Comparison of First-Line Chemotherapeutics and Validation of the EORTC Prognostic Index in Malignant Pleural Mesothelioma: Retrospective Single-Centre Experience

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ABSTRACT

Objective: To evaluate the efficiency of pemetrexed cisplatin in comparison with gemcitabine cisplatin and to validate the EORTC (European Organisation for Research and Treatment of Cancer) prognostic score in combination chemotherapy treatment for malignant pleural mesothelioma.

Study Design: An observational study.

Place and Duration of the Study: Department of Oncology, Dicle University Hospital, Diyarbakir, Turkiye, from October 2000 to November 2017.

Methodology: Malignant pleural mesothelioma (MPM) patients with EORTC score 0- were recruited. Factors affecting the prognosis of the disease and the effectiveness of first-line treatment were retrospectively analysed. EORTC prognostic score was calculated with a cut-off and survival analyses were used by the Kaplan-Meier method. Log-rank and univariable Cox regression tests were used to search for prognostic factors' impact on survival.

Results: Patients who received gemcitabine cisplatin treatment had a median progression-free survival (PFS) of 9 months, while those who received pemetrexed cisplatin therapy had a median PFS of 7 months. Median overall survival (OS) was 17 months in the gemcitabine cisplatin group and 18 months in the pemetrexed cisplatin group ($p = 0.051$). When the low-risk group was compared with the high-risk group, the median OS was found to be statistically significant ($p = 0.009$).

Conclusion: The EORTC prognostic score, which is used for prognostic prediction in the period when pemetrexed is not utilised in the treatment of MPM, accurately predicts prognosis subsequent to the administration of pemetrexed in treatment. In the context of first-line treatment, cisplatin in combination with gemcitabine and cisplatin in combination with pemetrexed demonstrated comparable efficacy with respect to both overall survival and progression-free survival.

Key Words: *Chemotherapy, Mesothelioma, Prognosis, Gemcitabine, Progression-free survival.*

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INTRODUCTION

Malignant pleural mesothelioma (MPM), which affects the pleural membrane surrounding the lungs, is a rare and aggressive disease; MPM is associated with aspes exposure. On average, there are 14,200 new cases of MPM each year.[1]

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The median survival rate in MPM varies from 8–14 months.[2-5] The average survival duration for patients with the epithelioid subtype is 13.1 months, but for those with the sarcomatoid subtype, it is 4 months.[2,3,5]

Trimodal therapy (surgery, chemotherapy, and radiotherapy) is used for the local stage treatment of MPM, while chemotherapy and immunotherapy are used for metastatic disease.[6-8] A phase 3 study found that the combination of cisplatin and pemetrexed raised overall survival at a mean of 3 months compared with cisplatin and was the standard first-line treatment.[9] In a study investigating the combination of cisplatin and gemcitabine, median PFS was found to be 8 months, and OS was 13 months.[10] While numerically the survival outcomes of gemcitabine and cisplatin are similar to those of the pemetrexed and cisplatin regimens, there is currently no study comparing these two regimens.

The identification of prognostic factors is important for the escalation and de-escalation of treatment. An advanced disease stage, the presence of sarcomatoid or biphasic type, poor performance status, advanced age, weight loss, high lactate dehydrogenase (LDH), leukocytosis, thrombocytosis, and anaemia are considered poor prognostic factors for MPM.[11,12] Several prognostic indices have been developed using these factors. The most commonly used indices are the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukaemia Group B (CALGB) scoring systems.[11,12] Many of the subsequently developed indices were obtained through the validation or modification of these indices. According to the EORTC group, factors such as high Eastern Cooperative Oncology Group Performance Status (ECOG PS), advanced age (>55), high WBC count (≥8.3 10^9/L), male gender, and the presence of sarcomatoid type are considered poor prognostic factors, and a prognostic index was developed using these factors.[12] The EORTC prognostic score was developed prior to the use of pemetrexed; at that time, single agents such as paclitaxel, mitoxantrone, epirubicin, and etoposide were used, while gemcitabine, cisplatin, pemetrexed, and their combinations were not used.

The primary objectives of this study were to assess the efficacy of pemetrexed and cisplatin as compared to gemcitabine and cisplatin as first-line treatments for MPM, and to validate the EORTC prognostic index with the use of pemetrexed and cisplatin in combination with gemcitabine and cisplatin.

