Original Article

The correlation between pre-treatment CEA levels and the EGFR mutation status in advanced lung adenocarcinoma

ABSTRACT

Background: The discovery of the epidermal growth factor receptor (EGFR) mutation, especially in adenocarcinoma, has led to a major change in the treatment of non-small-cell lung cancer (NSCLC). This study investigated the relationship between the EGFR mutation status and the carcinoembryonic antigen (CEA) levels at the time of diagnosis.

Materials and Methods: A total of 102 patients with EGFR mutation and tested CEA levels were recruited for this study. Of the patients, 24 were EGFR mutants (23.5%), while 78 patients (76.5%) did not harbor any EGFR mutations.

Results: The CEA levels did not differ across groups. Additionally, the CEA levels were analyzed between female and male patients separately due to EGFR mutations; no difference was observed. When the CEA levels were categorized as positive or negative based on different cut-off values, such as 5 and 10 ng/ml, no statistical difference was found between groups.

Conclusion: In this study, no relationship between EGFR mutation and pre-treatment CEA levels was observed. Despite positive trials having shown a predictive value of CEA levels for EGFR mutation, more clinical trials are needed to elucidate the racial, clinical, and pathological differences of the study populations. Most studies have been located in the Far East, but new trials in Caucasian, African, and Hispanic populations are still lacking.

KEY WORDS: CEA, EGFR mutation, lung adenocarcinoma, non-small-cell lung cancer

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INTRODUCTION

Lung cancer is reported to be one of the most frequent causes of cancer-related deaths and the discovery of the epidermal growth factor receptor (EGFR) mutation, especially in adenocarcinoma, has led to a major change in the treatment of non-small-cell lung cancer (NSCLC).[1-3] EGFR mutations tend to be positive in female, non-smoker, and Asian patients.[4] An EGFR mutation is a key factor for small tyrosine kinase inhibitors (TKI). The mutations that are sensitive to TKI therapies are mainly distributed in exons 19 and 21.[5-7]

The carcinoembryonic antigen (CEA) plays a role in homophilic-heterophilic cell-to-cell adhesions, tumor growth, and differentiation. Elevated levels of CEA can be observed in NSCLC.[8] The EGFR pathway also can regulate CEA levels. Kobayashi *et al*.[9] reported that EGFR mutation can lead to an alteration in CEA levels. In lung cancer, especially in the adenocarcinoma subtype, elevated CEA levels have been reported to be between 35% and 60%.[10-16] EGFR mutation testing is an expensive and complicated method that can be non-affordable in some countries, and clinical factors predictive of EGFR mutations are still needed. This study investigated the relationship between the EGFR mutation status and the CEA levels of patients at the time of diagnosis.

MATERIALS AND METHODS

Patient selection

In this study, patient records between 2013 and 2018 were retrospectively analyzed, and 935 lung cancer records were retrospectively analyzed. The study included 102 patients who had CEA levels and EGFR mutation status. The patients who did not have elevated CEA levels at the time of diagnosis

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and were not eligible for EGFR mutation testing were excluded. The age, gender, smoking period, and stages of the patients were recorded. The CEA cut-off levels were determined as 5 and 10 mcg/dl.

CEA measurements

The CEA levels were analyzed with an enzyme immunoassay. According to the manufacturer's instructions, the normal CEA levels were 3.4 ng/ml in smokers and 4.3 ng/ml in non-smokers. Although the optimal cut-off in lung cancer cannot be estimated, different cut-off values were analyzed.

Statistical analysis

The association between pre-treatment EGFR mutation status, categorized CEA levels, and other clinical categorical parameters were evaluated with Pearson's Chi-square test. The numerical CEA levels, age, and cumulative smoking time of the patients were compared between EGFR groups with the Mann–Whitney *U* test. A *P* value <0.05 was determined to be statistically significant.

Ethics

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations.

RESULTS

Overall, 102 patients were evaluated in this study. Of the patients, 24 were EGFR mutants (23.5%), while 78 patients (76.5%) did not harbor any EGFR mutations. The non-EGFR group included eight anaplastic lymphoma kinase (ALK; 8.8%) mutation carriers and two ROS proto-oncogene-1 (ROS-1; 2%) mutation carriers. All EGFR mutations were observed in exons 19 and 21. Of the patients, 33 (32.4%) had low CEA levels, while 69 (67.6%) had higher CEA levels. The mean age of the EGFR positive and negative groups was 63 and 64, respectively ($p = 0.8$). No difference between groups was found in terms of smoking status or duration of smoking.

