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Research Article

The Importance of Platinum Sensitivity in Metastatic Malignant Pleural Mesothelioma Patients

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Abstract

Objectives: Malignant pleural mesothelioma (MPM) accounts for approximately 80% of all mesothelioma cases.

Methods: Forty-three patients diagnosed with advanced MPM were included in our study. We aimed to investigate first-line therapy options and the importance of platinum sensitivity in patients diagnosed with MPM, who were de novo metastatic or progressed from the early to the metastatic stage.

Results: The mean age of the patients was 58.8±11.7 years, and 58.1% (25 patients) were male. The median overall survival (OS) was found to be 10.5 months (CI 95% 5.8-15.2). Median progression-free survival (PFS) of all MPM patients was 7.6 months (CI 95% 6.2-7.9). When comparing the platinum-sensitive group to the platinum-resistant group, the median OS of the platinum-sensitive group was found to be 10.5 months (CI 95% 4.6-16.5), and the median OS of the platinum-resistant group was 3.3 months (CI 95% 3.1-3.6) (p=0.02). The median PFS of the platinum-sensitive group was 7.9 months (CI 95% 5.9-9.9), while that for the platinum-resistant group was 2.4 months (CI 95% 2.1-2.8) (p<0.01).

Conclusion: Platinum-based chemotherapy regimens should be considered first at the metastatic stage.

Keywords: Chemotherapy, metastatic malignant pleural mesothelioma, platinum sensitivity

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Pleural malignant mesothelioma arises from mesothelial cells of the pleura. Approximately 80% of cases of malignant mesothelioma are of pleural origin. Exposure to asbestos and erionite are important risk factors for the development of malignant pleural mesothelioma (MPM).[1] The lifetime risk of developing mesothelioma among asbestos insulation workers is approximately 10%.[2]

Asbestos fibres reaching the alveoli undergo phagocytosis. If the inhaled fibres exceed the phagocytosis capacity, they accumulate in the lungs. Asbestos fibres accumulating in the alveoli can reach the pleura through lymphatics or direct penetration. Furthermore, they may cause fibrosis, pleural plaque, and malignant pleural mesothelioma.[3,4] Malignant mesothelioma is generally classified in histological subtypes as epithelioid, sarcomatoid, and biphasic.[5] The epithelioid subtype is the most common, accounting for approximately 60% of all mesotheliomas.[6]

Platinum/pemetrexed-based chemotherapy may be an option in patients who are clinically at stage 4, are not eligible for curative surgery, and whose Eastern Cooperative On-

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cology Group (ECOG) performance status is 0-2.[7,8] Patients with an ECOG PS of 3-4 can be followed up with the best supportive care.

In this study, we aimed to investigate first-line therapy options and the importance of platinum sensitivity in patients diagnosed with MPM, who were de novo metastatic or progressed from the early to the metastatic stage in our center.

Methods

Forty-three patients diagnosed with advanced MPM between 2010 and 2018 at Bursa Uludag University Faculty of Medicine, Medical Oncology Department, were included in the study. The demographic characteristics, histopathological features, chemotherapy regimens, response rates, and toxicity of therapy were evaluated retrospectively from the patients' electronic records. Patients were staged using MPM Tumor, Nodes, and Metastases staging American Joint Committee on Cancer 8th edition. The patients were divided into two groups according to their platinum sensitivity. Patients with early-stage disease relapsed with distant metastasis within 6 months after completing platinum-based chemotherapy, and patients with de novo metastatic disease who had progression within 6 months after completion of first-line platinum-based chemotherapy were accepted as a platinum-resistant group.

Outcomes

Progression-free survival (PFS) was defined as the time from the administration of first line chemotherapy to the progression of tumor or death, whichever was performed first. Overall survival (OS) was determined from the time of diagnosis until death from any cause.

