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Efficacy of pemetrexed plus a platinum rechallenge in the treatment of pleural mesothelioma

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ABSTRACT

Introduction. Pemetrexed-based rechallenge therapies can be used as an option in the treatment of pleural mesothelioma. We aimed to investigate the efficacy of pemetrexed-based rechallenge in mesothelioma.

Material and methods. A total of 132 patients who received chemotherapy for unresectable or metastatic pleural mesothelioma in the Medical Oncology Clinic of Dicle University Medical Faculty between 2005 and 2020 were included in our study. Pemetrexed plus platinum rechallenge treatments were compared with other chemotherapy regimens in terms of survival.

Results. In our study, 31 (23.4%) of a total of 132 patients received rechallenge pemetrexed plus platinum treatment. There was no statistically significant difference between median progression-free survival of patients who received pemetrexed plus cisplatin or gemcitabine plus cisplatin in the first-line therapy [5 months *vs.* 8 months (HR = 1.43; 95% CI 0.59–3.45; p = 0.376)]. In the second-line treatment, patients who received rechallenge pemetrexed plus platinum therapy had statistically significantly higher median PFS than those who received gemcitabine plus platinum [6 months *vs.* 4 months (HR = 0.46; 95% CI 0.22–0.94; p = 0.011)] due to a previous good response. In the second-line treatment, median overall survival was 15 months with gemcitabine plus platinum and 29 months with pemetrexed plus platinum rechallenge (p = 0.007).

Conclusions. This study demonstrated that the pemetrexed plus platinum regimen was more effective than gemcitabine plus platinum in the second-line treatment in terms of both progression-free and overall survival in patients who had previously benefited from pemetrexed-based chemotherapy and had not progressed up to 6 months after first-line treatment.

Key words: pleural mesothelioma, pemetrexed, rechallenge

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Introduction

Mesothelioma is a rare tumor arising from serous structures such as the pleura, pericardium, peritoneum, and tunica vaginalis. Mesothelioma is caused by asbestos exposure [1], and it is observed more frequently in Diyarbakır province and its surroundings compared to other regions of Türkiye due to natural asbestos exposure [2]. Pleural mesothelioma accounts for 80% of all mesotheliomas [3]. Currently, platinum-based chemotherapy and immunotherapy treatments are the standard first-line treatment options for advanced mesothelioma [4]. Phase III prospective randomized trials have shown that cisplatin and antifolate combination therapy is superior to single-agent cisplatin in the first-line treatment of advanced pleural mesothelioma. Early studies have historically shown that adding raltitrexed to cisplatin contributed an overall survival (OS) benefit

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of 2.6 months [5]. On the other hand, Vogelzang et al. [6] reported a 2.8-month OS benefit with the addition of pemetrexed to cisplatin compared to cisplatin alone. The addition of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), to combination chemotherapies in the first-line treatment has shown an OS advantage [hazard ratio (HR) = 0.77 (0.62–0.95); p = 0.0167] [7]. Second-line treatment of patients with mesothelioma with the use of pemetrexed and cisplatin provides better response and disease control rates and longer OS than cisplatin in pemetrexed naive patients [8]. Clinical studies are showing the benefit of vinorelbine and gemcitabine in patients progressing after pemetrexed-based chemotherapy administered in the first-line treatment [9, 10]. Rechallenge therapy with pemetrexed in subsequent steps is a strategy that can be used for patients who previously had a good response with pemetrexed [11].

In recent years, immune-checkpoint inhibitors have become a treatment option in addition to platinum-based therapies in pleural mesothelioma [12]. However, there are problems with access to immunotherapy in developing countries due to drug costs. Therefore, chemotherapy rechallenge therapies are used as an alternative treatment strategy. In this study, we aimed to investigate treatment efficacy of in patients who were followed up for pleural mesothelioma in our center and received pemetrexed-based rechallenge therapy in their next-line treatment.