The CEA levels did not differ between the groups. Additionally, the CEA levels were analyzed between female and male patients separately due to EGFR mutations; no difference was observed. The patients' characteristics between groups are described in Table 1. When the CEA levels were categorized as positive or negative as determined by the different cut-off values of 5 and 10 ng/ml, no statistical difference was found between groups. Additionally, when the ALK and ROS-1 mutated patients were excluded, no difference was found between the CEA levels.

Overall survival

Fourteen patients who harbored EGFR mutation received anti-EGFR treatment (erlotinib). The median overall survival rate was 14 months in both the EGFR mutant and non-mutant groups ($p = 0.5$). The median overall survival was 33 months in the EGFR mutant patients who received erlotinib, while patients who did not receive this treatment had an overall survival rate of 14 months ($p = 0.125$). The survival rate according to the CEA levels was 29 and 14 months in normal and elevated groups, respectively ($p = 0.127$). The highest overall survival was among patients who had EGFR mutation and normal CEA levels, while the lowest survival was observed in patients who were EGFR negative and had low CEA levels. Although a numerical difference was seen in survival between these groups, no statistical difference was found [Table 2 and Figures 1 and 2].

DISCUSSION

This study retrospectively analyzed pre-treatment CEA levels for the prediction of the EGFR mutation. In this study, no relationship was found between the EGFR mutation and the CEA levels at the time of diagnosis. However, EGFR mutations vary in different ethnicities. While Asian patients frequently harbor the EGFR mutation, this rate decreases in the Caucasian population.[17] Different results could be found for the relationship between EGFR mutation and CEA levels in studies of different ethnic populations.

CEA and cytokeratin fragment (CYFRA) 21-1 levels have been analyzed in multiple studies. High CEA levels have been associated with adenocarcinoma histology. Additionally, the extended stage of the disease was related to high CEA levels.

Table 1: Patient characteristics due to EGFR mutation status

	EGFR positive (*n*=24)	EGFR negative (*n*=78)	*P*
Age	63	64	0.7
Gender: Male/Female	62/38%	80/20%	0.08
Smoking Patients	48%	72%	0.28
Median Smoking Duration (years/package)	18	33	0.17
CEA Levels: Median	8.5	10	0.59
Histology	All patients had adenocarcinoma histology		

Table 2: Overall survival according to EGFR mutation and CEA levels

	Median OS (months)	*P*
EGFR Mutation		
Negative	20	0.310
Positive	23	
Erlotinib		
Received	33	0.125
Not Received	14	
CEA		
Normal	29	0.127
Elevated	14	
EGFR Mutant		
Low CEA	33	0.409
EGFR Wild Type		
High CEA	11	