Statistical Analysis

Continuous variables were expressed by mean and median values, and categorical variables were expressed by frequency and corresponding percentage values. Survival analysis was calculated by the Kaplan-Meier method, and the Log-rank test was used for the survival of intergroup comparisons. The data were statistically processed by IBM SPSS version 22 software. In all statistical analyses, $p<0.05$ was accepted as statistically significant for the results.

Results

The mean age of the patients was 58.8±11.7 years, and 58.1% (25 patients) were male. There were 10 patients with ECOG performance status of 0, 25 patients with 1, and 8 patients with 2. Asbestos exposure was detected in 18 patients. Thirty-nine patients had epithelioid, three patients had biphasic, and one patient had sarcomatoid histopathology. While 22 patients were clinically in the advanced stage at the time of diagnosis (abbreviated as mMPM), 21 patients were previously in stages 1-3A and progressed to the advanced stage (abbreviated as eMPM). The clinical and demographic characteristics of the patients studied are presented in Table 1.

Table 1. The clinical and demographic characteristics of the patients

Parameter	n (%)
Age (mean±SD) (years)	58.8±11.7
Gender (Male/Female) (n, %)	25 (58.1)/18 (41.9)
Asbestos exposure	18 (41.8)
Family History of Mesothelioma	4 (9.3)
Eastern Cooperative Oncology Group	
0	10 (23.2)
1	25 (58.1)
2	8 (18.7)
Place of birth (Region)	
Marmara	34 (79.1)
Central Anatolia	8 (18.6)
Black Sea	1 (2.3)
Smoking habit	
Smoker	19 (44.2)
Non-smoker	24 (55.8)
Histopathology	
Epithelioid	39 (90.7)
Biphasic	3 (7.0)
Sarcomatoid	1 (2.3)
Disease stage	
De novo metastatic	22 (51.2)
Early stage progressed to metastatic stage	21 (48.8)

The incidence of metastasis sites at the metastatic stage was 34.8% (15 patients) in the lung parenchyma, 34.8% (15 patients) in bone, 23.2% (10 patients) in the peritoneum, 13.9% (6 patients) in the liver, 9.3% (4 patients) in the lymph nodes, 4.6% (2 patients) in the cranium, and 2.3% (1 patient) in the adrenal glands (Table 2).

The treatment modalities of the 21 eMPM patients were as

Table 2. Site of metastasis at the time of diagnosis of metastatic stage

Site	n (%)
Lung parenchyma	15 (34.8)
Bone	15 (34.8)
Peritoneal	10 (23.2)
Liver	6 (13.9)
Lymph adenopathy	4 (9.3)
Cranial	2 (4.6)
Adrenal	1 (2.3)

follows: 1 (4.8%) of them was operated on without induction chemotherapy and subsequently received chemotherapy, 13 (61.9%) of them were operated on after induction chemotherapy, and 7 (33.3%) of them progressed to stage 4 while receiving induction chemotherapy. In the study, 43 patients received first-line, 30 patients received second-line, 10 patients received third-line, and 3 patients received fourth-line chemotherapy. First-line therapy regimens administered to metastatic MPM patients are presented in Table 3. In the first-line treatment, 81.5% of patients received a platinum-based regimen, while 60.6% were administered pemetrexed or raltitrexed. The response rate to first-line treatment is presented in Table 3. There were no patients with complete responses. The overall response rate was found to be 35%, and the disease control rate was found to be 56%. Progression was detected in 44% of patients under first-line treatment.

The median OS was found to be 10.5 months (CI 95% 5.8-15.2). The median PFS of all MPM patients was 7.06 months (CI 95% 6.2-7.9) (Fig. 1).

