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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

The prognostic analysis of the some clinicopathological parameters and gene protein expressions in malignant mesothelioma

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ABSTRACT

The prognostic analysis of the some clinicopathological parameters and gene protein expressions in malignant mesothelioma

Introduction: *Mesothelioma is an aggressive tumour that originates in serous surfaces. The primary end point of this study was to invastigate the relationship of progression free survival (PFS) and overall survival (OS) with the c-Met, EGFR, PTEN, PDGFR-alpha, PI3K/AKT and mTOR expression levels in the tumour tissue of pleural and peritoneal mesothelioma cases.*

Materials and Methods: *The study included 53 patients diagnosed with mesothelioma between 2005 and 2016. The cases were separated into 2 groups as pleural and peritoneal. The effects on OS and PFS were examined of the c-Met, EGFR, PTEN, PDGFR-alpha, PI3K/AKT and mTOR expression levels and also clinicopathological parameters and the treatments given. In the statistical analysis of the data obtained, IBM SPSS vn 20.0 software was used.*

Results: *Of the 53 patients included in the study, 39 (73.6%) were diagnosed with pleural mesothelioma and 14 (26.4%) with peritoneal mesothelioma. According to the c-Met and mTOR expression, OS and PFS of the peritoneal cases with high expression (2+, 3+) was seen to be significantly better than that of the peritoneal cases with low expression (0, 1+) ($p< 0.05$). According to the PDGFR expression, OS and PFS of the pleural cases with low expression (0, 1+) was seen to be significantly better than that of the pleural cases with high expression (2+, 3+) ($p< 0.05$).*

Conclusion: *The examination of c-MET, PDGFR-alpha and m-TOR expression in the in the tumor tissue of mesothelioma cases may be important in determining prognosis.*

Key words: *Mesothelioma; c-Met; PDGFR-alpha; mTOR*

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ÖZ

Malign mezotelyomada bazı klinikopatolojik parametrelerin ve gen protein ekspresyonlarının prognostik analizi

Giriş: *Mezotelyoma, seröz yüzeylerden kaynaklanan agresif seyirli bir tümördür. Bu çalışmanın birincil sonlanım noktası, progresyonsuz sağkalım (PS) ve genel sağkalım (GS) ile plevral ve peritoneal mezotelyoma olgularındaki tümör dokusunda c-Met, EGFR, PTEN, PDGFR-alfa, PI3K/AKT ve mTOR ekspresyon düzeylerinin ilişkisini incelemekti.*

Materyal ve Metod: *Çalışmaya 2005-2016 yılları arasında mezotelyoma tanısı konan 53 hasta dahil edildi. Olgular plevral ve peritoneal olmak üzere iki gruba ayrıldı. GS ve PS üzerindeki etkiler c-Met, EGFR, PTEN, PDGFR-alfa, PI3K/AKT ve mTOR ekspresyon düzeyleri ile klinikopatolojik parametreler ve verilen tedaviler açısından incelendi. Elde edilen verilerin istatistiksel analizinde IBM SPSS vn 20.0 yazılımı kullanıldı.*

Bulgular: *Çalışmaya dahil edilen 53 hastadan 39 (%73.6)'una plevral mezotelyoma, 14 (%26.4)'üne peritoneal mezotelyoma tanısı kondu. c-Met ve mTOR ekspresyonuna göre; yüksek eksprese olan (2+, 3+) peritoneal olguların GS ve PS oranlarının, düşük eksprese (0, 1+) olan peritoneal olgulardan anlamlı olarak daha iyi olduğu görüldü (p< 0.05). PDGFR ekspresyonuna göre; düşük eksprese olan (0, 1+) plevral olguların GS ve PS oranlarının, yüksek eksprese olan (2+, 3+) plevral olgulardan anlamlı olarak daha iyi olduğu görüldü (p< 0.05).*

Sonuç: *Mezotelyoma olgularının biyopsi ve operasyon materyallerinde c-Met, PDGFR-alfa ve mTOR ekspresyonunun incelenmesi prognozun belirlenmesinde önemli olabilir.*