METHODOLOGY

This study employed an observational methodology with a retrospective data collection. The data pertaining to the patients included in the study was obtained from the database of Dicle University Hospital, Diyarbakir, Turkiye. The study included patients aged between 18 and 90 years, diagnosed with MPM between October 2000 and November 2020, and who were treated and followed up at the hospital. Patients with an ECOG PS of 0-2 were included. Patients with a second primary tumour, peritoneal mesothelioma, those younger than 18 years of age, and those who were lost to follow-up were excluded from the study.

PFS and OS times were compared between the two treatment arms. The effects of age, gender, Eastern Cooperative Oncology Group (ECOG) performance score, histopathological certainty of diagnosis, presence of sarcomatoid type, LDH level at the time of diagnosis, haemoglobin level, and white blood cell (WBC) levels on prognosis were investigated. Age below and above 55 years, LDH level below and above 300 U/L, haemoglobin level below and above 15 g/dL in men and 13 g/dL in women, and WBC level below and above 8.3 10^9/L were used as the criteria for the values calculated in the EORTC group.[12] The prognostic scoring system used by the EORTC group is as follows: 0.55 (WBC >8.3) + 0.6 (ECOG PS 1-2), + 0.52 (histological diagnosis is not definite), + 0.67 (histological subtype sarcomatoid), + 0.6 (male gender). Those with a total score of ≤1.27 were classified as the low-risk group, while those with a total score of >1.27 were classified as the high-risk group. The effects of these groups on prognosis were then compared.[12]

For pretreatment staging, blood tests, contrast-enhanced computed tomography (CT) or positron emission tomography (PET CT) were performed. For treatment response evaluation, CT or PET CT was performed every 12 weeks, and the objective response rate in patients with measurable target lesions was evaluated according to response evaluation criteria in solid tumours (RECIST) version 1.1.[13]

Patients receiving gemcitabine plus cisplatin, cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 were administered on days 1 and 8, every three weeks.[14] In patients receiving cisplatin plus pemetrexed, pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 were administered every three weeks.[9] Prior to each treatment, a physical examination and haematological and biochemical blood tests were conducted.

Categorical variables were expressed as count and percentage (%), and continuous variables were represented as median and range. Descriptive statistical methods were used in the evaluation of the data. PFS was calculated as the time from treatment initiation to the first progression, and OS was calculated as the time from treatment initiation to the last follow-up or death. Survival analyses were estimated by the Kaplan-Meier method. The association of patient characteristics, treatment-related characteristics, and prognostic factors with survival was investigated using log-rank and univariate Cox regression tests. All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). All p-values lower than 0.05 were considered statistically significant, and results were calculated using 95% confidence interval (CI).

RESULTS

The research had 140 patients with 80 (57.2%) males and 60 (42.8%) females. The median age of patients was found to be 58 (32-90). Of the total, 43 (30.7%) patients had stage 1-2 disease, while 97 (69.3%) had stage 3-4 disease. Surgical procedures were performed on 61 (43.9%) patients. The number of smoking patients was 60 (42.9%). Adjuvant treatment was given to 38 (27.1%) patients, while 102 (72.9%) patients were not eligible for adjuvant treatment. Pemetrexed and cisplatin were given to 93 (66.4%) patients as a part of the first-line therapy, while 30 (21.4%) patients were given gemcitabine and cisplatin. The remaining 17 (12.2%) patients were treated with other regimens. During the analysis, 7 (5%) patients were alive, while 133 (95%) patients had died. The patients' characteristics were similar in the pemetrexed cisplatin and gemcitabine cisplatin groups (Table I).

The median follow-up period lasted for a length of 16 months. The median PFS was seven months (95% CI: 5.5-8.4) for those receiving pemetrexed and cisplatin and 9 months (95% CI: 7.7-10.3) for those receiving gemcitabine and cisplatin ($p = 0.72$). In terms of overall survival, the group treated with pemetrexed and cisplatin had a median survival of 18 months (95% CI: 12.9-23.0), whereas the group treated with gemcitabine and cisplatin displayed a median survival of 17 months (95% CI: 10.8-23.1, $p = 0.51$).

Table I: Patient characteristics in treatment groups.