On the subgroup analysis, the median OS was 9.3 months (CI 95% 7.6-11.0) in patients with eMPM, and 13.7 months (CI 95% 10.9-16.3) in patients with mMPM (p=0.035). The median PFS of eMPM patients was 5.8 months (CI 95% 0.1-12.3), while the median PFS of mMPM patients was 7.1 months (CI 95 6.5-7.6) (p=0.17). When 21 eMPM patients were divided into two groups according to platinum sensitivity at first-line treatment, 14 patients (66.7%) were accepted as having a platinum-sensitive disease and received platinum-based dual therapy. When comparing the platinum-sensitive group to the platinum-resistant

Table 3. Metastatic Stage 1st choice chemotherapy regimens and treatment responses

Chemotherapy Regimens	**n (%)**
Carboplatin+Pemetrexed	12 (27.9)
Cisplatin+Pemetrexed	10 (23.2)
Carboplatin+Gemcitabin	7 (16.2)
Gemcitabin	5 (11.6)
Gemcitabin+Cisplatin	3 (6.9)
Cisplatin+Raltitrexed	2 (4.6)
Raltitrexed	2 (4.6)
Vinorelbine	1 (2.3)
Carboplatin+Paclitaxel	1 (2.3)
Chemotherapy Responses	**n (%)**
Complete Response	0
Partial Response	15 (35)
Stable Disease	9 (21)
Progressive Disease	19 (44)

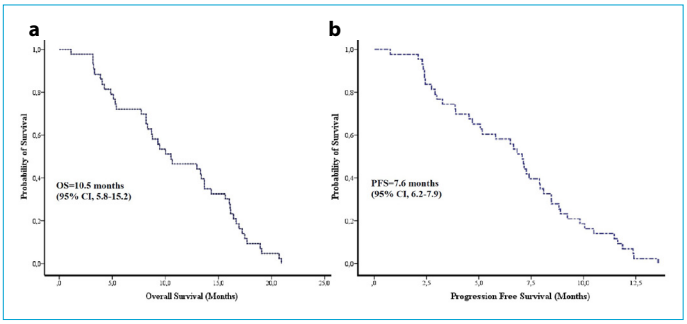

Figure 1. Overall survival (OS) and progression-free survival (PFS) for all patients with malignant pleural mesothelioma.

group, the median OS of the platinum-sensitive group was found to be 10.5 months (CI 95% 4.6-16.5), and the median OS of the platinum-resistant group was found to be 3.3 months (CI 95% 3.1-3.6) (p=0.02). The median PFS of the platinum-sensitive group at stage 4 was found to be 7.9 months (CI 95% 5.9-9.9), while the platinum-resistant group was found to be 2.4 months (CI 95% 2.1-2.8) (p<0.01) (Fig. 2).

In subgroup analysis, the median OS of the platinum-sensitive eMPM patients was 10.5 months (CI 95% 4.6-16.5), while the median OS of the mMPM patients was found to be 13.7 months (CI 95% 11.0-16.3) (p=0.25). The median PFS at stage 4 of platinum-sensitive eMPM was found to be 7.9 months (CI 95% 5.9-9.9), while the median PFS was found to be 7.1 months (CI 95% 6.5-7.6) (p=0.91) for mMPM patients.

Pemetrexed-based treatment was administered to 26 patients who were at stage 4, while the other 17 patients did not receive pemetrexed-based treatment. There was no statistically significant difference in term of OS (p=0.47) and PFS (p=0.27) between patients treated with pemetrexed-based therapy and patients that did not use pemetrexed-based therapy.

The adverse effects of first-line chemotherapies administered to advanced-stage MPM patients in our study are presented in Table 4. The most commonly encountered grade

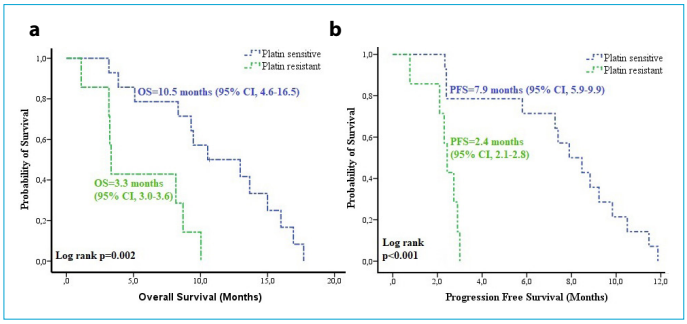

Figure 2. Overall survival (OS) and progression-free survival (PFS) of platinum-sensitive and platinum-resistant group.

