

ORIGINAL RESEARCH

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The Efficacy of Pemetrexed-Based Therapy in Advanced Lung Adenocarcinoma with Targetable Driver Mutation: A Real-Life Experience

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ABSTRACT Objective: Lung adenocarcinoma is the most common subtype of non-small cell lung cancer, and also, approximately 25% of lung adenocarcinoma patients have targetable driver mutations. Despite several novel therapeutic advances in the treatment of lung adenocarcinoma with targetable driver mutations, chemotherapy still has an important role to play. In this study, we aimed to evaluate the real-world efficacy of pemetrexed-based chemotherapy in lung adenocarcinoma with the targetable mutation. **Material and Methods:** The advanced lung adenocarcinoma patients with targetable driver mutations who received pemetrexed-based chemotherapy between 2014 and 2018 were enrolled in this study, retrospectively. The patients were stratified according to mutation type and pemetrexed-line as pre or post-tyrosine kinase inhibitor (TKI). The primary outcome of our study was considered as progression-free survival (PFS). **Results:** A total of 265 patients with the targetable mutation were screened and only 60 were enrolled in the study. In the entire group, the median PFS was 7.81. Median PFS was significantly higher in ALK-ROS1 positive subgroup than EGFR positive subgroup ($p=0.001$). The median PFS was higher in patients who received pre-TKI treatment in the ALK-ROS1 subgroup ($p=0.006$). In EGFR positive patients, PFS was similar between pre or post TKI groups ($p=0.28$). The overall response rate was 55%, 59.1%, and 52.6% in the entire group, ALK-ROS1 positive and EGFR positive subgroup, respectively. **Conclusion:** We showed that pemetrexed-based therapy is still an important choice for the patients who progress after targeted therapy and also for those who are not suitable for another targeted therapeutic agent.

Keywords: Lung cancer; pemetrexed; real-world; PFS

Lung cancer is one of the leading cause of cancer-related deaths.¹ Adenocarcinoma is the most common and the most investigated subtype among all the histological groups of lung cancer. Approximately 25% of patients with advanced adenocarcinoma have targetable driver mutations. This rate of occurrence is higher in non-smokers, young and female patients. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are the most common type of targetable driver mutations in non-small cell lung cancer (NSCLC). Besides, mutations in ROS-1, c-MET, B-RAF, and cErbB2 may occur rarely.

Recently, there have been many therapeutic advances like the development of targeted therapy and the use of immune-checkpoint inhibitors for the treatment of lung cancer, especially adenocarcinoma subtype. However, chemotherapy remains an indispensable treatment option in advanced lung cancer. Pemetrexed, a multitargeted antifolate chemotherapy agent, was found to be effective in patients with lung adenocarcinoma as the first-line, second-line and maintenance therapy.²⁻⁴ Pemetrexed was granted conditional approval by the Food and Drug Association (FDA) for several steps of non-squamous non-small cell lung cancer (NSCLC) treatment.

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Several lines of investigations show that tyrosine kinase inhibitors (TKI) that target ALK, EGFR, and ROS-1 were superior compared to the platinum-based chemotherapy as first-line and further treatment-line. However, the sequential use of targeted therapy has several issues despite many new therapeutic advances. Due to this, chemotherapy is still an option in patients who progress after targeted therapy and have left with no option. Although there have been many clinical trials that evaluated the efficacy of pemetrexed in lung cancer patients with the targetable mutation, limited trials were conducted to evaluate the real-world efficacy of pemetrexed-based chemotherapy.

In our study, we aim to investigate the real-world efficacy of pemetrexed-based chemotherapy in patients with targetable driver mutations and also to evaluate the difference in efficacy between mutation types and also pre or post-TKI therapy status.