		Pemetrexed + Cisplatin	Gemcitabine + Cisplatin	p-value
Age* (mean, std dev.)		55.2 ± 10.1	58.1 ± 13.2	0.25
Gender†		-	-	-
	Female	44 (47.3)	12 (40)	0.48
	Male	49 (52.7)	18 (60)	-
Smoking†				
	Yes	34 (43)	12 (52.2)	0.43
	No	45 (57)	11 (47.8)	-
Initial stage†				
	I-II	25 (26.9)	11 (36.7)	0.38
	III-IV	68 (73.1)	19 (63.3)	-
Primary surgery†				
	Yes	30 (32.2)	9 (30)	0.81
	No	63 (67.8)	21 (70)	-
Radiation therapy†				
	Yes	40 (43)	10 (33.6)	0.34
	No	53 (57)	20 (66.7)	

**Student's t-test. †Chi-square test.*

Table II: Prognostic factors for malignant mesothelioma (MM) analysed in a univariate Cox proportional hazard model (n = 140).

		n	Overall survival (month)	Hazard ratio	Confidence interval (CI)	p-value
EORTC						
	Low-risk	65	23	1.68	1.14-2.50	0.009
	High-risk	49	13			
Diagnosis						
	Definitive diagnosis	111	20	3.1	1.8-5.3	<0.001
	Possible diagnosis	21	10			
Pathology						
	Sarcomatoid	15	11	1.84	1.06-3.19	0.03
	Non sarcomatoid	95	21			
ECOG* performance status						
	PS0	7	24	1.67	0.73-3.82	0.2
	PS1	118	16			
Age						
	≤55	53	19	1.1	0.77-1.59	0.5
	>55	77	16			
LDH						
	<300 U/L	94	20	1	0.61-1.58	0.9
	≥300 U/L	25	16			
Anaemia						
	Available	28	21	1.2	0.79-1.86	0.3
	Absent	96	16			
White blood cell						
	<8.3 10^9/L	57	20	1.14	0.79-1.65	0.45
	≥8.3 10^9/L	67	15			
Platelets						
	<403 10^9/L	91	20	1.33	0.88-2.09	0.17
	≥40310^9/L	33	14			

**ECOG: Eastern Cooperative Oncology Group*

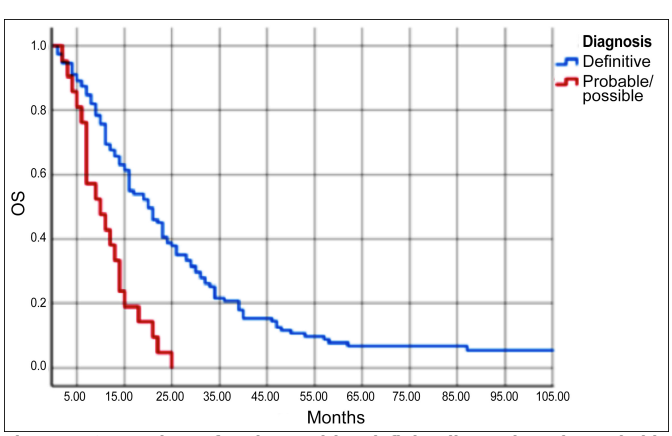

Figure 1: Comparison of patients with a definite diagnosis and a probable diagnosis in terms of OS.

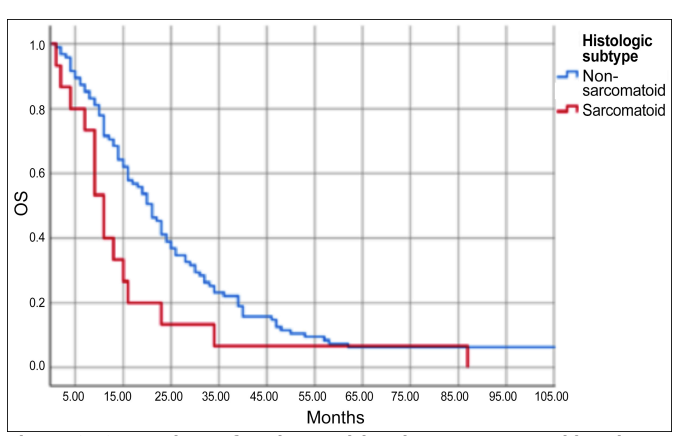

Figure 2: Comparison of patients with subtype sarcomatoid and non-sarcomatous in terms of OS.

