Original Article

# Evaluation of Effect and Side Effects of Pemetrexed in Patients with Advanced-Stage Lung Adenocarcinoma

# İleri Evre Akciğer Adenokarsinom Hastalarında Pemetrexed'in Etki ve Yan Etki Değerlendirmesi

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**ABSTRACT**

**Objectives:** The purpose of this study was to evaluate the effectiveness and dose-limiting side effects of pemetrexed use in patients with advanced-stage non-small-cell lung adenocarcinoma.

**Materials and Methods:** This study was conducted retrospectively by examining the files of patients who received treatment between 2017 and 2019. The dose-limiting side effects of the patients were evaluated by looking at the blood tests taken before each cycle and the notes in their files. All toxicities were classified by using the Common Terminology Criteria for Adverse Events verison 5.

**Findings:** The most common dose-limiting side effect was neutropenia, which developed in 50% of the patients. Side effects that affecting all blood series were observed in 28,1% of patients. The incidence of side effects of platinum given with pemetrexed was similar. Longer median survival was statistically correlated within patients receiving pemetrexed + platinum combination chemotherapy in the second and subsequent lines ($p<0.05$).

**Conclusions:** Pemetrexed is an easily tolerated and effective chemotherapy agent in advanced-stage non-small-cell lung carcinomas.

**Keywords:** Lung cancer, chemotherapy, pemetrexed, side-effects, efficacy

**ÖZET**

**Amaç:** Bu çalışmada ileri evre akciğer adenokarsinomu hastalarında pemetrexed kullanımının etkinliğini ve doz kısıtlayıcı yan etkilerini değerlendirmek amaçlanmıştır.

**Materyal ve metod:** Bu çalışma 2017–2019 yılları arasında tedavi almış hastaların dosyaları retrospektif olarak incelenerek yapılmıştır. Hastaların gelişmiş olan doz kısıtlayıcı yan etkileri, her kür öncesi alınan kan tetkikleri ve dosyalarındaki notlara bakılarak değerlendirildi. Tüm toksisiteler Common Terminology Criteria for Adverse Events version 5 kullanılarak sınıflandırıldı.

**Bulgular:** Hastalarda en sık doz kısıtlayıcı yan etki 50% hastada gelişen nötropeni oldu. Hastaların 28,1%'inde tüm kan serilerini etkileyen yan etki görülmüştür. Pemetrexedle birlikte verilen platinlerin yan etki insidansları benzerdi. Pemetrexed platin kombinasyon kemoterapisini ikinci ve sonraki basamaklarda alan hastalarda daha uzun median sağkalımla saptandı ($p<0,05$).

**Sonuç:** Pemetrexed ileri evre akciğer adenokarsinomunda kolay tolere edilebilen, etkili bir kemoterapi ajanıdır.

**Anahtar Kelimeler:** Akciğer kanseri, Kemoterapi, Pemetrexed, Yan Etki, Etkinlik

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## Introduction

Non-small-cell lung cancer is still among the leading causes of cancer-related death in both males and females worldwide. Platinum-based chemotherapy improves survival compared to palliative care in metastatic non-small-cell lung cancer patients with good performance scores. Platinum-based combined therapies including immunotherapy are among the standard treatments in first-line treatment in patients without driver mutation [1]. Of the two platinum used in lung cancer, cisplatin is superior to carboplatin in terms of survival, while carboplatin is a more tolerable treatment option [2].

As an antifolate metabolite, pemetrexed is a well-tolerated and effective cytotoxic agent in advanced-stage lung adenocarcinomas. Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase enzymes. As a result, RNA and DNA synthesis is inhibited. As used in non-small-cell lung adeno-carcinomas, it has been proven to be effective in malignant mesothelioma. It has recently been shown that the combination of pemetrexed and platinum-based chemo-therapy with pembrolizumab prolongs survival compared to chemotherapy regardless of PD-L1 level [3].

This study aimed to examine the effectiveness and toxicity profile of platinum + pemetrexed combination in patients with advanced-stage lung adenocarcinoma.

## Materials and Methods

This study was conducted retrospectively by examining the medical records of the patients with advanced-stage lung adenocarcinoma treated in Medical Oncology Department of Sanlıurfa Mehmet Akif Inan Training and Research Hospital. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before the study, ethical approval was obtained from the Harran University clinical research ethics committee (Desicion number: HRU /21.07.27 Date: 29 March 2021).