MATERIAL AND METHODS

This study was performed with the patients who were admitted to the Medical Oncology department of Ataturk Chest Disease and Chest Surgery Hospital, between 2014 and 2018. A total of 60 patients who were diagnosed with advanced lung adenocarcinoma and had targetable driver mutations were screened. However, only the patients who received pemetrexed-based chemotherapy at any line of treatment were enrolled in the study. The maintenance with pemetrexed treatment was allowed for enrolment. The patient's data were obtained by using the hospital electronic database, retrospectively. The patient's clinical and demographic features, mutation types and subtypes, and the number of pemetrexed-based chemotherapy cycles were recorded. The patients who had insufficient follow-up data and those who were not able to receive pemetrexed due to intolerance or any other reason were excluded from the study.

The patients were categorized according to pemetrexed treatment-line as the pre-TKI group and the post-TKI group for evaluation of the differences in the efficacy of pre or post-TKI pemetrexed-based therapy. The patients were also stratified according

to mutation types. The patients who had ALK and ROS-1 mutation were grouped together due to the relatively low number of patients with ROS-1 mutation, as the ALK-ROS1 positive subgroup and the other subgroup comprised of EGFR positive subjects. The primary outcome of this study was progression-free survival (PFS) of pemetrexed-based therapy. Another endpoint was the response rate. Tumor response was evaluated by CT scan or 18-FDG PET BT scan according to the Response Evaluation Criteria in Solid Tumors (RECIST).⁵ PFS was described as the time from initiation of crizotinib to RECIST-defined progression or death. Complete response (CR) was defined as total regression of all assessable lesions; partial response (PR) was defined as the 30% or more decrease in the target lesions; progressive disease (PD) was defined as more than a 20% increase in the diameter of the lesions or appearance of new lesions; the remaining patients who did not meet the criteria of PD or PR were categorized as stable disease (SD). The objective response rates (ORR) were calculated by the sum of CR and PR rates. The clinical benefit rate (CBR) was calculated by summing up the values of CR, PR, and SD rates.

Categorical variables were compared by using the Chi-square or Fisher's exact test. The variables were investigated using visual and Kolmogorov-Smirnov/Shapiro-Wilk's test to determine whether or not they are normally distributed. Mann-Whitney-U test and Spearman's test were used to compare non-normal or normally disturbed, ordinal variables, respectively. The differences in survival outcomes between mutational subgroups and also pre or post-TKI pemetrexed-based chemotherapy were investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. A p-value of less than 0.05 was considered to show a statistically significant result. Statistical analyses were performed by using the SPSS software version 23.

RESULTS

A total of 265 patients with the targetable driver mutation were screened and 60 of them were enrolled in the study. Thirty-eight of the 60 patients (63.3%) had EGFR mutation, 20 patients (33.3%) and 2 patients (3.3%) had ALK and ROS-1 mutations, respectively.

In EGFR mutation-positive subgroup, 17 of 38 patients (44.7%) had exon 19 deletion and 21 of 38 patients (55.3%) had exon 21 L858R mutation. Forty-four (73.3%) and 16 patients (26.7%) received pre-TKI and post-TKI pemetrexed, respectively. In EGFR mutation-positive subgroup, 60.5% of patients received pre-TKI and 39.5% of patients received post-TKI pemetrexed-based therapy. In the ALK-ROS1 positive subgroup, 21 of 22 patients received pemetrexed-based therapy as pre TKI treatment and only one patient received pemetrexed after progression with TKI. Detailed demographic data of patients are listed in Table 1. There were no statistically significant differences between the demographic features of ALK-ROS1 and EGFR mutation subgroups, except the presence of brain metastasis ($p=0.002$). In addition, the rate of pre-TKI pemetrexed was significantly high in the ALK-ROS1 positive subgroup than EGFR positive subgroup ($p=0.002$). There were no statistically significant differences between pre-TKI and post-TKI pemetrexed-based therapy in EGFR mutation-positive subgroup.