Anahtar kelimeler: *Mezotelyoma; c-Met; PDGFR-alpha; mTOR*

INTRODUCTION

Malignant mesothelioma is a tumour with an aggressive course that originates in serous surfaces such as the pleura, peritoneum, tunica vaginalis and pericardium, respectively according to frequency (1). The most important cause of pleural mesothelioma, is a history of exposure to asbestos (2). Although asbestos is a significant etiological factor for the development of peritoneal mesothelioma, a higher cumulative exposure is required compared to pleural mesothelioma (3). In the pathogenesis of mesothelioma, there are several molecules and signal transmission pathways that are responsible for cell growth, proliferation, motility, angiogenesis, invasion and metastasis. In this study, we examined that c-Met, EGFR (epidermal growth factor receptor), PTEN (phosphatase and tensin homologue), and PDGFR-alfa (platelet derived growth factor receptor alpha) molecules and the PI3K/AKT/mTOR (phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin) signal transmission pathway. While some studies have suggested that the expression levels of these molecules could have an effect on survival (4-7); some studies have found no significant difference in survival between negative and positive groups according to the expression level (8,9). The primary end point of this study was to examine the relationship of progression free survival (PFS) and overall survival (OS) with the level of these molecules in the tumour tissue of pleural and peritoneal mesothelioma cases. Secondary end points were the association between PFS and OS with the clinicopathological parameters and the treatments given.

MATERIALS and METHODS

Fifty-three cases with histologically diagnosed malignant mesothelioma were included in the study. The cases treated and followed up between 2005 and 2016 in the medical oncology department were seperated into two groups as pleural and peritoneal mesothelioma. The effect of the levels of c-Met, EGFR, PTEN, PDGFR-alpha, PI3K/AKT and mTOR expression on OS and PFS was examined. The demographic characteristics, exposure to asbestos, smoking status, histopathological type, localisation, and treatments applied were evaluated. Poor performance (Eastern Cooperative Oncology Group performance-status score ≥ 2) was accepted in all the groups as a reason for not administering chemotherapy.

Study Design

Biopsy (surgical or not) samples of the all patients were fixed in 10% formaldehyde. Sections 5 microns in thickness were cut from the embedded tissue into paraffin blocks. With an ultraView UniversalDAB Detection kit (Ventana, 760-500) in an automatic Ventana BenchMark XT immunohistochemical staining device, the following antibodies were applied: Rabbit Anti- Human mTOR Polyclonal Antibody (E18594, Spring Bioscience), Rabbit Anti-Human c-Met Polyclonal Antibody (E10612, Spring Bioscience), Rabbit Anti-PTEN (SP218) Monoclonal Antibody (M5180, Spring Bioscience), PDGFR alpha Polyclonal Antibody (PA5-16742, Thermo Scientific), CONFIRM anti-Epidermal Growth Factor Receptor (3C6) Primary Antibody (790-2988, Ventana), Phospho-Akt (Ser473)

(736E11) Rabbit mAb (3787, Cell Signaling). The results were evaluated under a Nikon Eclipse E200 light microscope. Although PDGFR-alpha was generally cytoplasmic stained, cytoplasmic and membranous staining was accepted positive as previously described (10). EGFR is based on a membranous staining pattern and PTEN is detected in the cytoplasm (5). For PI3K/AKT and mTOR pathway the percentage of stained tumor cells was scored in a whole section, and the average percentage and intensity of tumor cell staining was calculated as a semiquantitative histo score method as described previously (11). For c-Met, stain localization to the cell cytoplasm, cytoplasmic membrane, or both was recorded. For all biomarkers grading was made according to the intensity and ratio of staining as negative (0), weak (+1), moderate (+2) and strong (+3). Evaluation was made according to the ratio of stained cells as negative (0), 0%-20% weak (+1), 20%-60% moderate (+2) and 60%-100% strong (+3) (12,13). Comparisons were made between the (2+, 3+) groups and and the (0, 1+) groups.