Material and methods

A total of 132 patients who received chemotherapy for unresectable or metastatic pleural mesothelioma in the Medical Oncology Clinic of Dicle University Medical Faculty between 2005 and 2020 were included in our study. We analyzed retrospectively clinicopathologic characteristics [age, sex, smoking, Eastern Cooperative Oncology Group (ECOG) performance status, stage at presentation, and histologic subtype], treatment modalities (surgery, radiotherapy, chemotherapy), treatment responses, and survival times based on the hospital archive system. The postoperative period, first and second-line treatments, and treatment responses were evaluated. Survival rates were compared between the pemetrexed plus platinum rechallenge treatment and other chemotherapy regimens after the pemetrexed plus cisplatin treatment in the postoperative period or first-line treatment.

Patient characteristics

All patients included in the study had histopathologically confirmed mesothelioma diagnoses. Patients whose cancers were resectable at the time of diagnosis underwent pleurectomy/decortication or extrapleural pneumonectomy. In patients who underwent complete resection, pemetrexed plus platinum ± radiotherapy was given postoperatively.

Some of the patients who had received postoperative chemotherapy with pemetrexed plus platinum and who developed relapse 6 months after the end of treatment were given pemetrexed plus platinum rechallenge first-line treatment. Other patients who had postoperative treatment received first-line gemcitabine plus platinum treatment because they relapsed earlier than after 6 months. The number of patients who received immunotherapy or bevacizumab plus chemotherapy was low, and they were not included in the study.

In unresectable or relapsed patients, some of the patients who received pemetrexed plus platinum treatment in the first-line treatment and achieved at least partial response and in whom no progression was observed 6 or more months after the end of treatment were given rechallenge pemetrexed plus platinum treatment in the second-line treatment. Others received second-line gemcitabine plus platinum treatment.

Treatments and definitions

Disease staging was performed according to the American Joint Committee on Cancer (AJCC) classification (version 8 — 2017). The performance status of patients at the beginning of treatment was determined according to ECOG criteria.

Pemetrexed plus platinum regimen — pemetrexed 500 mg/m^2 (day 1) plus cisplatin 75 mg/m^2 or carboplatin AUC 5 (day 1) — was used every 3 weeks (vitamin B12 and folic acid prophylaxis were routinely administered). The gemcitabine plus platinum regimen included gemcitabine 1000 mg/m^2 (days 1 and 8) plus cisplatin 75 mg/m^2 or carboplatin AUC 5 (day 1) every 3 weeks. Postoperative treatment was administered for 6 cycles. In the first- and second-line treatment, chemotherapy was completed in 6 cycles in patients who did not show progression in the first 3 cycles.

Tumor response evaluation was performed every 3 months by computed tomography (CT) or positron emission tomography (PET) according to the RECIST v 1.1 criteria. Progression-free survival (PFS) was calculated as the time from treatment initiation to progression, and OS was calculated as the time from metastatic disease diagnosis to death.

Statistical analysis

PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were used to evaluate parameter frequency and patient characteristics,

Student's t-test was used for parametric tests with normal distribution, and the Mann-Whitney U test was used for the analysis of non-parametric variables and parametric variables without normal distribution. Kaplan-Meier survival analysis was used for survival analysis, based on log-rank p value. Cox regression analysis was used for univariate and multivariate analysis of survival times. The enter method was used for univariate analysis, and the backward stepwise likelihood ratio method was used for multivariate analysis. The confidence interval (CI) of 95% and two-way p significance value < 0.05 were accepted.

Results

A total of 132 patients, 58 (43.9%) females and 74 (56.1%) males, were included in our study. The median age at diagnosis was 57 (32–78) years. The majority — 83.2% (n = 111) of patients were ECOG 0–1 at diagnosis, and most of them (68.9%) were diagnosed with stage III–IV disease. The most commonly diagnosed was the epithelioid subtype with a rate of 73.6% (n = 84). Almost one-third [33.3% (n = 44)] of patients had undergone surgery. In total, 29 (22%) patients received postoperative pemetrexed plus cisplatin regimen. A total of 55 (41.7%) patients underwent radiotherapy for postoperative, palliative, or drain areas. In the first-line treatment, 71.2% (n = 94) patients received pemetrexed plus cisplatin, 22.7% (n = 30) patients received gemcitabine plus cisplatin, and 6.1% of patients received other treatment regimens. There were 49 (37.1%) patients on second-line treatment. As a second-line treatment regimen, 30.6% (n = 15) of patients received pemetrexed plus platinum, and 69.4% (n = 34) of patients received gemcitabine plus platinum. In total, 31 (23.4%) patients received rechallenge pemetrexed plus platinum treatment. Of the patients who underwent rechallenge treatment, 16 (51.6%) received the same treatment in the postoperative setting and were, therefore, rechallenged in the first-line setting. The remaining 15 (48.4%) patients had received pemetrexed plus platinum in the first-line treatment and were rechallenged with pemetrexed plus platinum in the second-line treatment due to good response during initial chemotherapy. The clinicopathologic features of the patients are presented in Table 1.

