To cite this article: Ercaliskan A, Turna Z. Background of the need for targeted therapy options and platinum-based therapy responses in EGFR and ALK-mutated lung adenocarcinoma. Turk J Clin Lab 2023; 3: 645-650

Research Article

Background of the need for targeted therapy options and platinum-based therapy responses in EGFR and ALK-mutated lung adenocarcinoma

EGFR ve ALK mutasyonu taşiyan akciğer adenokarsinomlarinda platin bazli tedavi yanitlari ve hedefe yönelik tedavi ihtiyacinin arka plani

Abdulkadir Ercaliskan*[1], Zeynep Turna[2]

[1]Division of Hematology, Department of Internal Medicine, Ataturk State Hospital, Duzce, Turkey, [2]Division of Oncology, Department of Internal Medicine, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey.

Abstract

Aim: To present our experience in EGFR and EML-4/ALK-mutated lung adenocarcinoma patients.

Material and Methods: 2580 patients were retrospectively evaluated. Only stage-4 lung adenocarcinoma patients who treated with at least 2-cycles of platinum-based regimens at frontline were included.

Results: Among 105 eligible patients, EGFR and EML-4/ALK mutations was detected in 14 and 4 patients. 75 were wild-type for both mutations. The median age and age of diagnose was 61 and 58.5, respectively. 81% was male and 78% was smoker. EGFR and EML-4/ALK-mutant patients were predominantly female and non-smoker (EGFR; p=0.025 and 0.002, EML-4/ALK; p=0.003 and 0.012,respectively). EML-4/ALK- mutant patients were significantly younger than EML-4/ALK wild-type (p=0.02) (Table 1). EGFR exon-19, 20 and 21 mutations were associated with liver, bone and pleural metastases, respectively (p=0.046, 0.05 and 0.035,respectively). After firstline platinum-based chemotherapy, complete remission (CR) and partial remission (PR) rates were 4.7% and 24.6%,respectively. Concurrent radiotherapy and absence of bone metastases at diagnosis were significant factors influencing firstline platinum-based therapy responses (p=0.004 and p=0.046,respectively). EGFR or EML-4/ALK mutation status didn't show significant difference in terms of platinum-based treatment response (p=0.933 and 0.184,respectively). Median progression-free survival (PFS) was 10 months. The observed effect of concurrent radiotherapy and the presence of bone metastases on treatment response didn't reflected in the PFS results (p=0.079 and 0.285,respectively).

Conclusion: The presence of EGFR and ALK mutations does not effect the treatment response of platinum-based regimens. The association of EGFR exon subsets with metastasis points is worth investigating.

Keywords: EGFR, EML-4/ALK, ALK, platinum, lung adenocarcinoma

Corresponding Author*: Abdülkadir Erçalışkan Düzce, Atatürk State Hospital, Department of Internal Medicine, Division of Hematology, Düzce, Turkey
Orcid: 0000-0002-1795-5773
Email: drercaliskan@gmail.com
Doi: 10.18663/tjcl.1346853
Recevied: 20.07.2023 accepted: 27.09.2023

TJCL Volume 14 Number 3 p: 645-650

Öz

Amaç: EGFR ve EML-4/ALK mutasyonlu akciğer adenokarsinomu hastalarındaki deneyimlerimizi sunmak.

Gereç ve Yöntemler: 2580 hasta retrospektif olarak değerlendirildi. Çalışmaya yalnızca evre 4 akciğer adenokarsinomu olup ilk sıra en az 2 siklus platin bazlı rejimlerle tedavi edilen hastalar dahil edilmiştir.

Bulgular: Çalışmaya uygun 105 vakanın 14'ü EGFR, 4'ü EML-4/ALK mutant iken 75 vaka her iki mutasyonu da taşımıyordu. Medyan yaş ve tanı yaşı sırasıyla 61 ve 58.5 idi. %81'i erkekti ve %78'i sigara içiyordu. EGFR ve EML-4/ALK-mutant hastalar ağırlıklı olarak kadındı ve sigara içmiyordu (sırasıyla EGFR; p=0.025 ve 0.002, EML-4/ALK; p=0.003 ve 0.012). EML-4/ALK-mutant hastalar, bu mutasyonu taşımayanlara göre daha gençti (p=0,02) (Tablo 1). EGFR ekson-19, 20 ve 21 mutasyonları sırasıyla karaciğer, kemik ve plevral metastazlarla ilişkiliydi (sırasıyla p=0.046,

0.05 ve 0.035). Birinci basamak platin bazlı kemoterapiden sonra tam remisyon ve kısmi yanıt oranları sırasıyla %4,7 ve %24,6 idi. Eşzamanlı radyoterapi ve tanı sırasında kemik metastazlarının olmaması birinci basamak platin bazlı tedavi yanıtlarını etkileyen faktörlerdi (sırasıyla p=0.004 ve p=0.046). EGFR veya EML-4/ALK mutasyon durumu platin bazlı tedavi yanıtı açısından anlamlı fark göstermemiştir (sırasıyla p=0,933 ve 0,184). Medyan progresyonsuz sağkalım 10 ay iken eşzamanlı radyoterapi ve kemik metastazının tedavi yanıtı üzerinde gözlenen etkisi PFS sonuçlarına yansımamıştır (sırasıyla p=0,079 ve 0,285).