### Patients

Advanced-stage non-small cell lung cancer patients with a histologically confirmed diagnosis of adenocarcinoma who received treatment between January 1, 2017 and December 31, 2019 were included in the study. Inclusion criteria for the study were defined as being 18 years or older, before treatment having a platelet count of $100x10^9$ cells/L, a neutrophil count of more than $1.5x10^3$ cells/L, a total bilirubin level less than two times the upper limit of normal, aspartate aminotransferase (AST) level is less than three times the upper limit of normal or less than five times of normal in those with liver metastases, glomerular filtration rate (GFR) calculated with the Cockcroft-Gault formula being more than 45 ml/min, and an ECOG performance score being two or less.

### Study Design

The histological diagnosis date of all patients was determined as the starting point. All patient's height, weight, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, total leukocyte count, neutrophil count, and platelet count were recorded before treatment. Body mass index (BMI) was calculated from height and weight values.

Patients with bone, liver, and brain metastases were identified. It was determined in which line pemetrexed was used and which platinum agent it was given with (cisplatin or carboplatin). During the treatment, patients who were given erythrocyte suspension were determined due to the decrease in hemoglobin value (below 10g/dl), and symptoms such as

 

tachycardia and dizziness they showed. The patients who developed neutropenia (neutrophil count below $1.5x10^3$ cells/dl) and thrombopenia (platelet count below $100x10^9$ cells/L) during treatment were determined. Nephrotoxicity was defined as a decrease of 25% or more from the baseline glomerular filtration rate (GFR). Those with AST levels were higher than three times the upper limit of normal or in patients with liver metastases, those with a value higher than five times the upper limit of normal were evaluated as hepatotoxicity. Toxicity assessments were made by examining blood tests taken before each treatment and were classified using the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5).

Treatments

All patients received treatment at a dose of 500 mg/$m^2$ pemetrexed every 21 days. Before the treatment, 400 µg folic acid supplementation was provided to all of them daily. All patients were given 1000 µg of vitamin B12 before treatment and repeated every nine weeks. The treatment scheme was continued until disease progression or development of unacceptable toxicity. Cisplatin, together with pemetrexed was given at a dose of 75 mg/$m^2$ every 21 days. Carboplatin was calculated according to the area under curve ((GFR+25)*AUC) Calvert formula and was given every 21 days. Platinums were not given after 6 cycles and pemetrexed was applied alone. All patients received routine premedication and supportive treatments such as antiemetics.

Statistical analysisThe Statistical Package for Social Sciences (SPSS) for Windows 21.0 program was used for the statistical analysis of the findings of the study. The Shapiro-Wilk test was used for the normality distribution analysis of independent samples. Continuous variables presented as mean+SD. Independent sample T-test was used for parametric data and Mann Whitney U test was used for the analysis of non-parametric data. Kaplan Meier analysis and Log-rank (mantel-cox) analysis were performed for survival analysis. The results were evaluated at the $p<0.05$ level and 95% confidence interval.

**Findings**

There were 32 patients in this study. The average age was 57.9±1.9 overall (range, 34 to 77 years), while it was 59±2 in males (n=27), and 52.2±6 in females (n=5). The average BMI of all patients was found to be 25.4±0.8, the mean BMI of male patients was 24.8±0.8, and the mean BMI of female patients was 28.5±2.4.

There were eight patients with bone metastases and nine patients with brain metastases. There were no bone and brain metastases in 18 patients. There was no patient with liver metastasis. The characteristics of the patients are given in Table 1.

The mean neutrophil count of the patients before the first cycle was 6400±2700/$mm^3$ (minimum 1990/$mm^3$, and maximum 11670/$mm^3$). The mean lymphocyte was found to be 2000±1000/$mm^3$ (minimum 310/$mm^3$, and maximum 6556/$mm^3$). Neutropenia did not develop in 16 patients during the treatment, and grade 1-4 neutropenia (<1500/$mm^3$) developed at least once in 16 patients. Grade 1-2 neutropenia developed in six patients, while grade 3-4 neutropenia developed in ten patients. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of development of neutropenia (p=0.296).

The mean hemoglobin value of the patients before treatment was 12.8±2.5 g/dl (minimum 7.42 g/dl, and maximum 16.58 g/dl). While taking pemetrexed and platinum combination, 11 patients did not need transfusion throughout the treatment. At least one unit of

 