When patient characteristics were compared between the groups, patients who received and did not receive postoperative pemetrexed plus cisplatin had similar characteristics in terms of age, sex, smoking, performance status, and histologic type. Again, when the patients who received pemetrexed plus platinum rechallenge in the second step were compared with those who received gemcitabine plus platinum, no statistically significant difference was observed between the clinicopathologic features in both groups (Tab. 2).

Table 1. Characteristics of patients

	n = 132 (%)
Age (median, range)	57 (32–78)
Sex	
Female	58 (43.9)
Male	74 (56.1)
Smoking	
Yes	50 (37.9)
No	59 (44.7)
Unknown	23 (17.4)
ECOG performance status	
0–1	111(83.2)
≥ 2	21 (16.8)
Initial stage	
I–II	41 (31.1)
III–IV	91 (68.9)
Histologic subtypes	
Epithelioid	84 (73.6)
Non-epithelioid	22(16.7)
Unknown	26 (19.7)
Surgery	
P/D	39 (29.5)
EPP	5 (3.8)
No	90 (66.7)
Adjuvant chemotherapy	
Yes	29 (22)
No	103 (78)
Radiation therapy	
Yes	55 (41.7)
No	77 (58.3)
First-line treatment options	
Pemetrexed + cisplatin	94 (71.2)
Gemcitabine + cisplatin	30 (22.7)
Others	8 (6.1)
Second-line treatment options (n = 49)	
Pemetrexed + platin	15 (30.6)
Gemcitabine + platin	34 (69.4)
Pemetrexed re-challenge (n = 31)	
In the first line	16 (51.6)
In the second line	15 (48.4)

ECOG — Eastern Cooperative Oncology Group; EPP — extrapleural pneumonectomy; P/D — pleurectomy/decortication

Table 2. Comparison of patients according to the treatments they receive in the first and second line

All patients (n = 132)	Previously received postoperative treatment (n = 29)	Previously not received postoperative treatment (n = 103)	p value
Age (mean, std dev.)	55.3 (± 11.4)	56.6 (± 10.4)	0.55*
Sex			0.91**
Female	13 (44.8)	45 (43.7)	
Male	16 (55.2)	58 (56.3)	
Smoking (n = 109)			0.10**
Yes	13 (61.9)	37 (42)	
No	8 (38.1)	51 (58)	
ECOG performance status			0.37**
0–1	26 (89.7)	85 (82.5)	
≥ 2	3 (10.3)	18 (17.5)	
Histologic subtypes (n = 106)			0.07**
Epithelioid	23 (92)	61 (75.3)	
Non-epithelioid	2 (8)	20 (24.7)	
Second line (n = 49)	**Pemetrexed + platin rechallenge n = 15 (%)**	**Gemcitabine + platin n = 34 (%)**	**p value**
Age (mean, std dev.)	54.6 (± 9.02)	53.6 (± 10.3)	0.75*
Sex			0.07**
Female	9 (60)	11 (32.4)	
Male	6 (40)	23 (67.6)	
Smoking (n = 41)			0.32**
Yes	6 (42.9)	16 (59.3)	
No	8 (57.1)	11 (40.7)	
ECOG performance status			0.41***
0	14 (93.3)	28 (82.4)	
≥ 1	1 (6.7)	6 (17.6)	
Histologic subtypes (n = 46)			0.41***
Epithelioid	13 (92.9)	26 (81.3)	
Non-epithelioid	1 (7.1)	6 (18.8)	
Initial stage			0.78**
I–II	5 (33.3)	10 (29.4)	
III–IV	10 (66.7)	24 (70.6)	
Primary surgery			0.93**
Yes	9 (60)	20 (58.8)	
No	6 (40)	14 (41.2)	
Radiation therapy			0.83**
Yes	7 (46.7)	17 (50)	
No	8 (53.3)	17 (50)	