Sonuçlar: EGFR ve ALK mutasyonlarının varlığı, platin bazlı rejimlerin tedavi yanıtını etkilememektedir. EGFR ekson alt gruplarının metastaz noktaları ile ilişkisi araştırılması gereken bir nokta olarak saptanmıştır.

Anahtar Kelimeler: EGFR, EML-4/ALK, ALK, platin, akciğer adenokarsinomu.

Introduction

Primary lung cancer is the second most common malignancy after non-melanoma skin cancer and is the most common cause of malignancy related death. Non-small cell lung cancers constitute 80-90% of primary lung cancers and due to the decrease in tobacco use in recent years, the frequency of squamous cell type has decreased while the adenocarcinoma type has become dominant [1]. Frontline platinum-based therapy response rates for lung adenocarcinoma have been reported to range from 30 to 40%. [2]. To increase these low response rates, EGFR and ALK gene mutations have emerged as important focal points in the development of targeted therapies.

Increased tyrosine kinase activity resulting from mutations effecting the tyrosine kinase domain of EGFR and inversion of the short arm of the chromosome 2, which causes the fusion of the ALK gene with the EML-4 gene, play an important role in the etiopathogenesis of non-small cell lung cancer. Therefore, current guidelines recommend routine screening of these genes regardless of the clinical status [1,3].

In this study, based on the rarity of these mutations and studies with limited number of patients, we aimed to present our single center experience and make a contribution to the literature.

Material and Methods

2580 lung cancer patients who applied to our clinic between 2007 – 2016 were retrospectively evaluated for the study. Only stage 4 lung adenocarcinoma patients who treated with at least 2 cycles of platinum-based regimens as firstline therapy and investigated for EGFR Exon 18-19-20-21 mutations and/or the EML-4/ALK transfusion gene were included in the study. Patients treated with regimens other than platinum-based or without interim and/or end-of-treatment PET-CT imagining results were excluded. 12 patients were negative for EGFR mutations but their ALK mutation status was unknown. These patients also excluded from EGFR and EML-4/ALK wild-type group during statistical analysis.

The presence of activating mutations of the EGFR gene was investigated with the Enterogen EGFR Mutation Analysis Kit in the ABI7500 Real-time PCR device after DNA isolation from the slides of the tumor tissue. The exon 18 codon 719 region, exon 19 deletions, exon 20 insertions and codon 768 and 790 regions, exon 21 codon 858 and 861 regions of the EGFR gene were analyzed. The presence of EML-4/ALK gene translocation was examined immunohistochemically using CST D5F3 antibody. FISH analysis were also performed using the FDA-approved Abbott-Vysis LSI ALK Break Apart Rearrangement probe.

In evaluation of treatment response, evaluation was made according to RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) criteria for computed tomography. PERCIST (Positron Emission Tomography Response Criteria In Solid Tumors) criteria were used for response evaluations with PET-CT. In the light of these criteria, patients who showed complete remission and partial remission after firstline treatment were considered to have responded to treatment. Patients with stable disease and progression were considered unresponsive to treatment.

While evaluating the findings obtained in the study, SPSS 21.0 statistical package program was used for statistical analysis. Pearson Chi-Square test and Fisher Exact test were used to compare qualitative data. The effect of risk factors on survival was analyzed by Kaplan-Meier and Log-rank tests. The results were evaluated at the 95% confidence interval, at the $p<0.05$ significance level.

This study is approved by Istanbul University Clinical Research Ethics Committee with the decision numbered 83045809/604.01/02.381409 dated 3 December 2015 and conducted in accordance with the Helsinki Principles Declaration.

Results

Among 105 eligible patients, 14 patients harbored EGFR gene mutations while EML-4/ALK transfusion was detected in 4 patients. 75 patients were wild-type for both mutations. Median age of entire cohort was 61 while median age of diagnose was 58.5. 81% was male and 78% was smoker. The most frequent metastasis sites were bone (38%), brain (35%) and contralateral lung (32%) (Table 1).

Table 1. Demographic and clinical results (WT/WT: Wild-type for EGFR and EML4/ALK mutations). All p values belong to the comparisons of the cases carrying gene mutations with the WT/WT group.