Table 1: Characteristics of patients

| Characteristics of patients | n (%) |
|---|---|
| Age | |
| ≤60 | 20(61,3%) |
| >60 | 12(38,7%) |
| Sex | |
| Male | 27(84,4%) |
| Female | 5(15,6%) |
| Driver Gene Mutation | |
| Yes | 4(12,6%) |
| No | 28(87,4%) |
| Sites of Metastates | |
| Bone | 8 (25%) |
| Brain | 9(28,1%) |
| Liver | 0(0%) |
| Bone+Brain | 3(9,3%) |
| Pemetrexed+Platinum | |
| Cisplatin | 15(46,9%) |
| Carboplatin | 17(53,1%) |
| The Line of Using Pemetrexed | |
| First-Line | 22(68,8%) |
| Second and Subsequent Lines | 10(31,2%) |
| Toxicities (Grade 1-4) | |
| Anemia | 11(34,4%) |
| Neutropenia | 16(50%) |
| Thrombocytopenia | 12(37,5%) |
| Anemia+ Thrombocytopenia+ Neutropenia | 9(28,1%) |
| Without Hematological Toxicity | 8(25%) |
| Nefrotoxicity | 7(21,9%) |
| Hepatotoxicity | 2(6,3%) |

erythrocyte suspension was transfused to 21 patients. All the hemoglobin decreases that developed were at the level of grade 1-2. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of the development of anemia (p=0.909).

The mean platelet count of the patients before treatment was 283000±110000 /mm$^3$. While taking pemetrexed and platinum combination, thrombocytopenia (<100,000/mm$^3$) did not develop in 20 patients, but it did develop in 12 patients. Grade 3-4 thrombocytopenia developed in two patients, and grade 1-2 in ten patients. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of thrombocytopenia development (p=0.242). There was no statistically significant difference between those taking cisplatin and carboplatin in terms of any hematological toxicity development (p=0.546).

The mean AST level of the patients was 21.9±11.5 and the mean ALT level was 25.9±27. During the treatment period, hepatotoxicity developed in two patients, but not in 30 patients and all hepatotoxicity cases that developed were grade 1-2. Hepatotoxicity developed in two patients receiving carboplatin. There was no statistically significant difference between those taking cisplatin and carboplatin in terms of hepatotoxicity development (p=0.177).

The mean GFR of the patients was found to be 89.5±18, the lowest GFR was 53 ml/min, the highest GFR was 120 ml/min. During the treatment period, nephrotoxicity developed in seven patients, but not in 25 patients. No patient developed renal failure requiring dialysis. All nephrotoxicities were at a level that could be treated with fluid replacement. Nephrotoxicity developed in five patients receiving ciplatin and two patients receiving carboplatin. There was no statistically significant difference between those taking

Table 2: Distribution of advers event in first and second or subsequent lines treatments

| Advers event | First line treatment n(%) | Second or next line treatment n(%) | p |
|---|---|---|---|
| Any hematological toxicity | 14(63,6%) | 10(100%) | 0.035 |
| Need of transfusion | 12(54,5%) | 9(90%) | 0,106 |
| Neutropenia | 7(31,8%) | 9(90%) | 0.006 |
| Thrombocytopenia | 6(27,3%) | 6(60%) | 0.119 |
| Nephrotoxicity | 5(22,7%) | 2(20%) | 1 |
| Hepatotoxicity | 1(4,5%) | 1(10%) | 0,534 |

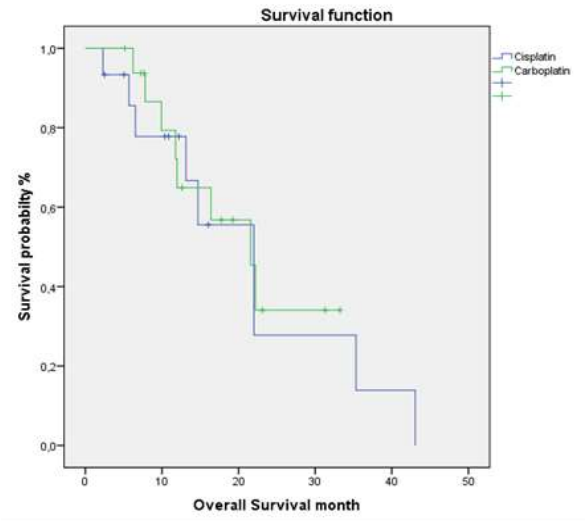


Figure 1: Analysis of overall survival among patients receiving Cisplatin or Carboplatin