At the time of the data cut-off, the median follow-up time was 22.4 months (1.61-64.69), and the

median cycle of pemetrexed-based therapy was 5 (3-6). Only three out of 60 patients (5%) received maintenance pemetrexed therapy. In the entire group, 57 events occurred, and the median PFS was 7.81 months (5.9-9.6) (Figure 1). In subgroups analyzed between mutation types, median PFS was significantly higher in the ALK-ROS1 positive group than the EGFR mutation group (9.06 vs. 6.31 months, $p=0.01$) (Figure 1). The survival advantage of pemetrexed-based chemotherapy was seen in patients who received pre-TKI pemetrexed-based therapy. Median PFS was 10.54 months and 6.01 months in ALK-ROS1 positive and EGFR positive subgroup, respectively ($p=0.006$) (Figure 2). In EGFR positive subgroup, PFS was not significantly different between pre-TKI and post-TKI pemetrexed. (Median PFS: 6.01 for pre-TKI vs. 6.83 for post-TKI, $p=0.28$). On the other hand, the survival analysis of post-TKI pemetrexed cannot be conducted due to the low number of patients who received post-TKI pemetrexed in ALK-ROS1 positive subgroup.

The ORR was 55%, and CBR was 88.3% in the entire group. In the ALK-ROS1 positive subgroup, ORR was 59.1% whereas, in the EGFR positive sub-

TABLE 1: Demographic and clinical features of patients.

Parameter	Entire Group	ALK-ROS1 and EGFR Subgroup		P
		ALK-ROS1 mut	EGFR mut	
Age (median, min-max)	56 (32-75)	51.5 (32-67)	57 (41-75)	0.056
Sex (M/F)	61.7%/38.3%	63.6%/36.4%	60.5%/39.5%	0.81
Smoking				
Never	47.5%	45.5%	48.6%	0.072
Current smoker	16.9%	4.5%	24.3%	
Former Smoker	35.6%	50%	27%	
Cigarette Consumption (package/year-median)	21.5 (3-90)	20 (5-45)	30 (3-90)	0.224
ECOG PS				
0	2.6%	9.1%	2.6%	0.22
1	71.1%	50%	71.1%	
2	26.3%	40.9%	26.3%	
Brain Metastasis (Y/N)	20%/80%	40.9%/59.1%	7.9%/92.1%	0.03
Liver Metastasis (Y/N)	11.7%/88.3%	13.6%/86.4%	10.5%/89.5%	0.71
Adrenal Metastasis (Y/N)	18.3%/81.7%	13.6%/86.4%	21.1%/78.9%	0.47
Bone Metastasis (Y/N)	35%/65%	27.3%/72.7%	39.5%/59.5%	0.295
Pleura Metastasis (Y/N)	30%/70%	22.7%/77.3%	34.2%/65.8%	0.35
Lung Metastasis (Y/N)	56.7%/43.3%	54.5%/45.5%	57.9%/42.1%	0.80

ECOG PS: Eastern Cooperative Oncology Group performance status; M: Male; F: Female; Y: Yes; N: No; Mut: Mutation.