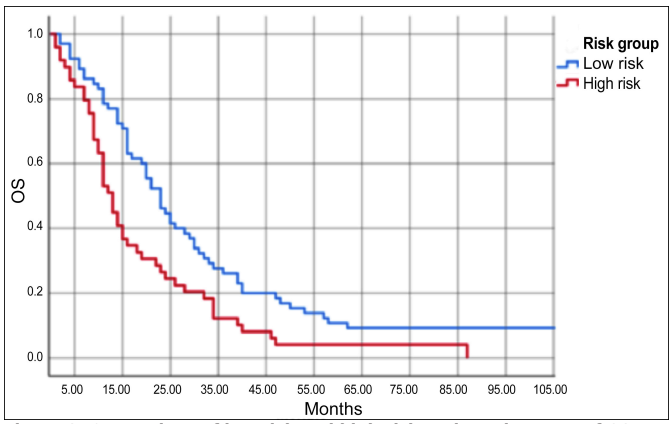

Figure 3: Comparison of low-risk and high-risk patients in terms of OS.

Of the 140 patients, 111 had a definitive diagnosis, and 21 had a probable / possible diagnosis. While the median OS was 20 months (95% CI: 16.4–23.5) in patients with a definite diagnosis, it was 10 months (95% CI: 4.0–15.9) in those with a probable / possible diagnosis ($p < 0.001$; Figure 1). There were 15 patients with sarcomatoid MPM and 95 patients with non-sarcomatoid MPM.

The median OS was 11 months (95% CI: 8.0–13.9) for those with sarcomatoid MPM and 21 months (95% CI: 17.5–24.4) for those with non-sarcomatoid MPM, with a significant difference ($p = 0.03$, Figure 2). Patients with a white blood cell count of less than 8.3×10^9/L had a median OS of 20 months (95% CI: 15.3–24.6), while those with a count above 8.3×10^9/L had a median OS of 15.0 months (95% CI: 11.7–18.2; $p = 0.45$). According to the EORTC scoring system, there were 65 patients in the low-risk group and 49 patients in the high-risk group. The median OS was 23 months (95% CI: 18.4–27.5) in the low-risk group and 13 months (95% CI: 10.7–15.2) in the high-risk group, with a statistically significant difference between the two groups ($p = 0.002$; Figure 3). There was no statistically significant difference in survival comparisons based on age, gender, platelet count, LDH level, haemoglobin level, and ECOG PS ($p > 0.05$, Table II).

DISCUSSION

The research findings indicated that gemcitabine and cisplatin were as efficacious as pemetrexed and cisplatin. Furthermore, the EORTC prognostic index was validated, demonstrating its ability to distinguish the low-risk group from the high-risk group, even in the context of combination chemotherapy including pemetrexed.

Asbestos deposits are prevalent in rural areas of the Eastern and South Eastern Anatolia regions of Turkiye. These asbestos fibres present in the soil have been used for decades in the painting of houses.[15,16] This study was conducted in the city of Diyarbakir, situated in South Eastern Turkiye, where a multitude of asbestos deposits have been employed in house painting. In contrast to occupational exposure observed in other countries, environmental exposure is more prevalent in Turkiye in the development of MPM.[17,18]

Malignant pleural mesothelioma is an uncommon illness, and there are few reports in the literature. In one study, the average age of patients was found to be 59 years.[19] The mean age in this sample was 58 years, which was similar. In a study investigating MPM resulting from occupational exposure, 83% of patients were males while 17% were females.[5] Of the patients in this research, 43% were females and 57% were males. The high female gender prevalence observed in this study may be attributed to environmental asbestos exposure rather than occupational exposure. Indeed, in another study investigating MPM resulting from environmental exposure, the male / female ratio was 1:4, which was similar to this study.[19] In the literature review, the epithelial type accounted for 55-60% of MPM cases, the biphasic type accounted for 25-30% of cases, and the sarcomatoid type accounted for 10-15% of cases.[20,21] In this study, 62.9% of the patients had the epithelioid type, while 37% of the patients had the non-epithelioid type, which is similar to the literature.