Statistical Analysis

Statistical analyses of the data were made using IBM SPSS vn 20.0 software. Descriptive statistics were shown as mean, median, standard deviation, minimum and maximum values as appropriate. Progression-free survival was evaluated as the time from diagnosis to recurrence, metastasis or death from other reasons with no development of recurrence. Overall survival was calculated from diagnosis of malignancy until death due to any cause. All patients died when the study was performed. Survival analysis was performed using Kaplan-Meier curves and the significance was verified by a long-rank test. All p values were determined by two-sided tests and p values < 0.05 were considered significant. (2+, 3+) groups were defined as high expression and (0, 1+) groups were defined as low expression.

RESULTS

The study included 53 patients who presented at the medical oncology department and were diagnosed with malignant mesothelioma. The demographic and clinical characteristics of the patients are shown in Table 1. Occupation was recorded as housewife in 25 (47.2%) cases, farmer in 14 (26.4%), and various other occupations in the other 14 cases. The localisation of the tumour was in the pleura in 39 (73.6%) patients and in the peritoneum in 14 (26.4%). No significant difference was determined between the two groups in respect of OS, as median 15 months in the pleural cases and 12 months in the peritoneal cases (p= 0.559). And also no statistically significant difference was determined between the two groups in respect of PFS, as median 10 months in the pleural cases and 6 months in the peritoneal group (p= 0.432).

Table 1. Demographic and clinical characteristics of the patients

Parameter	Number (%)
Gender	
Female	27 (50.9)
Male	26 (49.1)
Median age (min-max) (years)	58 (28-80)
Topography	
Pleural	39 (73.6)
Peritoneal	14 (26.4)
Histological type	
Epithelial	41 (77.4)
Sarcomatous	2 (3.8)
Biphasic	10 (18.9)
Asbestos exposure	
Positive	24 (45.3)
Negative	29 (54.7)
Cigarette smoking	
Positive	22 (41.5)
Negative	31 (58.5)

In 24 (45.3%) of all patients there was a history of asbestos exposure, and when the effect on OS was examined, in the group with pleural mesothelioma the OS was determined to be 15 months in those with asbestos exposure and 18 months in the group not exposed to asbestos (p= 0.367). In the group with peritoneal mesothelioma, OS was determined as 12 months in those with asbestos exposure and 13 months in those without (p= 0.501). Of the total patients, 22 (41.5%) smoked and 31 (58.5%) did not smoke. Of the pleural mesothelioma group, OS was 12 months for those who smoked and 18 months for the non-smokers (p= 0.657). Of the peritoneal mesothelioma group, OS was 8 months for those who smoked and 12 months for the non-smokers (p= 0.844).

Surgery and Survival

The surgical treatment methods applied to the 39 pleural mesothelioma cases with no metastasis were recorded as partial decortication in 7 (17.9%), total

decortication in 10 (25.6%) and extrapleural pneumonectomy in 10 (25.6%). No surgery was applied to the 12 (30.8%) patients with metastatic disease. In the pleural mesothelioma patients, OS was determined as 6 months in patients not applied with surgery, 9 months in those applied with partial decortication, 24 months for total decortication, and 29 months for extrapleural pneumonectomy. Of the 14 malignant peritoneal mesothelioma cases in the study, omentectomy was applied to 6 (42.9%) patients. OS was determined as 12 months in those applied with omentectomy and 8 months in those who did not undergo surgery.

Chemotherapy and Survival

First line chemotherapy was administered to 27 (69.2%) of the cases with pleural mesothelioma. Pemetrexed + cisplatin was administered to 21 (77.8%) cases, gemcitabine + cisplatin to 4 (14.8%) and pemetrexed + carboplatin to 2 (7.4%). OS was 18 months for those who received first line chemotherapy and 3 months for those who did not. The difference between the groups was statistically significant (p= 0.004). Second line chemotherapy was administered to 17 (43.6%) of the pleural group. Vinorelbine was administered as the single agent to 1 (5.9%) patient, gemcitabine + vinorelbine to 1 (5.9%) patient, cisplatin + pemetrexed to 2 (11.8%) patients, gemcitabine + carboplatin to 2 (11.8%) patients, and gemcitabine + cisplatin to the remaining 11 (64.7%) patients. OS was determined as 29 months for those who received second line chemotherapy and 7 months for those who did not. The difference between the groups was statistically significant (p< 0.001).