Table 4. Metastatic Stage 1st choice chemotherapy adverse effects

Adverse Effects	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	6 (13.9)	16 (37.2)	2 (4.6)	-
Thrombocytopenia	3 (6.9)	5 (11.6)	3 (6.9)	1 (2.3)
Neutropenia	3 (6.9)	3 (6.9)	1 (2.3)	-
Liver Enzyme Elevation	4 (9.3)	3 (6.9)	1 (2.3)	-
Acute Kidney Injury	2 (4.6)	1 (2.3)	1 (2.3)	-
Weakness	8 (18.6)	6 (13.9)	2 (4.6)	-
Nausea/Vomiting	7 (16.2)	5 (11.6)	-	-

1 side effect was weakness, grade 2 side effect anemia, and grade 3-4 side effect thrombocytopenia.

Discussion

Advanced-stage pleural mesothelioma consists of unresectable disease and metastatic disease. The existing literature is limited to studies evaluating patients with metastatic pleural mesothelioma only. In the present study, we aimed to evaluate the efficacy and toxicity of chemotherapy in patients with de novo metastatic disease and in early-stage disease progressed to stage 4. In our study, the median OS in the advanced stage was 10.5 months and the advanced-stage median PFS was 7.06 months. In subgroup analysis, no significant differences in OS and PFS were detected in mMPM patients compared to eMPM patients. However, after grouping the patients according to platinum sensitivity, both PFS and OS in platinum-sensitive patients were significantly longer than in platinum-resistant patients.

In the treatment of many malignant tumours, different chemotherapy regimens are recommended in second-line therapy when there is disease progression after first-line therapy. In the study conducted by Pfisterer et al.[9] investigating ovarian cancer, patients who relapsed more than 6 months after first-line carboplatin plus paclitaxel treatment were considered platinum-sensitive. Response to platinum re-treatment has been observed in this patient group. In the study conducted by Hayashi et al.,[10] a pemetrexed/platinum combination for retreatment was suggested as an option for recurrent MPM patients with partial or complete response of more than 6 months with first-line platinum/pemetrexed-based chemotherapy. The statistically significant difference in OS and PFS in the platinum-sensitive group compared to the platinum-resistant group emphasized the importance of platinum-based therapy in platinum-sensitive patient groups that progressed from the early stage to the advanced stage.

In the subgroup analysis, no statistically significant difference was found between the median OS of platinum-sensitive eMPM patients and the median OS (p=0.304) and metastatic stage median PFS (p=0.174) of mMPM patients. This finding supports the effect of platinum sensitivity in the survival of metastatic MPM patients rather than their being de novo metastatic at the time of diagnosis (mMPM) or progressing from early to the metastatic stage (eMPM).

There was no statistically significant difference found in OS (p=0.47) and PFS (p=0.27) between patients receiving and not receiving pemetrexed-based therapy. The limited number of patients receiving pemetrexed and the study's retrospective nature may cause pemetrexed efficacy not to be seen. Jassem et al.[11] and Zucal et al.[12] recommend reusing pemetrexed in patients who used pemetrexed in the previous steps and obtained a significant response.

Patients who were not eligible for surgery were randomized into two groups, cisplatin plus pemetrexed and cisplatin plus placebo, by the EMPHACIS study. In this study, patients who were not eligible for surgery in the pemetrexed plus cisplatin group included 45% with stage 4 disease, 32% with stage 3 disease, 16% with stage 2 disease, and 7% with stage 1 disease.[7] This study reported a statistically significant longer OS and PFS in the pemetrexed plus cisplatin arm and made cisplatin plus pemetrexed the standard treatment in surgically unresectable MPM. In the study conducted by Ceresoli et al.,[8] it was found that in cases where cisplatin cannot be administered, a carboplatin plus pemetrexed combination may be a viable option. This study included 102 patients; 48% patients with stage 4 disease, 33% with stage 3 disease, and 11% with stage 2 disease, and reported objective response rate as 18.6%. Unlike the studies in the literature that make treatment recommendations for metastatic disease, our study included 22 patients (51.2%) at de novo metastatic disease and 21 patients (48.2%) progressing from the early stage to the metastatic stage.

