THE ROLE OF SERUM CARCINOEMBRYONIC ANTIGEN TO PREDICT RESPONSE OF TREATMENT IN NON-SMALL CELL LUNG CANCER PATIENTS

Karsinoembriyonik Antijeninin Küçük Hücreli Dışı Akciğer Kanseri Hastalarında Tedavi Yanıtını Tahmin Etmedeki Rolü

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ABSTRACT

Objective: We aimed to determine tumor marker levels in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) at the time of diagnosis, to investigate the sensitivity and specificity of changes in Carcinoembryonic antigen (CEA) level in the assessment of treatment response along with the prognostic significance of this marker.

Material and Methods: The study included 100 patients with NSCLC diagnosed in our institution. Age, stage, histologic subtype, tumor marker levels at the time of diagnosis, the change in serum CEA levels and the association with treatment response were analyzed. The treatment responses of the patients were evaluated either clinical response or progressive disease.

Results: CEA level was stable or decreased in 86 (86%) clinical response, in contrary to elevation of CEA levels in 26 (74.3%) progressive response. The response to therapy and the change in CEA level were shown 86% ratio of sensitivity and 74.2% ratio of specificity in all patients regardless of baseline CEA levels. On the other hand, in patients with high baseline levels of CEA, sensitivity of the change in CEA level was 95% and specificity was 71.4%. Positive predictive value and negative predictive value were calculated as 90.5% and 65%, respectively.

Conclusion: Change of CEA levels were associated with treatment response in patients with NSCLC. Given that it can be readily measured in serum samples, serum CEA level is a beneficial marker in follow-up and treatment response monitorization of these patients. The baseline level of CEA was not a prognostic factor.

Keywords: *Carcinoembryonic Antigen; Non-Small Cell Lung Cancer; Prognosis*

ÖZET

Amaç: Lokal ileri veya metastatik küçük hücreli dışı akciğer kanseri (KHDAK) tanılı hastalarda tanı anında tümör belirteç düzeylerini belirlemeyi, tedavi yanıtının değerlendirilmesinde Karsinoembriyonik antijen (CEA) düzeyindeki değişikliklerin duyarlılığını ve özgüllüğünü prognostik önemi ile birlikte değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmaya 100 KHDAK tanılı hasta dahil edildi. Tanı anındaki yaş, evre, histolojik alt tip, tümör belirteçleri, serum CEA seviyelerindeki değişim ve tedavi yanıtı ile ilişkisi analiz edildi. Hastaların tedavi yanıtları, klinik yanıt alındı veya alınmadı şeklinde değerlendirildi.

Bulgular: CEA düzeyi 26 (%74,3) progresif yanıtta yükselmesine karşın 86 (%86) klinik yanıtta stabil veya azalmıştı. Tedaviye yanıt ve CEA düzeyindeki değişiklik, başlangıç CEA düzeylerinden bağımsız olarak tüm hastalarda %86 duyarlılık oranı ve %74,2 özgüllük oranı göstermekteydi. Öte yandan, CEA başlangıç düzeyi yüksek olan hastalarda, CEA düzeyindeki değişikliğin duyarlılığı %95 ve özgüllüğü %71,4 idi. Pozitif prediktif değer ve negatif prediktif değer sırasıyla %90,5 ve %65 olarak hesaplandı.

Sonuç: KHDAK hastalarında CEA düzeylerindeki değişiklik tedavi yanıtı ile ilişkilendirilmiştir. Serum örneklerinde kolaylıkla ölçülebildiği düşünüldüğünde, serum CEA düzeyi bu hastaların takip ve tedaviye yanıt monitörizasyonunda yararlı bir belirteçtir. CEA'nın başlangıç seviyesi prognostik bir faktör olarak belirlenmemiştir.

Anahtar Kelimeler: *Karsinoembriyonik Antijen; Küçük Hücreli Dışı Akciğer Kanseri; Prognoz*

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INTRODUCTION

Lung cancer, the first leading cause of cancer death in the world, is generally diagnosed at advanced stages, with a 5-year survival rate of 18% (1). Non-small cell lung cancer (NSCLC) represents about 85% of all lung cancers (2). Concurrent radiation therapy and tyrosine kinase receptor inhibitors may be preferred in addition systemic chemotherapy in patients with advanced-stage NSCLC. Improved response rates have also been reported following the introduction of angiogenesis inhibitors, epidermal growth factor receptor inhibitors in selected patient groups (3).