ECOG — Eastern Cooperative Oncology Group; *Student's t-test; **Chi-square test; ***Fisher's exact test

There was no statistically significant difference between median PFS of patients who received rechallenge pemetrexed plus platinum in the first-line therapy and patients who received gemcitabine plus platinum in the first-line therapy [5 months *vs.* 8 months (HR = 1.43; 95% CI 0.59–3.45; p = 0.376)] (Fig. 1). In the second-line treatment, patients who received rechallenge pemetrexed plus

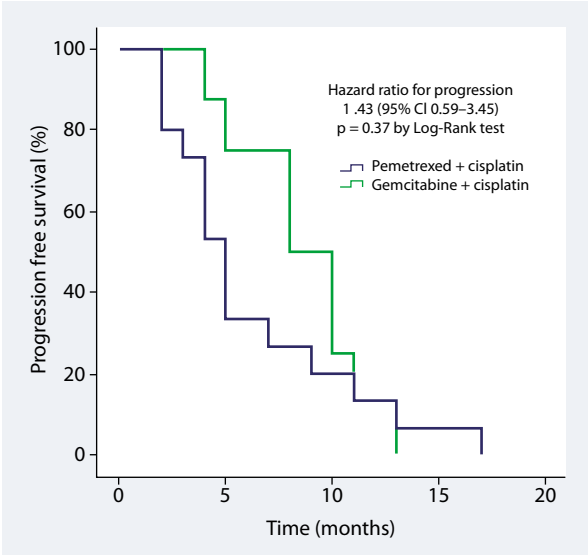

Figure 1. Comparison of progression-free survival results of rechallenge pemetrexed plus cisplatin and gemcitabine plus cisplatin treatments in first-line treatment in patients who developed relapse after adjuvant chemotherapy; CI — confidence interval

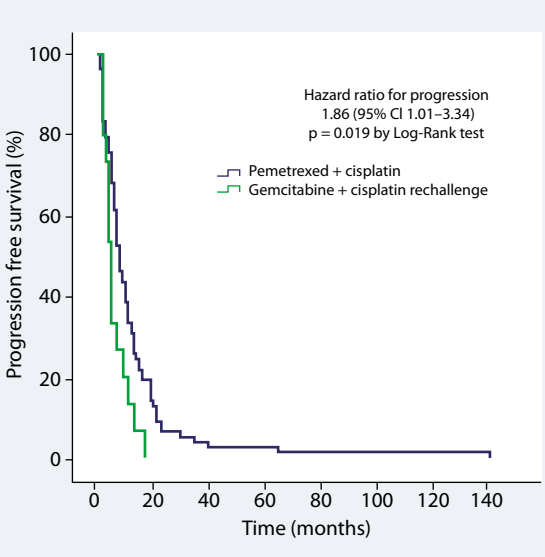

Figure 3. Comparison of progression-free survival results of rechallenge pemetrexed plus cisplatin as first-line treatment in patients with relapse after ajuvant therapy and upfront pemetrexed plus cisplatin treatments in unresectable patients who have not received any previous treatment; CI — confidence interval

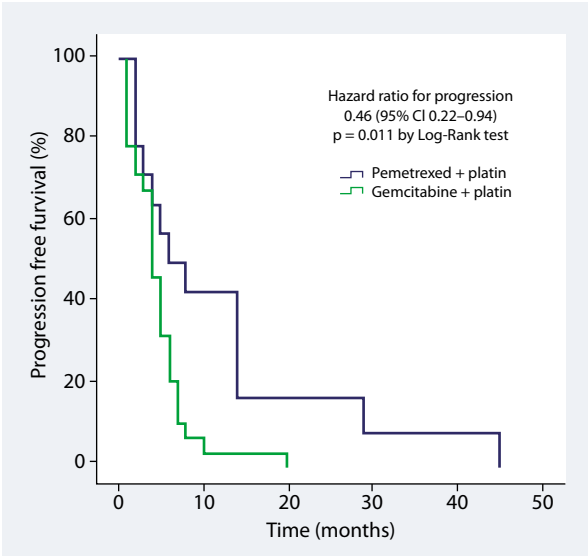

Figure 2. Comparison of progression-free survival results of rechallenge pemetrexed plus platinum and gemcitabine plus platinum treatments in second-line treatment; CI — confidence interval

