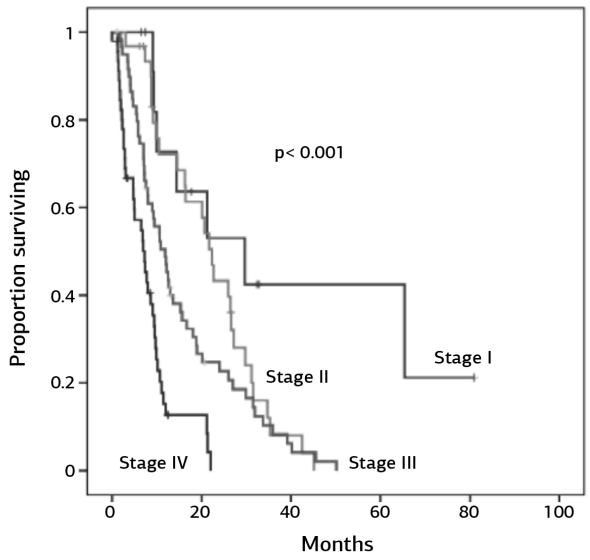

Figure 1. Progression free survival of patients with different disease stages.

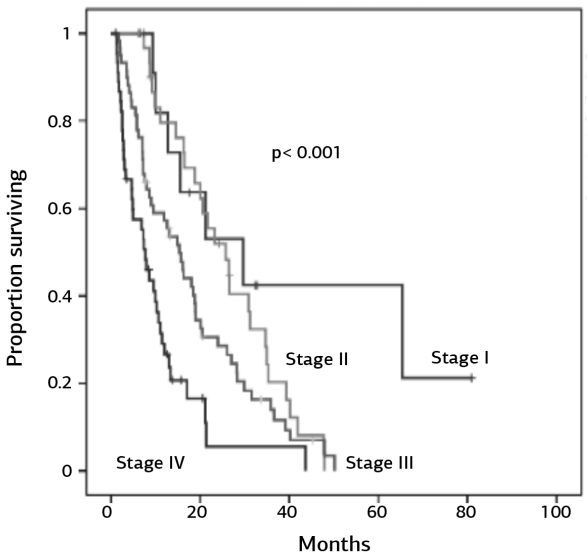

Figure 2. Overall survival of patients with different disease stages.

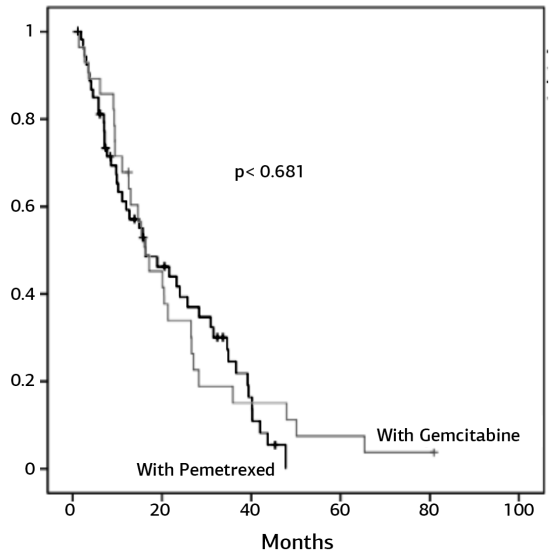

Figure 3. Overall survival of patients with Pemetrexed and Gemcitabine therapy.

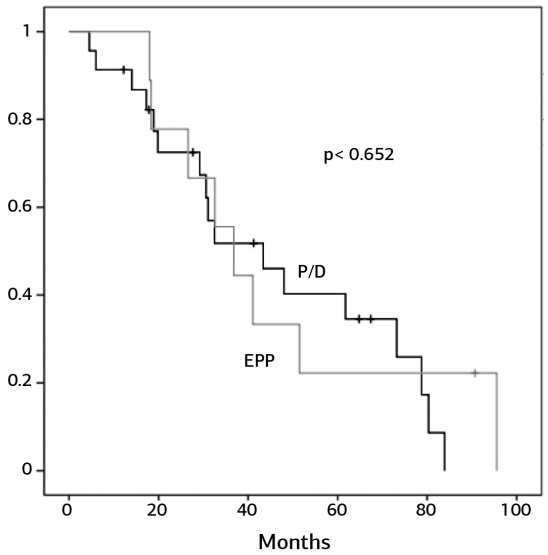

Figure 4. Overall survival of patients with pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP).

ference in PFS and OS according to chemotherapy types (P/C and G/C) (p=0.008 and p=0.022, respectively). Getting chemotherapy in early stage prolonged survival.

In multivariate analysis, ECOG PS and stage were independent prognostic factors affecting survival (Table 3). High leukocyte counts were significantly correlated with survival. PFS and OS were 14.4 and 18.9 months in patients with normal leukocyte count and in patients with leukocytosis they were 8.9 and 8.6 months (p=0.019 and p=0.005, respectively). Patients with hemoglobin > 10 g/Dl had better PFS and OS than those with hemoglobin < 10 g/dL (p=0.681 and p=0.437, respectively). Also no statistically significant difference in terms of PFS and OS was observed between the groups with or without thrombocytosis (p=0.886 and p=0.491, respectively). Similarly, no statistically significant difference between LDH and PFS and OS was registered (p=0.878 and p=0.385, respectively).