Objective treatment response assessment in lung cancer is difficult, expensive and time-consuming due to the lack of measurable lesions on computed tomography (CT) in some patients as well as the presence of factors that interfere with radiologic assessment such as atelectasis, pleural effusion. Thus, easier and cheaper methods for monitoring treatment response have been investigated. Serum tumor markers are among the candidates for this purpose (4). To date, several serum tumor markers have been studied in lung cancer patients including carcinoembryonic antigen (CEA), cytokeratin 19 fragments 21-1 (CYFRA 21-1), carbohydrate antigen 19-9 (CA19-9), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA-125), and squamous cell carcinoma antigen (SCC-Ag) (5). Herein, we aimed to determine tumor marker levels in patients with locally advanced or metastatic NSCLC at the time of diagnosis, to investigate the sensitivity and specificity of changes in CEA level in the assessment of treatment response along with the prognostic significance of this marker.

MATERIAL AND METHOD

A total of 100 patients who were diagnosed at our center between 2013 and 2018 with stage III and IV NSCLC were included. One patient was evaluated for treatment response in more than one therapy line and 135 treatment responses were evaluated. The inclusion criteria were as follows: Histologically or cytologically confirmed NSCLC patients of locally advanced, unresectable or metastatic disease with ≥1 measurable carcinoma focus, administration of ≥2 cycles of chemotherapy. Only patients with available serum tumor markers from medical records were included. Patients with history of previous malignancy other than NSCLC, those with malignant disease such as colorectal tumors leading to elevated CEA or with disease such as colitis and pancreatitis were excluded. Date of diagnosis, age, gender, stage, histologic subtype, smoking status, treatment regimens, date of initiation of therapy, date of disease progression and treatment responses were collected from patients' medical records retrospectively. Patients received maximum four-line therapies and treatment regimens consisted of conventional chemotherapy agents and tyrosine kinase receptor inhibitors (TKI). Staging was done according to the American Joint Committee on Cancer (AJCC) seventh edition staging system. At least after 2 cycles of chemotherapy, radiological response was assessed by CT or Positron emission computed tomography (PET CT) based on RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Response to treatment was categorized as progressive disease (PD), partial response (PR), complete response (CR) or stable disease (SD). The study was approved by the Local Ethics Committee (permit: 242/2018).

Blood samples were collected from patients prior to treatment and at least after 2 cycles of chemotherapy. CEA, CA 19-9, CA125 and CA15-3 were measured as tumor markers. Tumor marker levels were measured by electrochemiluminescence immunoassay (ECLIA) using a Roche cobas e601 modular analyzer (Roche Diagnostics, Germany). Serum levels of CEA, CA19-9, CA125 and CA15-3 were considered elevated when the values were ≥6.5 ng/mL, ≥39 U/mL, ≥35 U/mL and ≥25 U/mL, respectively. These tumor marker cut-off values were based on reference values of the kits used on the dates specified in our hospital.

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago) Chi-square ($\chi 2$) test or Fisher's exact test was used to assess the association of CEA level with clinicopathologic characteristics and treatment response. Sensitivity and specificity for the CEA level changes were calculated. The overall survival (OS) was defined as the duration from the date of diagnosis to the date of the last follow-up or death. Kaplan-Meier method was used for survival analysis. Log-rank test was used to compare and analyze the

survival data. p<0.05 was considered statistically significant.

RESULTS

Seventy-four (74%) patients were male and the median age was 57.5 (range 23-83) years. Thirty-two (32%) patients had locally advanced and inoperable disease, while the remaining 68 (68%) had metastatic disease. Most patients (73%, n=73) had adenocarcinoma. Twenty-one (21%) of the patients had never smoked. Sixty-six (66%) patients received chemotherapy and 34 (34%) received TKI. Baseline patients and tumor characteristics were shown in Table 1.

CEA (61.4%; 54/88), CA15-3 (74.4%; 29/39) and CA125 (79.1%; 34/43) levels were found to be elevated in the majority of the patients of whom these markers were measured, while elevation in CA19-9 (28.6%; 20/70) level was less common at the time of diagnosis. CEA levels were significantly higher in adenocarcinoma subtype (p<0.001). There was no correlation between CEA level and age (p=0.305), but higher levels were found in the advanced stage (p=0.015) and male sex (p=0.021) (Table 2).

Of 135 evaluated responses; clinical response was

Table 1. Baseline patients and tumor characteristics

N=100	Median (min-max)	Patients (n)	(%)
Age (years)	57.5 (23-83)		
Gender			
Women		26	26
Men		74	74
Smoking history			
Smoker		79	79
Non-smoker		21	21
Clinical Stage			
III		32	32
IV		68	68
Histology			
Adenocarcinoma		73	73
Squamous cell		25	25
Others		2	2
Treatment regimens			
Chemotherapy		66	66
TKI		34	34
Baseline CEA	16.2 (1.53-1000)		
Baseline CA19-9	16 (0.6-1611)		
Baseline CA125	70 (7-1111)		
Baseline CA 15-3	42 (8.4-895)		
Tumor response†			
Evaluation (N=135)			
Chemotherapy		95	70.4
TKI		40	29.6
Complete/Partial/Stable Disease		100	74.1
Progressive Disease		35	25.9