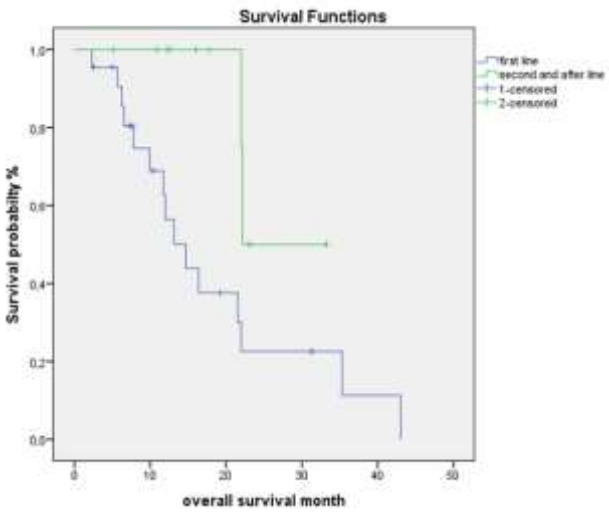


Figure 2: Relationship between pemetrexed use treatment line and overall survival analysis

cisplatin and carboplatin in terms of development of nephrotoxicity (p=0.147). There was no correlation between BMI measured before treatment and nephrotoxicity (p=0.618) The incidence of advers event in the first line treatment and second or subsequent lines treatments are given in Table 2.

While 15 patients were treated with the combination of cisplatin and pemetrexed, 17 patients were treated with the combination of carboplatin and pemetrexed. All patients received an average of 6.5±6.7 cycles of treatment (minimum of 1 and a maximum of 38 cycles of treatment). The median overall survival time of the patients was 12.41 months (95% CL 2.30-43.77 months). The median survival time from the start of pemetrexed was calculated as 8.86 months (95% CI 1.00-43.03 months). The median overall survival of those receiving cisplatin was 12.2 months (95% CI 2.3-43.07 months), and the median overall survival of those receiving carboplatin was 12.63 months (95% CI 5.13-33.13 months) as illustrated in Figure 1.

The combination of pemetrexed + platinum (cisplatin or carboplatin) was used in 22 patients in the first-line and in ten patients in the second or later lines. A median survival of 11.06 months (95% CI 2.3-43.07months) was

 

achieved in patients used in first-line. The median survival was found to be 16.9 months (95% CI 5.13-33.23 months) in patients used in the second and subsequent lines. The survival of patients who received pemetrexed in the second or later lines was statistically significantly longer than those who received it in the first-line ($p<0.05$), as illustrated in Figure 2.

**Discussion**

Non-small-cell lung cancer is the leading cause of cancer-related death worldwide. According to the 2016 report of national cancer statistics, the most common cancer in male at all ages is lung cancer [4]. While current treatment guidelines are category 1 option for all metastatic non-small-cell lung cancers, they also recommend examining PDL-1 for an immunotherapy option and molecular testing to detect driver mutations in non-adenocarcinoma types. Treatment is directed according to the results from these molecular tests.

In today's modern treatment protocols, tyrosine kinase inhibitors are the primary treatment option in patients with driver mutations. Immunotherapy is also a treatment option that has proven itself with its effectiveness in recent years and has come to the fore with its safe side-effect profile compared to chemotherapy. In recent years, the addition of chemotherapy to these treatment protocols has been investigated and a difference in survival is observed [3]. Surely, the addition of new generation agents to combination therapies changes the incidence, type, and degree of side effects. In this case, the evaluation of the side effects and knowing the agent causing the side effects are crucial in the management of the patients.

As a folate antagonist, pemetrexed is among the treatment options in nonsmall-cell nonsquamous lung cancer and malignant mesothelioma, and its effectiveness has been proven in all treatment lines [5]. Pemetrexed has side effects such as fatigue, nausea, vomiting, loss of appetite, and diarrhea due to folic antagonism. In addition to these, there are potentially serious side effects such as hepatotoxicity, nephrotoxicity, and hematological toxicities. These side effects are either limit the use or require a dose change.

Pemetrexed-associated hepatotoxicity is usually mild. It is associated with low-to-moderate liver serum enzyme elevations, but the findings are usually mild and transient. There is no jaundice and no accompanying symptoms. Enzyme elevations are more than three times the upper limit of normal in only 1-6% of patients. It is usually treated with dose intensity variation. Rarely, dose modification or discontinuation of treatment is required. No cases of significant liver injury attributed to pemetrexed have been reported. The mechanism of liver damage develops mostly as a result of folate metabolism. The hepatic metabolism of pemetrexed is minimum, it is mostly excreted by the kidneys [6]. Pemetrexed-associated hepatotoxicity is more common in patients with pre-existing liver injury. In our study, hepatotoxicity developed in 6.3% (n=2) patients and was found to be compatible with the literature. In this study, liver dysfunction was found at grade 1-2 level. Severe hepatic impairment did not develop in any of the patients. In cases where hepatotoxicity is encountered in patients using pemetrexed, other causes must be investigated. During this period, treatments should be delayed until the values return to normal.