Discussion

The average age at diagnosis of patients with MPM is 60 years, and disease appears more frequently in men [18,19]. In our study, the patient median age was 55 years. In terms of histological

Table 3. Multivariate analysis of risk factors affecting relapse and overall survival

Factors	*Relapse*		*Overall survival*	
	Hazard ratio (95% CI)	*p-value*	*Hazard ratio (95% CI)*	*p-value*
ECOG		0.030		0.016
ECOG 2 - ECOG 1	2.070 (1.189-3.602)	0.010	2.150 (1.219-3.794)	0.008
ECOG 3 - ECOG 1	1.965 (0.462-8.352)	0.360	2.974 (0.680-13.009)	0.148
Stage		<0.001		<0.001
Stage 2- Stage 1	2.131 (0.696-6.522)	0.185	1.611 (0.524-4.952)	0.405
Stage 3- Stage 1	4.287 (1.480-12.417)	0.007	3.448 (1.171-10.150)	0.025
Stage 4- Stage 1	9.007 (2.997-27.069)	<0.001	5.568 (1.844-16.814)	0.002

types, epithelioid type ranges from 55 to 60% [20]. Histological subtype was specified in 112 of our patients and 57.2% of them had epithelioid type. Such histological types have been determined with similar rates in a study conducted in our region [20].

Generally, OS ranges between 6 and 17 months [21]. OS was 14.8 months (95% CI: 11.5 – 18.2) in our study, in line with the literature. Our study showed that early stage (stage I and II), epithelioid type histology, and low ECOG PS significantly prolonged both PFS and OS, similar to the findings of another study [22]. Epithelioid type had the best survival (p<0.001) (median 20.1 months) in our study. In the study conducted by Sugarbaker et al., patients with epithelioid histology had the best OS compared with other histological types (26 months, p=0.001) [23]. A study has reported that average OS in cases other than epithelioid histology was 4 to 12 months [24]. In the present study, PFS and OS decreased significantly from stage 1 to stage 4 (p<0.001). In a study, OS was 26, 15 and 8 months in stages 2,3 and 4, respectively [25]. Furthermore, ECOG PS was shown to be an important predictive and prognostic factor [22]. Median OS in ECOG PS 1 was 16 months and 8.5 months in ECOG PS 3 in this study (p=0.018), and high leukocyte counts were significantly correlated with survival. However, there was no statistically significant difference in hemoglobin, platelets, and the level of LDH in terms of both PFS and OS . In the literature, ECOG PS score, histological type, stage, grade, gender, LDH, platelet, hemoglobin, leukocyte values and age were shown as significant prognostic factors [26-28]. Low hemoglobin, high white blood cell count, and thrombocytosis were associated with poor prognosis in other studies [6,23]. MPMs are known to produce stimulating factors of myeloid cells, that trigger the production of extra white blood cells. Treatments of MPMs that target the immune system were found to be negatively correlated with OS in patients with non-epithelioid types [29].

In the survival analysis performed, it was proved that surgery did not influence survival (p=0.095). Trimodal treatment applications produced the best survival, however without statistical difference in our study. Furthermore, the type of surgery (P/D or EPP) produced no statistically significant difference in survival. Moreover, survival in patients who had EPP was shorter and this may be attributed to the high surgical morbidity and mortality of the method. It is problematic to decide which patient will have EPP and which P/D. Some authors reported that patients in the P/D group are generally selected among early stage (stage Ia) tumors. On the contrary, most of the patients in the EPP group had stage II or III [7,30]. EPP and P/D have been compared in a study that proved non-recurrent survival period was significantly higher in the EPP group, while no difference was found for OS [30]. In another similar study no difference was found (p=0.85) [31]. In the study of Flores et al. conducted to compare surgical treatments, survival was worse in patients with EPP than in patients with P/D (hazard ratio=1.4; p<0.001) [32]. Two-year OS rates have been reported to range between 10 and 37% for patients with EPP along with chemotherapy and radiotherapy. Sugarbaker et al. performed EPP in 176 patients and found an average survival of 19 months and 2-year OS 38% for all patients [32,33]. This study outlined that EPP provides a high survival rate. However, a study showed that the type of surgery does not have a significant effect on survival [9]. It should be emphasized that there was not any homogeneity between patient groups to be compared [9]. The option of surgery for MPM is controversial, because data from randomized controlled trials are not available [9,34]. Surgery should be performed in selected patients

by experienced thoracic surgeons. Therefore, P/D may be a better choice for many patients and showed better survival than EPP in a retrospective analysis [32]. In a recent study where EPP and chemotherapy were compared, it has been shown that there was not any survival difference between the two groups in terms of EPP-induced mortality [10]. This study shows that no clear consensus has been reached over the surgical treatment of MPM patients.

Clinical studies indicated that response and survival rates obtained with P/C or G/C chemotherapy are satisfactory [11,35]. In a retrospective study comparing P/C (N=34) and G/C (N=38) no difference in median survival was shown [36]. In another retrospective study, Elkiran et al. comparing P/C vs G/C reported no difference in terms of survival (p=0.15) [31]. In our study with Abakay et al. study, P/C therapy proved superior to G/C in terms of OS.

In conclusion, it was shown that ECOG PS, histological type, stage and the presence of leukocytosis are important prognostic factors in MPM. It was also observed that there was no statistically significant difference in survival between patients operated or not. Furthermore, no survival difference between P/D and EPP was noted. Survival rates in patients who received P/C or G/C as front-line chemotherapy were similar. Due to the different results in studies on MPM, reliable prospective studies are needed.

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