In the peritoneal mesothelioma group, 10 (71.4%) of 14 patients received first line chemotherapy. Of these, 9 were administered pemetrexed + cisplatin, and 1 with pemetrexed + carboplatin. OS was determined as median 15 months for those who received first line chemotherapy and 1 month for those who did not. The difference between the groups was statistically significant (p= 0.001). Second line chemotherapy was administered to 7 patients in the peritoneal group, as cisplatin + pemetrexed to 3 (42.8%), and gemcitabine + cisplatin to the remaining 4 patients. OS was determined as median 18 months for those who received second line chemotherapy and 4 months for those who did not. The difference between the groups was statistically significant (p= 0.014).

Radiotherapy

In 8 (20.5%) of the pleural mesothelioma cases, palliative radiotherapy was applied for the relief of pain and shortness of breath. Survival analysis was not examined in respect of palliative radiotherapy. OS and PFS results of the pleural and peritoneal mesothelioma cases according to c-Met, EGFR, PTEN, PDGFR-alpha, PI3K/AKT and mTOR expressions and also frequencies of the positivity of the expression are shown in Tables 2 and 3.

Table 2. OS and PFS rates of the patients with pleural mesothelioma according to expression levels

Marker	Expression level	No of patients (%)	Median OS (months)	p value (OS)	Median PFS (months)	p value (PFS)
c-Met	0, +1	11 (28.2)	10	0.46	6	0.26
	+2, +3	28 (71.8)	18		10	
EGFR	0, +1	8 (20.5)	9	0.28	6	0.34
	+2, +3	31 (79.5)	18		10	
PTEN	0, +1	1 (2.6)	32	0.70	12	0.91
	+2, +3	38 (97.4)	15		10	
PDGFR-alpha	0, +1	30 (76.9)	18	**0.003**	11	**0.02**
	+2, +3	9 (23.1)	8		4	
PI3K/AKT	0	32 (82.1)	15	0.075	10	0.18
	+1	7 (17.9)	38		14	
mTOR	0, +1	8 (20.5)	9	0.67	6	0.32
	+2, +3	31 (79.5)	15		10	

OS: Overall survival, PFS: Progression free survival.

Table 3. The OS and PFS rates of the patients with peritoneal mesothelioma according to expression levels

Marker	Expression level	No of patients (%)	Median OS (months)	p value (OS)	Median PFS (months)	p value (PFS)
c-Met	0, +1	2 (14.3)	1	**0.005**	1	**0.005**
	+2, +3	12 (85.7)	13		6	
EGFR	0, +1	3 (21.4)	12	0.74	6	0.91
	+2, +3	11 (78.6)	13		6	
PTEN	0, +1	1 (7.1)	1	0.056	1	0.056
	+2, +3	13 (92.9)	13		6	
PDGFR-alpha	0, +1	8 (57.1)	3	0.37	3	0.36
	+2, +3	6 (42.9)	13		6	
PI3K/AKT	0	13 (92.9)	13	0.54	6	0.60
	+1, +2	1 (7.1)	12		6	
mTOR	0, +1	2 (14.3)	1	**0.047**	1	**0.047**
	+2, +3	12 (85.7)	13		6	

OS: Overall survival, PFS: Progression free survival.

DISCUSSION

In a retrospective study of biopsy samples of 341 cases with pleural mesothelioma, Opitz et al. reported that immunohistochemically, PTEN expression of 62% of patients was negative, and the survival of all the positve groups (weak, moderate, strong staining) was better than that of the negative group (14). Agarwal et al. showed negative PTEN expression in 26.7% of 86 cases with pleural mesothelioma, and unlike the previous study, there was no statistically significant difference between the groups in respect of survival (15). In the current study, PTEN expression negativity was determined in only 2.6% of the pleural mesothelioma cases, and almost all the cases (97.4%) were stained (2+, 3+). When PTEN expression was examined as two groups (0, 1+ vs. 2+, 3+), no statistically significant difference was determined in respect of OS. The same was true for PFS in pleural mesothelioma and for both OS and PFS in peritoneal mesotheloma. This could be due to the low number of patients in the study and that there were only 2 cases with negative and (1+) PTEN expression. The PI3K/AKT/mTOR pathway is known to be active in mesothelioma.