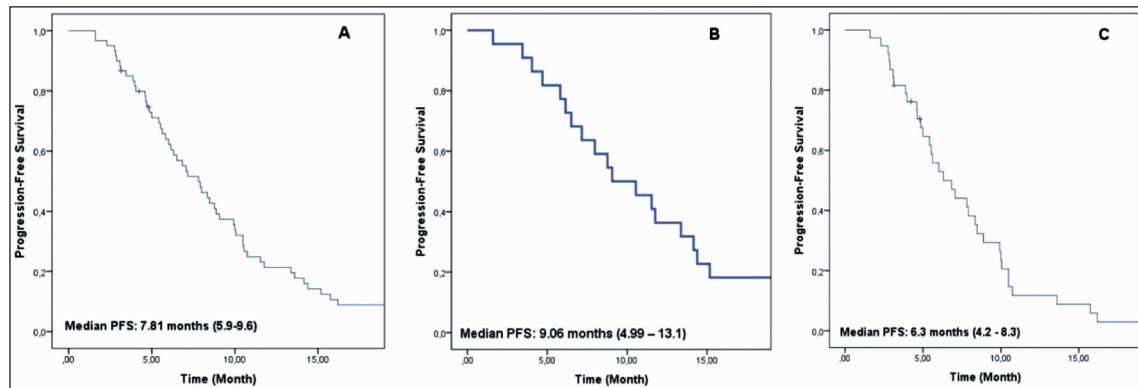


FIGURE 1: The comparison of the efficacy of pemetrexed-based chemotherapy. **(A)** In ALK-ROS1 and EGFR mutation-positive subgroup, median PFS: 9.06 vs. 6.31 months, $p=0.01$, respectively; **(B)** In pre-TKI ALK-ROS1 and EGFR mutational positive subgroup, median PFS: 10.54 months vs. 6.01 months, $p=0.006$, respectively.

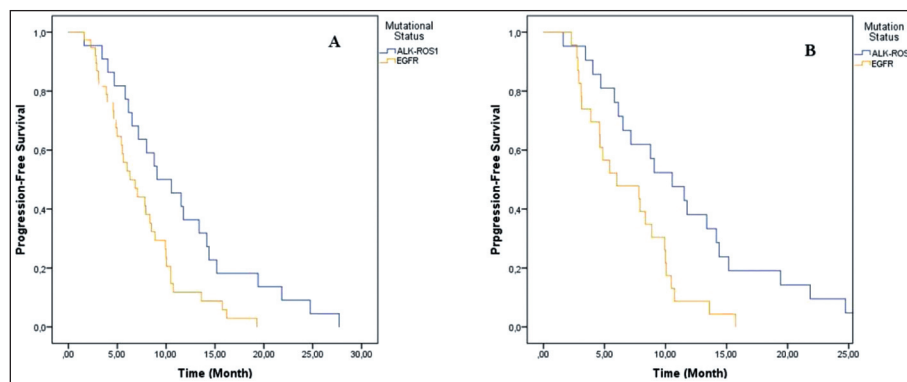


FIGURE 2: Progression-free survival graphics in the entire group **(A)**, ALK-ROS1 mutation-positive subgroup **(B)** and EGFR mutation-positive subgroup **(C)**.

group, ORR and CBR were 52.6% and 81.6%, respectively. The ORR of pre-TKI and post-TKI pemetrexed-based therapy were 60.9% and 40% in EGFR positive subgroup, respectively.

DISCUSSION

In this study, we found that PFS in pemetrexed-based chemotherapy was 7.81 months in the entire group. In the subgroup analysis, PFS was significantly longer in ALK-ROS1 positive arm when compared with the EGFR positive arm. Besides, PFS was also significantly longer in ALK-ROS1 positive patients who received pre-TKI pemetrexed-based chemotherapy. There were no statistically significant PFS differences between pre and post-TKI pemetrexed-based chemotherapy in EGFR mutation-positive arm. The comparison of the efficacy of post-TKI pemetrexed-based chemotherapy in the ALK-ROS1 mutation-positive subgroup could not be performed. ORR of

pemetrexed-based chemotherapy was found as 55%, 59.1% and 52.6% in the entire group, ALK-ROS1 positive subgroup, and EGFR positive subgroup, respectively.

In previous clinical trials, the median PFS in pemetrexed-based chemotherapy (allowed pemetrexed maintenance) was found between 5.5-6.9 months in treatment-naïve EGFR mutation-positive patients.^{6,7} In a phase 2 trial that compared the erlotinib and pemetrexed monotherapy as second-line treatment, median PFS was 3.9 months in pemetrexed arm, and there were no significant differences between the treatment groups.⁸ According to the results of the meta-analyses in EGFR mutation-positive patients who progressed after first-line TKI, median PFS and ORR were 5.09 months and 30.19% with pemetrexed-based combination regimens or pemetrexed monotherapy.⁹ The median PFS in patients treated with pemetrexed monotherapy was between