platinum therapy had statistically significantly higher median PFS than those who received gemcitabine plus platinum [6 months *vs.* 4 months (HR = 0.46; 95% CI 0.22–0.94; p = 0.011)] (Fig. 2). However, patients who received rechallenge pemetrexed plus platinum therapy in the first-line treatment had lower median PFS than patients who received front-line pemetrexed plus platinum therapy [5 months *vs*. 8 months (HR = 1.89; 95% CI 1.01–3.34; p = 0.019)] (Fig. 3). Median OS in chemotherapy-naive patients on first-line treatment was 14 months with pemetrexed plus cisplatin, 12 months with gemcitabine plus cisplatin, and 7 months with pemetrexed plus platinum rechallenge. No statistically significant difference was observed between the groups. In the second-line treatment, median OS was 15 months with gemcitabine plus platinum and 29 months with pemetrexed plus platinum rechallenge (p = 0.007). Objective response rates and other details are given in Table 3.

When evaluated together with other potential prognostic factors in multivariate analysis, there was no statistically significant difference between median PFS of patients who received pemetrexed plus platinum in the postoperative treatment and during the first-line treatment and median PFS of patients who received gemcitabine plus platinum (HR = 2.06; 95% CI 0.59–7.14; p = 0.25) (Tab. 4). In the second-line setting, median PFS was significantly higher in the rechallenge pemetrexed plus platinum arm than in the gemcitabine plus platinum arm, independently of other prognostic factors (HR = 0.39; 95% CI 0.18–0.85; p = 0.018) (Tab. 5).

In subgroup analysis, when rechallenge pemetrexed plus platinum treatment was compared with gemcitabine plus platinum treatment in terms of PFS, rechallenge pemetrexed plus platinum treatment had higher PFS than gemcitabine plus platinum treatment in patients with good response to pemetrexed plus platinum and a history of radiotherapy (Fig. 4, Tab. S1 — supplementary).

Table 3. Comparison of rechallenge pemetrexed treatment with other treatment arms

	n	ORR [%]	mPFS [mo]	p value*	HR	95% CI	mOS [mo]	p value*
First-line (patients received pemetrexed) n = 94				**0.019**				0.097
Pemetrexed + cisplatin (Chemonaive)	78	36.4	8		reference		14	
Pemetrexed + cisplatin (Re-Ch.)	16	31.3	5		1.89	1.01–3.34	7	
First-line (previously received postoperative treatment P + C) n=24				0.376				0.85
Gemcitabine + cisplatin	8	37.5	8		reference		12	
Pemetrexed + cisplatin (Re-Ch.)	16	31.3	5		1.43	0.59–3.45	7	
Second-line n = 49				**0.018**				**0.007**
Gemcitabine + platin	34	11.7	4		reference		15	
Pemetrexed + platin (Re-Ch.)	15	20	6		0.46	0.22–0.94	29	

CI — confidence interval; HR — hazard ratio; mo — months; mPFS — median progression-free survival; ORR — objective response rate; *log-rank P

Table 4. Univariate and multivariate analysis of first-line progression-free survival outcomes in patients who previously received postoperative pemetrexed plus cisplatin

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	0.99	0.97–1.01	0.68			
Sex (female*/male)	1.57	1.09–2.27	0.015			
ECOG PS (0–1*/> 2)	1.09	0.67–1.77	0.71			
Histological subtypes (epithelioid*/others)	1.92	1.17-3.13	0.009			
Smoking (no*/yes)	1.66	1.11–2.49	0.014			
Radiation therapy (no*/yes)	0.97	0.68–1.40	0.89	0.43	0.12-1.52	0.19
Chemotherapy regimen (Gem + P*/Pem + P Rch)	1.43	0.59-3.45	0.42	2.06	0.59–7.14	0.25