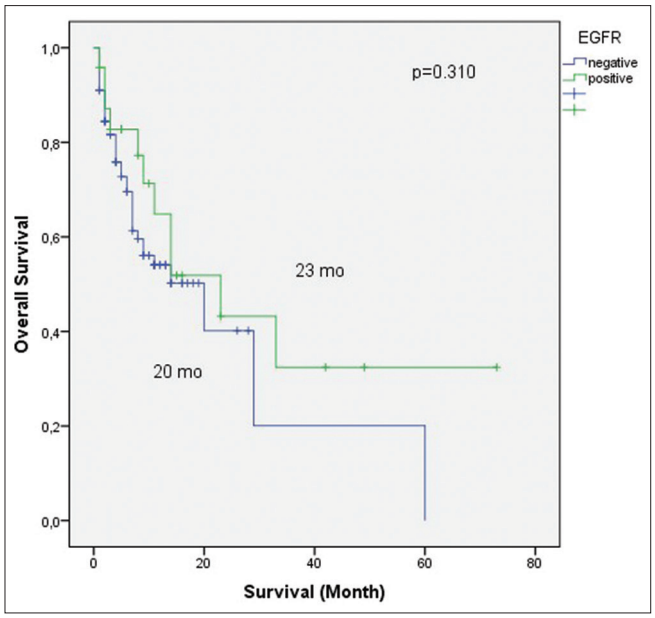

Figure 1: Overall survival according to EGFR mutation

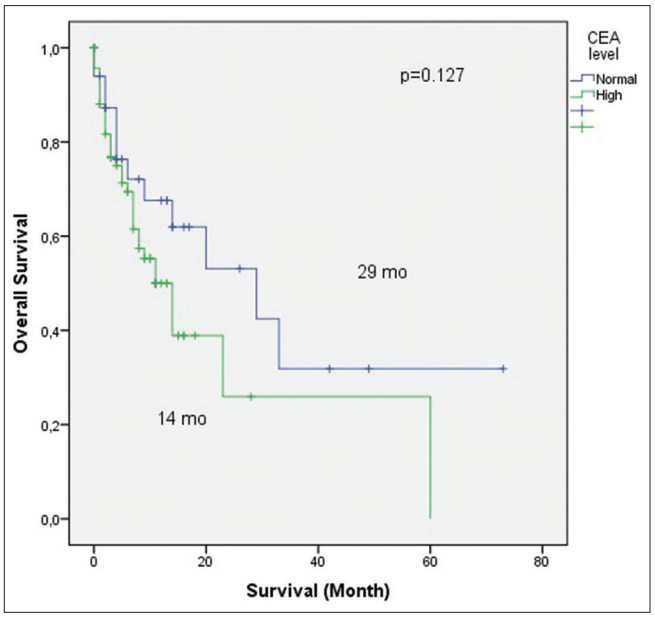

Figure 2: Overall survival according to CEA levels

Fiala *et al.*[18] found that high CEA levels were predictive of EGFR mutation status and were an indicator of poor prognosis with the treatment of erlotinib. In contrast to these findings, however, high CEA levels have also been reported as a good prognostic factor for anti-EGFR treatment; this has been hypothesized to be related to activated protein kinases (AKT) and signal transducer and activator of transcription 3 and 5 (STAT3/5) pathways.[19]

The elevation of CEA levels has also been reported as associated with greater EGFR mutation in patients. EGFR mutations were found to be 18.75%, 36.36%, and 62.5% with levels of CEA <5, 5 to 19, and ≥20 ng/ml, respectively. In this study, when the pre-treatment levels of CEA reached 20~49 ng/ml, the incidence of EGFR mutations was determined to be 85.7%. The specificity of CEA levels for EGFR mutations decreased above 50 ng/ml.[20]

In a previous small study, elevated levels of CEA were reported to be associated with EGFR mutations, not at the time of diagnosis but at the time of recurrence after surgery. Elevated levels of CEA were found more frequently in non-smoker female patients and were reported to have better disease control rate and progression-free survival (PFS). However, the utility of CEA levels to determine EGFR mutation was not seen in this article.[21]

In this study, no relationship between EGFR mutation and pre-treatment CEA levels was observed. Despite positive trials that show predictive value of CEA levels for EGFR mutation, more clinical trials are needed to elucidate the racial, clinical, and pathological differences of study populations. Most of the studies have been conducted in the Far East, and new trials in Caucasian, African, and Hispanic populations are still lacking.

Generally, higher CEA levels correlate with the tumor burden, which results in decreased survival in lung cancer.[22-24] In the present study, while the overall survival was consistent with the literature, no statistical difference was found between the groups. The lowest survival rate (11 months) was seen in EGFR-negative, high CEA-level patients.

This study had a retrospective design that led to some information about the patients being inaccessible. The high smoking rates in the EGFR mutant patients may have led to elevated CEA levels. Most of the patients in the EGFR mutant group were male, which, according to the authors' current knowledge, is not the specific population for EGFR mutation. However, this could not be demonstrated in this study. Additionally, an unknown Kirsten rat sarcoma (KRAS) mutation status may have affected CEA levels. The low access rates to anti-EGFR agents also made it impossible to determine PFS and overall survival.

CONCLUSION

As a result, this study found no relationship between pre-treatment CEA levels and EGFR mutation status. Although most of the articles published on the Asian population have shown this relationship, more studies are needed for Caucasian patients to evaluate the predictive value of pre-treatment CEA levels for EGFR mutation. As a result of this study, the decreased survival among patients who were EGFR negative and had elevated CEA levels may be a directive factor for clinicians regarding the prognosis of lung cancer patients.

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Conflicts of interest
There are no conflicts of interest.

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