Recently, the use of systemic biomarkers for prognostic prediction has become increasingly widespread in many types of cancer. According to a study conducted by Remon *et al.* in 2020, the survival rate of the epithelioid type was better than sarcomatoid type in multivariate analysis (HR = 2.05 [1.378–3.057], $p < 0.01$).[22] In a separate study evaluating the efficacy of chemotherapy in MPM, the median survival rate was reported as 21.3 months in patients with epithelioid histology and 9.6 months in non-epithelioid patients.[23] In this study, the median OS for epithelioid-type patients was 21 months, while it was 11 months for sarcomatoid-type patients. In this study, the epithelioid type had better survival than the sarcomatoid type, and the results were consistent with the literature. A literature review indicated that there are studies showing an association between the female gender and a good prognosis.[24,25] However, in this study, gender did not have an effect on prognosis. It is possible that gender was not a prognostic factor in this study because MPM is more commonly caused by environmental exposure to asbestos than occupational exposure. The EORTC group classified MPM patients into high-risk groups and low-risk based on ECOG PS, age, WBC level, gender, diagnostic certainty, and sarcomatoid type.[12] In the research stated above, the low-risk group had a median OS of 10.8 months, whereas the high-risk group had a median OS of 5.5 months. In this research, a comparison was made between low-risk and high-risk patients using an identical scoring system. The analysis revealed that the median survival rate for low-risk patients was 23 months, but for high-risk patients it was 13 months ($p = 0.002$). In the EORTC study, only single-agent chemotherapy agents other than platinum were used, while in this study, gemcitabine and cisplatin or pemetrexed and cisplatin

were used. The survival difference in both studies may be related to the use of more effective combination drugs. At the time of the EORTC group's study, cisplatin, pemetrexed, and gemcitabine were not used in the therapeutic approach for MPM. This study validated the EORTC prognostic scoring index, demonstrating its efficacy in patients undergoing gemcitabine-cisplatin and pemetrexed-cisplatin combination therapies.

A comparative trial directly evaluating the efficacy of pemetrexed plus cisplatin *versus* gemcitabine and cisplatin as first-line treatment for patients with MPM has not been conducted. In a comparative research examining the efficacy of pemetrexed and cisplatin *vs*. single-agent cisplatin, PFS was seen to be 3.9 months in the cisplatin group and 5.7 months in the pemetrexed and cisplatin group. Additionally, the OS was found to be 9.3 months in the cisplatin group and 12.1 months in the pemetrexed and cisplatin group.[9] In this study, OS was 18 months for patients who received pemetrexed and cisplatin and PFS was 7 months. In another study, the combination of gemcitabine and cisplatin was evaluated. The PFS value was 8 months, and the OS value was 13 months in treatment-naive patients.[10] In the present study, the PFS was 9 months, and the OS was 17 months for patients who received gemcitabine and cisplatin. The high median survival values observed in this study can be attributed to the retrospective nature of the study, which may have resulted in some patients declining treatment, dropping out of follow-up, or dying before the follow-up period was reached. The primary objective of this study was to compare the efficacy of cisplatin plus gemcitabine with that of cisplatin plus pemetrexed in first-line treatment. The analysis revealed that the median PFS was 7 months and the median OS was 18 months in the pemetrexed plus cisplatin arm, while the median PFS was 9 months and the median OS was 17 months in the cisplatin plus gemcitabine arm. To the best of the authors' knowledge, this is the first study to demonstrate that the gemcitabine–cisplatin combination is as effective as the pemetrexed-cisplatin combination in the first-line setting for MPM. Therefore, in cases where pemetrexed cannot be used, the gemcitabine-cisplatin combination can be safely administered as a first-line treatment.

This study had several limitations, including that it was a single-centric retrospective study and had a small number of patients with the sarcomatoid subtype immunotherapy and bevacizumab medicines. These medicines are now standardised in the treatment of MPM and were not used in the majority of this study's patients. This was another limitation of this study.

CONCLUSION

This is the first study in which the EORTC prognostic score was analysed after the use of peme-trexed in the treatment of MPM and the score is still valid. Based on the results of this study, the EORTC prognostic scoring system can be used for prognosis prediction in patients receiving pemetrexed. In addition, cisplatin plus pemetrexed and cisplatin plus gemcitabine combinations had similar efficacy in terms of survival. Based on this result, gemcitabine can be offered as an alternative treatment option when pemetrexed is not available.

ETHICAL APPROVAL:
This study was approved by the Ethics Committee of the Diyarbakir Gazi Yasargil Training and Research Hospital and the ethical approval letter was issued. (ERC no: 324/2019, Dated: 04.07.2019).

PATIENTS' CONSENT:
As this study employed a retrospective file review methodology, obtaining the patient consent was not a viable option.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YS: Conception, data acquisition, analysis, and drafting.
OK: Acquisition and analysis of the data.
SI: Critical revision.
SE: Manuscript drafting and reviewing.
ST: Data collection and analysis and manuscript writing.
ZU: Conception of the study and overall supervision.
All authors approved the final version of the manuscript to be published.

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