CI — confidence interval; ECOG PS — Eastern Cooperative Oncology Group performance status; Gem + P — gemcitabine plus platin; HR — hazard ratio; mo — months; Pem + P Rch — pemetrexed plus platin rechallenge; *Reference category

Table 5. Univariate and multivariate analysis of progression-free survival in second-line therapy in patients who had previously used pemetrexed plus cisplatin

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.02	0.99–1.05	0.14	1.01	0.98–1.05	0.31
Sex (female*/male)	1.22	0.66–2.22	0.51			
ECOG PS (0–1*/> 2)	1.17	0.51–2.64	0.70			
Histological subtypes (epitheloid*/others)	0.98	0.40–2.38	0.97			
Smoking (no*/yes)	1.08	0.56–2.09	0.80			
Radiation therapy (no*/yes)	0.73	0.40–1.31	0.29			
Surgery (no*/yes)	1.14	0.63–2.06	0.66	1.55	0.79–3.00	0.19
Chemotherapy regimen (Gem + P*/Pem + P Rch)	0.42	0.20–0.88	0.02	0.39	0.18–0.85	0.018

CI — confidence interval; ECOG PS — Eastern Cooperative Oncology Group performance status; Gem + P — gemcitabine plus platin; HR — hazard ratio; mo — months; Pem + P Rch — pemetrexed plus platin rechallenge; *Reference category

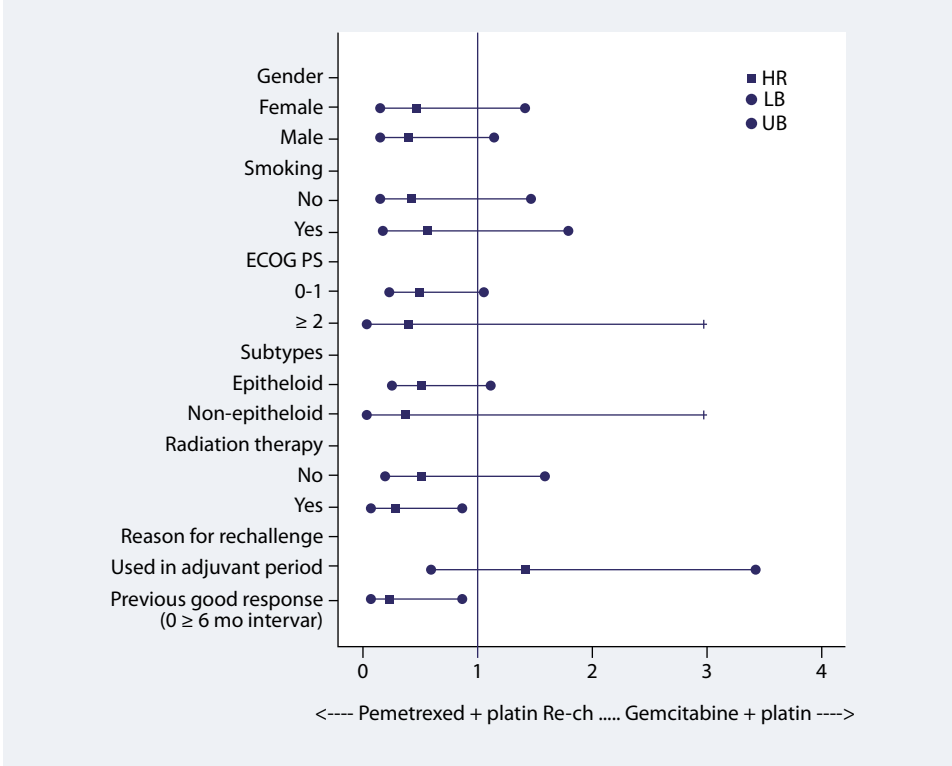

Figure 4. The subgroup analysis for patients who previously received pemetrexed plus platinum in adjuvant treatment included first- and second-line treatments. All other subgroup analysis results were for second-line treatment only; ECOG PS — Eastern Cooperative Oncology Group performance status; HR — hazard ratio; LB — lower bounder; UB — upper bounder

While rechallenge with pemetrexed plus platinum had better results in almost all subgroups, the benefit was greater with rechallenge treatment, especially in patients with a good response to previous pemetrexed plus platinum treatment and a history of radiotherapy.