†Treatment response evaluation was done more than once for some patients.
TKI= tyrosine kinase receptor inhibitors, CEA = Carcinoembryonic antigen, CA19-9 = Carbohydrate antigen 19-9, CA125 = Carbohydrate antigen 125, CA15-3 = Carbohydrate antigen 15-3

Bozok Tıp Derg 2020;11(1):6-12
Bozok Med J 2020;11(1):6-12

Table 2. Comparison of baseline CEA level with clinicopathological characteristics

	Baseline CEA		
	High	**Normal**	**p value**
Age (years)			0.305
<70	46(85.2)	32(94.1)	
≥70	8(14.8)	2(5.9)	
Gender (n%)			0.021
Men	38(70.4)	31(91.2)	
Women	16(29.6)	3(8.8)	
Smoking history (n%)			0.071
Smoker	41(75.9)	31(91.2)	
Non-smoker	13(24.1)	3(8.8)	
Clinical Stage (n%)			0.015
III	12(22.2)	16(47.1)	
IV	42(77.8)	18(52.9)	
Histology (n%)			<0.001
Adenocarcinoma	49(90.7)	14(41.2)	
Others	5(9.3)	20(58.8)	

CEA = Carcinoembryonic antigen

achieved in 100 (74.1%) and disease progression was detected in 35 (25.9%). CEA level was stable or decreased in 86 (86%) clinical response on the contrary of elevation of CEA levels in 26 (74.3%) of the 35 cases with progressive disease. The sensitivity and specificity of serum CEA level in predicting the response to therapy was 86% and 74.2%, respectively and regardless of the pre-treatment CEA levels. More importantly, the sensitivity of serum CEA level was higher (95%) in patients with high pre-treatment CEA levels, with a specificity of 71.4%. The positive predictive (PPV) and negative predictive value (NPV) were calculated as 90.5% and 65%, respectively. In the TKI subgroup, serum CEA level predicted the response to therapy with 88.5% ratio of sensitivity and 78.6% ratio of specificity. PPV and NPV for TKI therapy were calculated as 88.5% and 78.6%, respectively.

The baseline level of CEA was not a prognostic factor in neither group (p=0.825 and p= 0.687, respectively) (Figure 1). The median OS was 16.5 months for all the patients and for the TKI group (95% CI, 8.83-24.23, 95% CI, 9.04-25.01, respectively). The median OS was 17.5 months (95% CI, 6.08-28.8) for the patients with high pre-treatment CEA levels and 16.5 months (95% CI, 13.78-19.28) for the patients with low pre-treatment CEA levels.

DISCUSSION

In this study, we investigated the role of serum CEA level in the treatment response assessment and its effect on OS. Our results suggest that serum CEA level could predict to response to therapy regardless of the pre-treatment CEA levels. More importantly, the sensitivity of serum CEA level was higher in patients with high pre-treatment CEA levels. However, baseline level of CEA was not a prognostic factor.

Imaging techniques are routinely used in NSCLC patients to monitor response to chemotherapy. However, in daily clinical practice, due to use of different methods in evaluation of response to new agents, difficulties in target lesion selection and early detection of progressive disease with imaging modalities not being cost-effective, a search is ongoing to find alternative methods (6,7). We investigated the efficiency of serum tumor markers for this purpose.

Tumor markers may be elevated in cancer patients with progressive disease and/or recurrence and a significant decrease in serum tumor marker levels has been

demonstrated in case of partial or complete response (8). Among the markers studied to date, CEA may be a potential predictive marker for early evaluation of response to therapy in NSCLC (9). Chiu et al. assessed serum CEA, CA125 and CA19-9 levels in 89 gefitinib treated patients with adenocarcinoma and baseline levels were high in 71, 72 and 40 patients, respectively. The most common tumor type was adenocarcinoma and the authors observed a significant correlation between radiologic response and tumor marker levels after four weeks of treatment (10). Liu et al. have also reported that CEA level decreased in almost 85% of the patients with partial response following 2 courses of chemotherapy, while CEA level was elevated up to 60% of the patients with progressive disease (11). We observed that CEA and CA125 were elevated in the majority of the patients and CA19-9 were also elevated in some patients. The most common histological subtype was adenocarcinoma similar to the studies. CEA level was stable or decreased in 86 (86%) with clinical response on the contrary of elevation of CEA levels in 74% with progressive response. The change in CEA level was consistent with treatment response, supporting previous studies.