2.7 to 6.4 months and those treated with a combination of pemetrexed with platinum was also between 4.4 to 6.4 months.¹⁰⁻¹³ In our knowledge, our study is the first study that compared the efficacy of pemetrexed-based combination chemotherapy on the basis of pre or post-TKI usage. In our trial, median PFS in the entire group, pre-TKI, and post-TKI were 6.31, 6.01 and 6.83 months, respectively. In addition, PFS was not significantly different between the use of pre or post-TKI in pemetrexed-based chemotherapy. The results of our real-world study were consistent with the results of previous clinical trials. The importance of these results was the demonstration of an approximately six months long progression-free survival with pemetrexed-based chemotherapy, regardless of treatment-line in EGFR mutation-positive patients.

In the previous clinical trials that have been done in patients with ALK-rearrangement, median PFS in first-line pemetrexed-based chemotherapy was found between 7-8 months.^{14,15} In addition to PFS, ORR was between 25-45% with first-line pemetrexed-based chemotherapy. In patients who progressed after first-line crizotinib, median PFS was approximately 1.5 months with pemetrexed monotherapy.^{16,17} In addition to clinical trials, there are limited studies in the real world that evaluated pemetrexed-based chemotherapy in patients with ALK-rearrangement. In these trials, median PFS in front-line pemetrexed-based chemotherapy was between 6.6-9 months and ORR was between 25-44%.¹⁸⁻²¹ In addition to ALK mutation, the median PFS in patients with ROS-1 mutation who received first-line pemetrexed-based chemotherapy was between 6.8-7.8 months in retrospective small studies.²¹⁻²³ In our study, it was observed that patients with ALK-ROS1 mutation had longer PFS and high ORR as compared with previous trials. We think that this difference may be related to the small sample size and patient characteristics of our study.

Consistent with the findings of the previous studies, we demonstrated that the efficacy of pemetrexed-based chemotherapy was superior in patients with ALK mutation than EGFR mutation.^{19,22} Previously, Shaw et al. found that thymidylate synthase (TS) enzyme level was lower than the median TS value established in resected lung adenocarcinomas.²³ The superior efficacy of pemetrexed-based

chemotherapy in patients with ALK-rearrangement compared with others may be related to the low level of TS. However, the exact mechanism of this finding has yet not been established. Further research may be conducted to clarify the increase in the efficacy of pemetrexed in ALK mutation-positive lung cancer.

The retrospective design and the limited number of patients are the major limitations of the present study. Mainly, due to the very low number of patients who received post-TKI pemetrexed-based chemotherapy, we could not analyze the efficacy of post-TKI pemetrexed-based therapy in ALK-ROS1 mutation-positive arm.

In conclusion, it is now widely accepted that the primary treatment of advanced lung cancer with targetable driver mutations is targeted therapy. However, chemotherapy is still an important treatment option when drug resistance developed toward targeted therapeutic drugs during the course of the treatment. The results of this study demonstrated the efficacy of pemetrexed in the real world. According to the results of our study, pemetrexed-based therapy is still a good choice for the patients who progress after targeted therapy and also who are not suitable for another targeted therapeutic agent.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Burak Bilgin; **Design:** Burak Bilgin, Şebnem Yücel, Ülkü Yılmaz; **Control/Supervision:** Şebnem Yücel, Ülkü Yılmaz; **Data Collection and/or Processing:** Burak Bilgin, Şebnem Yücel; **Analysis and/or Interpretation:** Burak Bilgin; **Literature Review:** Burak Bilgin, Şebnem Yücel; **Writing the Article:** Burak Bilgin, Şebnem Yücel; **Critical Review:** Ülkü Yılmaz; **References and Fundings:** Burak Bilgin, Şebnem Yücel, Ülkü Yılmaz; **Materials:** Burak Bilgin.

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