Discussion

Although pleural mesothelioma is a rare disease, it has a very poor prognosis [13]. Most patients present with unresectable disease. In these patients, pemetrexed plus cisplatin treatment is mostly used in the first-line treatment in regions where access to immunotherapy is problematic [6]. In our study, the majority of patients (66.7%) presented with unresectable disease. The number of patients who underwent surgery for pleural mesothelioma and subsequently developed relapsed metastatic disease was 44 (33.3%). Very few patients with mesothelioma are suitable for surgery. The majority of these patients relapse after surgery. Therefore, pemetrexed and cisplatin combination therapy, which is effective in first-line treatment, may be used in postoperative treatment [14]. In our study, 29 (22%) of the operated patients had received pemetrexed plus cisplatin as adjuvant treatment.

In our study, 94 patients received pemetrexed plus cisplatin combination therapy as first-line treatment. Of these patients, 16 (17%) had previously received pemetrexed plus platinum in the postoperative setting. Rechallenge pemetrexed plus platinum treatment resulted in an objective response rate (ORR) of 31.3% and median PFS of 5 months, while in patients who received no prior treatment, the ORR was 36.1% and median PFS was 8 months. Median PFS was longer in patients who received no prior treatment (HR = 1.89; 95% CI 1.01–3.34; p = 0.019). For those who received pemetrexed-based therapy postoperatively, gemcitabine-based therapies had similar PFS outcomes to rechallenge pemetrexed-based therapy in first-line treatment (HR =1.43; 95% CI 0.59–3.45; p = 0.37). Taylor et al. [15] compared single-agent pemetrexed therapy in chemotherapy-naive patients with patients who had previously received pemetrexed-based therapy and had achieved benefits. In their study, time to progression in chemotherapy-naive patients was 6 months and the ORR reached 10.5%, while time to progression was 4.9 months and the ORR was 12.1% in patients who had received previous treatment [15]. Jänne et al. [16] compared a pemetrexed single agent with pemetrexed plus cisplatin combination therapy in the treatment of previously treated malignant mesothelioma in a phase

III study. In their results, the ORR was found to be 5.5% with single-agent pemetrexed and 32.5% in the combination arm [16]. In our study, median PFS was 5 months and the ORR was 31.3% with first-line pemetrexed platinum rechallenge therapy. Our response rates were similar to the literature. However, in patients who had received pemetrexed plus cisplatin in the postoperative setting, the use of pemetrexed-based combination therapy in first-line treatment was not superior to the use of gemcitabine plus platinum. The addition of bevacizumab to pemetrexed plus cisplatin treatment in first-line treatment improved PFS [7]. Patients receiving bevacizumab were not included in our study. In addition, recent studies with immunotherapy combination have shown that nivolumab plus ipilimumab treatment is effective in the first-line treatment of malignant mesothelioma [17]. In our country, very few patients received immunotherapy because of the problem of access. Therefore, patients receiving immunotherapy were excluded from the study. In countries where access to immunotherapy is problematic, rechallenge therapy remains an important treatment option.

Patients who have not progressed under pemetrexed treatment in first-line treatment have the potential to benefit from pemetrexed treatment in second-line treatment [18]. However, especially as it is understood from retrospective studies, patients in whom the time from the end of first-line treatment to progression is longer than 6 months are more likely to benefit from pemetrexed treatment [19, 20].

In patients who had received platinum in first-line treatment, re-adding platinum in the second-line treatment increased both the disease control rate (70.6% *vs*. 44.6%) and median PFS duration (6.6 months *vs*. 2.5 months). Zucali et al. [21] found that pemetrexed rechallenge therapy in second-line treatment reduced the risk of progression, especially in patients < 65 years of age and time to progression ≥ 12 months. Bearz et al. [19] reported median PFS of 4 months with rechallenge pemetrexed single-agent and 5.7 months with pemetrexed plus platinum in second-line treatment. In another study, Ceresoli et al. [20] found a 19% ORR with pemetrexed single agent and a 48% ORR with platinum combination.