It is thought that with loss of PTEN protein expression, there is PIP3 accumulation and structural activation of AKT, which could extend cell life. Activation could occur in the PI3K/AKT/mTOR pathway with this loss, suggesting that this could be a target for treatment in selected mesothelioma cases (16-18). When the PI3K/AKT expression was examined in the pleural mesothelioma cases of the current study, no statistically significant difference was determined between the OS of the (0) and (1+) groups. The same was true for PFS in pleural mesothelioma and for both OS and PFS in peritoneal mesothelioma, which could be attributed to the limited number of patients and that the vast majority were negative. mTOR, which is of key importance between anabolic and catabolic metabolisms, is an intracellular serin-treonin protein kinase, located at a central point in the intracellular signal cascade (19). As mTOR is a kinase with a key function in the downward-flowing P13K/AKT pathway, its inhibition is considered to be an important potential therapeutic target (20). In the current study, while no difference was seen in OS and PFS between the (0; 1+) and (2+; 3+) groups of mTOR expression in the pleural mesothelioma cases, in the peritoneal cases, OS of the (0; 1+) mTOR expression group was seen to be statistically significantly longer than that of the (2+ ; 3+) group. In the immunohistochemical examination of biopsy samples of 71 patients with malignant pleural mesothelioma, Gaafar et al. reported the median overall survival to be 12 months in the group with positive EGFR expression and 8 months in the negative group, but the difference was not evaluated as statistically significant (21). There is known to be an increase in the EGFR expression of the majority of peritoneal mesothelioma cases. From this starting

point, a Phase II study showed that the use of EFGR inhibitors was of no significant clinical benefit (22). In the current study, no statistically significant difference was determined in OS or PFS in both the pleural and peritoneal malignant mesothelioma cases when examined as two groups of low (0; 1+) and high (2+ ; 3+) EGFR expression.

c-Met is a receptor tyrosine kinase encoded by MET proto-oncogene located in chromosome 7q31 region. In comparison with normal pleura, it has been shown to be expressed more in pleural mesothelioma tissues (23). In the current study, no statistically significant difference was determined in OS or PFS in the pleural mesothelioma cases when examined as two groups of low (0; 1+) and high (2+ ; 3+) c-Met expression. In the peritoneal mesothelioma cases, OS was seen to be statistically significantly longer in the high (2+; 3+) c-Met expression group than in the low expression (0; 1+) group, and this was similar in respect of PFS. Progress in cancer biology has led to an increasing discovery of oncogenic alterations of the platelet-derived growth factor receptors (PDGFRs) in cancers. In addition, their overexpression in numerous cancers invariably makes PDGFRs and platelet-derived growth factors (PDGFs) prognostic and treatment markers in some cancers (24). In the current study, OS was seen to be statistically significantly longer in the low (0+; 1+) PDGFRalfa expression group than in the high (2+; 3+) expression group pleural mesothelioma cases, and this was similar in respect of PFS. No statistically significant difference was seen in the OS and PFS between the low (0; 1+) and high (2+; 3+) expression groups of PDGFR-alpha in the peritoneal mesothelioma cases.

OS in malignant pleural mesothelioma in the literature has been shown to vary between 5 and 22 months and in the current study, OS was determined as 15.8 months. OS of peritoneal mesothelioma is approximately 1 year (25,26). Similarly, in the current study, OS of patients with peritoneal mesothelioma was 12 months. OS and PFS in all the patient groups was seen to be better in the chemotherapy group.

CONCLUSION

The results of this study suggest that the examination of c-Met, PDGFR-alpha, and mTOR expressions in mesothelioma biopsy and operating materials could be important for the determination of prognosis. There is a need for further more extensive studies on this subject.

CONFLICT of INTEREST

No conflict of interest declared by the authors.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MT, MB, İOK, DG, EB

Analysis/Interpretation: MT, İOK, DG, EB

Data Acquisition: MT, MB

Writting: MT, MB, İOK

Critical Revision: MT, MB, İOK

Final Approval: All of authors.

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