In the EMPHACIS study, the median OS was 12.1 months, and the median PFS was 5.7 months.[7] In the study conducted by Ceresoli et al.,[8] the median OS was 12.7 months, and the median PFS was 6.5 months. In our study, the median OS in the advanced stage was 10.5 months, and the advanced-stage median PFS was 7.06 months. The reason why the OS is lower than other studies may be related to the fact that all patients in our study were at the metastatic stage. In the study conducted by Katirtzoglou et al.,[13] the median PFS was found to be 7 months in the chemotherapy-naive unresectable MPM patients receiving a carboplatin plus pemetrexed-based regimen. Median PFS was found to be similar to that indicated in the literature.

In the MAPS study[14] pemetrexed and cisplatin plus bevacizumab was administered to MPM patients, in the study conducted by Popat et al.[15] pembrolizumab was administered, and in the study conducted by Scherpereel et al.[16] nivolumab plus ipilimumab was administered. However, neither immunotherapy nor bevacizumab is reimbursed by the healthcare system in our country so we could not administer immunotherapy and targeted therapy to our patients.

In our study, grade 1-4 adverse effects of first-line chemotherapies were manageable. No drug-related deaths were detected in retrospective records. In the EMPHACIS[7] study administering pemetrexed plus cisplatin, three treatment-related deaths were reported. In the study conducted by Ceresoli et al.,[8] no drug-related deaths were reported in patients receiving pemetrexed plus carboplatin.

When MPM metastasis sites were examined, cranial metastasis, which is a rare site of metastasis, was observed in our study at a rate of 4.7%. In the study conducted by Dearbhaile et al.,[17] cranial metastasis was reported at a rate of 3%. The first case was a patient who progressed from the early to the metastatic stage. The physical examination revealed headache and loss of strength in the right extremity. A cranial magnetic resonance imaging (MRI) was performed, the detected metastatic lesion was surgically removed, and the patient subsequently received chemoradiotherapy. The second case was at the metastatic stage at the time of diagnosis, developed headache and syncope complaints during the treatment, underwent surgery for the metastatic lesion detected on a cranial MRI, and then received chemoradiotherapy. MPM patients should be carefully monitored for central nervous system metastases when they progress from the early to the metastatic stage or during the de novo metastatic stage.

Limitations

The limitations of our study include being retrospective, a low number of patients, a low number of biphasic and sarcomatoid subgroups, and an inability to use bevacizumab and immunotherapy. Due to the retrospective nature of our study, non-laboratory adverse effects could not be entirely reported.

Conclusion

In the existing literature, information on chemotherapy efficacy in patients with metastatic MPM has been obtained from unresectable patients at stages 1-4. In our study, in which we only investigated patients with metastatic MPM, PFS and OS were found to be related to platinum sensitivity, similar to the literature. OS was found to be lower compared to the studies in the literature due to the presence of metastatic stage patients only. Central nervous system metastases are rarely encountered in patients with MPM.

Disclosures

Ethics Committee Approval: The study was in accordance with the ethical standards of the with the 1964 Declaration of Helsinki and approved by the clinical research ethics committee of Bursa Uludag University Faculty of Medicine (Approval number: 2020-3/7). Since retrospective planning, patient informed consent was not required.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.O.; Design – B.O., A.B.S.; Supervision – B.O.; Materials – B.O., A.B.S.; Data collection and/or processing – B.O., B.D., H.U.O., N.H.S.; Analysis and/or interpretation – B.O.; Literature search – B.O., SO.O.; Writing – B.O.; Critical review – B.O., T.K., A.D., E.C., TE.

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