Studies on second-line treatment in mesothelioma have reported median PFS of 3–6 months and OS of 10–12 months with other chemotherapy regimens [22–28]. Second-line immunotherapy produced median PFS of 2.8–6.2 months with tremelimumab and 4 months with avelumab, while the ORRs were found to be 20% with pembrolizumab and 13.2% with nivolumab [29–33]. In our study, the ORR were observed in 15 of 49 patients (30.6%) who received rechallenge pemetrexed plus platinum. The remaining 34 (69.4%) patients were treated with gemcitabine plus platinum. Although both treatment arms had clinicopathologic similarities (Tab. 2), patients who received a rechallenge had a better clinical course compared to the other arm. In the arm receiving rechallenge pemetrexed plus platinum, the ORR was 20%, median PFS was 6 months and median OS was 29 months. In the gemcitabine plus platinum arm, the ORR was 11.7%, median PFS was 4 months, and median OS was 15 months. Both ORR, median PFS, and median OS values were higher in the rechallenge arm (HR for PFS = 0.46; 95% CI 0.22–0.94; p = 0.018), (log-rank p = 0.007 for OS). We found that pemetrexed plus platinum combination therapy may be an effective treatment option for second-line treatment in patients with time to progression ≥ 6 months for whom this therapy has shown efficacy after first-line treatment. In our study, when evaluated together with other potential prognostic factors in multivariate analysis, the use of rechallenge pemetrexed plus platinum in the second line was the only independent prognostic factor for PFS. In the subgroup analysis performed in patients receiving rechallenge pemetrexed treatment, radiotherapy and benefit from previous pemetrexed treatment (response with previous pemetrexed treatment and time to progression ≥ 6 months) were observed as predictive factors for PFS. Zucali et al. [21] reported that patients aged < 65 years and with time to progression ≥ 12 months achieved better PFS than rechallenge treatment patients. However, many retrospective data have reported that if time to progression is ≥ 6 months, the potential to benefit from rechallenge treatment may be high [19, 20].

The limitations of our study were that it was a single-center retrospective study, the patient groups were heterogeneous, and the number of patients was small. In addition, the group of patients who underwent rechallenge consisted of patients with a better clinical course. This should be taken into account when evaluating the results of the study.

Conclusions

We found that pemetrexed plus cisplatin treatment after postoperative use of the same regimen had similar efficacy to gemcitabine plus cisplatin treatment. In second-line treatment, we found that pemetrexed plus platinum was a more effective therapeutic option than gemcitabine plus platinum in patients who had previously benefited from pemetrexed-based treatment and had not progressed up to 6 months after first-line treatment.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles defined in the Declaration of Helsinki (permit no: 10/2021).

Author contributions

Z.U.: conception and design of the study, writing of the article.
S.E.: data analysis and interpretation
Z.O.: acquisition of clinical data.
M.A.K.: data analysis and interpretation.
M.K. and Z.K.: acquisition of clinical data.
A.I.: data analysis and interpretation.
All authors have read and approved the final version of this manuscript and have consented for publication.

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Conflict of interest

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Supplementary material

Supplementary Table S1.

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Supplementary material

Table S1. Pemetrexed plus platin *versus* gemcitabine plus platin subgroup analysis results

	HR	CI 95%	p value
Sex			
Male	0.38	0.12–1.15	0.88
Female	0.46	0.15–1.42	0.17
Smoking			
Yes	0.56	0.17–1.78	0.33
No	0.44	0.13–1.47	0.18
ECOG PS			
0–1	0.49	0.23–1.05	0.06
≥ 2	0.02	0.01–104	0.38
Subtypes			
Epithelioid	0.52	0.24–1.13	0.10
Others	0.36	0.01–264	0.46
Radiation therapy			
Yes	0.27	0.08–0.88	0.03
No	0.53	0.17–1.60	0.26
Reason for rechallenge			
Previous good response (≥ 6 mo interval)	0.22	0.06–0.87	0.03
Used in adjuvant period	1.43	0.59–3.45	0.42

CI — confidence interval; ECOG PS — Eastern Cooperative Oncology Group performance status; HR — hazard ratio; mo — months