In our study, serum CEA level had 86% sensitivity and 74% specificity in predicting the response to therapy regardless of baseline CEA levels. On the other hand, in patients with high baseline levels of CEA, the sensitivity increased to 95% with a slight decrease in the specificity (71.4%). The PPV and NPV were calculated as 90.5% and 65%, respectively. The sensitivity and specificity of CEA in monitorization of response to therapy varies in the literature and there is also no established cut-off level. Arrieta et al. have documented the correlation of serum CEA levels with response to therapy as a 14% decrease in CEA level showed 90% sensitivity and specificity for clinical response (12). On the other hand, 18% increase in CEA level had 85% sensitivity and a very low specificity (15%) for progressive disease prediction. A 20% decrease in serum CEA level has been associated with a lower sensitivity (55%) and moderate specificity (75%) in predicting clinical response in another study reporting that PPV was 63% and NPV was 68% (4). In another study of patients with resectable NSCLC and found a significant decrease in serum CEA levels in patients with partial response to neoadjuvant chemotherapy. Objective response with a 60% reduction in CEA level had 82.8% sensitivity and 69.2% specificity (13).

Although the prognostic value of CEA is well known in colorectal tumors, its prognostic value in NSCLC is controversial (14-16). Kim at al. have found that patients with high baseline CEA level had better treatment response and longer progression-free

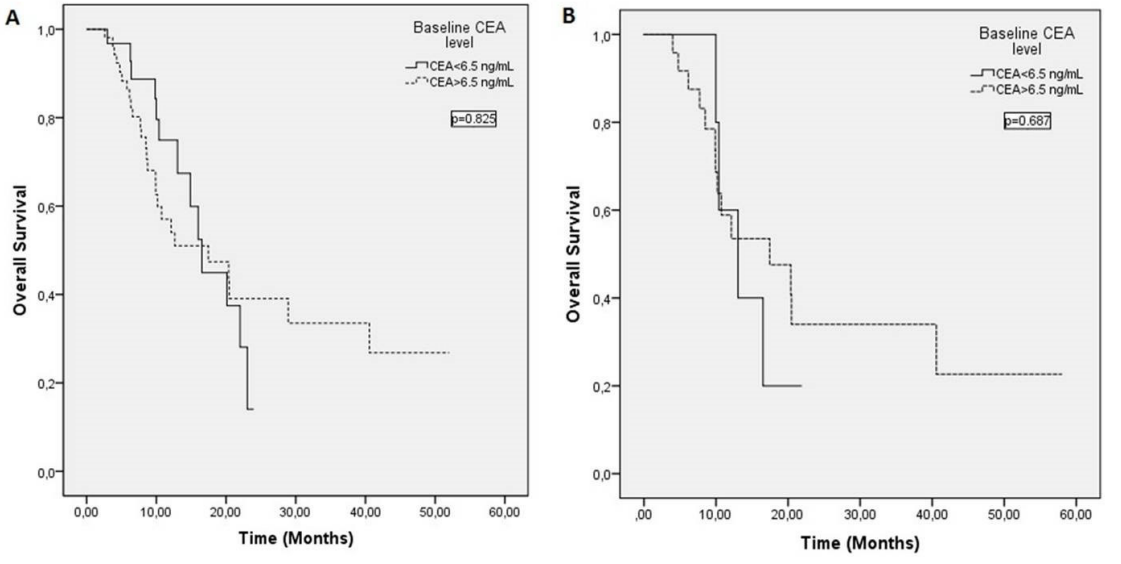

Figure 1. The correlation between overall survival and the baseline serum CEA levels for all the patients (A) and for the patients whose received tyrosine kinase receptor inhibitors (B)

survival (PFS) in erlotinib or gefitinib treated NSCLC patients (17). Jin et al. have also reported that CEA can be used in the treatment response assessment, baseline CEA level and CEA level alteration with treatment are important predictive markers for OS (18). In another study consisted of 140 patients treated with TKI, baseline CEA value was not correlated with survival, but patients who had CEA response to treatment had a longer PFS and OS (19). Similarly, Ardizzoni et al. have found no correlation between baseline CEA level and OS, however, patients that had a decrease in CEA levels by treatment had better survival (4). Liu et al. have not found any association between alterations in CEA levels and survival (11). We did not find any correlation between baseline CEA levels and survival or between decrease in CEA level and survival for all the patients and for the TKI group.

Retrospective design and low number of patients are among the limitations of our study. However, we think that this study provides useful preliminary information regarding the potential use of serum tumor markers in evaluation of response to therapy in NSCLC.

CONCLUSION

In conclusion, change of serum CEA level is associated with treatment response in patients with NSCLC. Given that it can be readily measured in serum samples, serum CEA level is a beneficial marker in follow-up and treatment response monitorization of these patients. However, it should be noted that baseline CEA does not seem to be prognostic factor in NSCLC.

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