Pemetrexed is excreted by renal elimination. 70-90% of the drug is excreted unchanged by the kidney in the first 24 hours. Previous studies have shown that its pharmacokinetics are directly related to creatinine clearance. Therefore, pemetrexed should be recommended to those with adequate renal function. Greater exposure with decreased creatinine clearance is known to be associated

 

with hematological toxicity. It is not recommended if the glomerular filtration rate is below 45 ml/min [7,8].

Cancer patients are usually patients with comorbid diseases and using many nephrotoxic drugs. These patients are likely to develop nephrotoxicity and, like all other drugs, chemotherapeutic agents should be chosen carefully [9]. Nephrotoxicity is an important treatment-limiting effect for pemetrexed therapy and a significant problem in patients who receive and respond to pemetrexed combination chemotherapy. In the Paramount study, it is reported that 7.8% of the patients encountered renal toxicity, and 4% had to stop the treatment. Moreover, they mentioned the cumulative effect of kidney toxicity in the treatment arm [10]. In our study group, the rate of nephrotoxicity was found to be 21.9% (n=7). Taking cisplatin or carboplatin with pemetrexed did not change the risk of developing nephrotoxicity. There was no relationship between BMI measured before treatment and the development of nephrotoxicity. While this nephrotoxicity may be due to pemetrexed, reasons such as higher GFR due to sarcopenia developing in cancer patients and insufficient hydration due to loss of appetite should be considered. Although the causes of nephrotoxicity development in our study were different, there may be a different actual result than the calculated value because the patients were gathered on a common ground. In order to determine the risk of developing nephro-toxicity, a research can be done with the data obtained by following the patients throughout the treatment.

Most clinical studies have reported pemetrexed-related hematological toxicities. Its effect on folate metabolism is shown as the cause. Vitamin B12 and folic acid supplementation is recommended to reduce pemeterexed-related hematological toxicities. All three series are affected by pemetrexed toxicity. When toxicity develops, the dose of pemetrexed should be reduced by 50% if the platelet count is below 50,000; if the platelet count is between 50,000-100,000 and the neutrophil count is below 500 $mm^3$/dl, the pemetrexed dose should be reduced by 25% [11,12]. In our study group, anemia developed in 11 patients, neutropenia in 16 patients, and thrombocytopenia in 12 patients. Nine patients were affected by all three series. No hematological toxicity was observed in eight patients. In general, hematological toxicities are more common than other toxicities, but they can be easily managed. While giving treatment, it should be remembered that hematologic toxicities can be seen in most patients.

The combination of pemetrexed and platinum has been tested at various lines in many studies. Scagliotti et al. compared the effect of pemetrexed with gemcitabine/cisplatin and pemetrexed/cisplatin combinations in first-line [12]. In Scagliotti et al. study, median overall survival was found to be 12.6 months in lung adenocarcinoma patients receiving pemetrexed. In a phase III randomized study by Grønberg et al., the combination of pemetrexed + carboplatin was tested in the first line. In that study, a median survival of 7.3 months was reached [13]. In a randomized phase III study conducted by Hanna et al. in 2004, pemetrexed and docetakel were compared in the second-line. The median survival for pemetrexed was found to be 8.3 months [14].

Although the number of patients in our study was very small for evaluation of efficacy and survival, our results were found to be consistent with the literature. In this study, patients who received pemetrexed in second or subsequent lines had better survival. This seems like a surprising result at first view. However, there were only 10 patients receiving pemetrexet in the second or subsequent series and four of them had a driver mutation. These are the patients who received targeted therapy in the first series and

 

has already a better survival than patients without a mutation. It should also be noted that lung cancer has a very short survival, especially in patients without a driver mutation. Patients who can receive second-line therapy may have a possibly slower course of disease or they may have a good responded to the first line treatment. As a result, we think that the better survival of those who received pemetrexed in the 2nd line may be related to these factors. We cannot present this data as the drug was more effective in the second lines.

The first limitation of this study was small number of patients. Secondly, because it was a retrospective study, we could not present the side effects that we could observe clinically, such as nausea, vomiting, and fatigue. The positive aspect of our study was that we were able to document side effects with detailed and closely followed laboratory tests.

## Conclusions

In our study, pemetrexed combinations used in all treatment lines were beneficial in patients with advanced-stage lung adenocarcinoma. The combination of pemetrexed and platinum has an acceptable toxicity profile. The toxicity profile did not change with the platinum selection. The most common toxicity is hematological toxicities, primarily neutropenia. Another significant and frequent side effect is nephrotoxicity. Early detection and management of toxicities seems possible with close clinical and laboratory evaluation.

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