		Total Cohort (n=105)	*EGFR* (n=14)		*ALK* (n=4)		WT/WT (n=75)
				p		p	
Age (y)		61	60	0,79	48	**0,026**	61
Age at Diagnosis (y)		58,5	58,5	0,93	47	**0,028**	60
Gender (n)	F	20	6	**0,025**	3	**0,020**	10
	M	85	8		1		65
Tobacco Use (n)		82	6	**0,002**	1	**0,037**	65
Metastasis Sites (n)							
Brain		37	2	0,06	2	0,40	28
Bone		40	7	0,24	3	0,13	25
Liver		8	2	0,29	1	0,31	5
Pleura		12	3	0,2	0	0,56	9
Contralateral Lung		34	7	0,11	1	0,57	23
Soft Tissue		4	2	0,51	0	0,87	2
Adrenal Gland		19	1	0,44	1	0,56	14

EGFR and EML-4/ALK mutant patients were predominantly female and non-smoker compared to wild-type patients (EGFR; p=0.025 and 0.002, EML-4/ALK; p=0.003 and 0.012, respectively). Additionally, EML-4/ALK mutant patients were significantly younger than EML-4/ALK wild-type (p=0.02) (Table 1). Although metastasis sites did not differ according to EGFR mutation status, when subgroup analysis was performed, exon 19, 20 and 21 mutations significantly appeared to be associated with liver, bone and pleural metastases, respectively (p=0.046, 0.05 and 0.035, respectively).

After firstline platinum-based chemotherapy, complete remission (CR) and partial remission (PR) rates were 4.7% and 24.6%, respectively. Stable disease status was observed in 4.7% while 66% of patients showed progression. Concurrent radiotherapy (RT) and absence of bone metastases at diagnosis were statistically significant factors influencing firstline platinum-based therapy responses. Concurrent radiotherapy with platinum based chemotherapy (n=35) showed significantly superior treatment response rates comparing patients who did not recieve radiotherapy (p=0.004). Relaps rates of patients with and without bone metastasis were %77.5 and. %58.5 after platinum based therapy, respectively (p=0.046). EGFR or EML-4/ALK gene mutation status did not able to show any significant difference in terms of platinum-based treatment response (p=0.933 and 0.184, respectively). The effect of EGFR exon mutations on treatment response or survival results did not performed due to low numbered subgroups.

Median progression-free survival (PFS) duration of entire cohort was 10 months. Median PFS durations of EGFR, EML-4/ALK and WT/WT groups were also comparable which were 10.8, 12 and 10.2 months, respectively (p=0.506) (Figure 1). The observed effect of concurrent radiotherapy and the presence of bone metastases on treatment response is not reflected in the PFS results (p=0.079 and 0.285, respectively). Brain metastasectomy was performed in 8 (21.6%) of 37 cases with brain metastases and no positive effect was detected in terms of PFS and treatment response rates (p=0.127 and p=0.465). Estimated overall survival (OS) rate of entire cohort was 17% at first year.

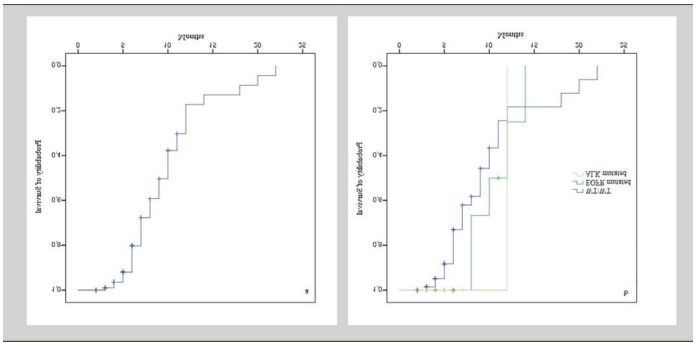

Figure 1. Cumulative PFS of entire cohort (a) and mutation groups (b).

Discussion

Lung cancer is still among the most common cancers but with the decrease in tobacco use and the addition of targeted therapy agents to conventional chemotherapy regimens, a halving of incidence and mortality rates has been observed in the last two decades [12]. As the details of the cancer development process are clarified, new possibilities for treatments emerge. Point mutations in exon 18 and 21, Exon 19 deletion and Exon 20 insertion of the EGFR gene effect the receptor tyrosine kinase domain of the transmembrane cell receptor protein. Similarly, translocation of the ALK gene on the short arm of chromosome 2 with the EML-4 gene causes an increase in intracellular tyrosine kinase activity and this pathway plays a critical role in cancer pathogenesis. Targeted therapies for EGFR and ALK genes, which have been shown to be important in lung non-small cell cancer, are among the most important developments in this regard.

Frequencies of EGFR and EML-4/ALK transfusion gene mutations in lung adenocarcinoma were reported as 10-20% and 2-5%, respectively [1]. Patients harbouring these mutations are presenting a different clinical profile compared to wild types. Most

studies showed that, EGFR and EML-4/ALK-mutated lung adenocarcinoma patients are mostly non-smoker females and also EML-4/ALK positive patients are significantly younger [4-6,7]. Results of our cohort were consistent with these findings.

In our study, EGFR mutant patients were unable present significant difference regarding response to platinum-based chemotherapy, PFS or OS comparing EGFR wild-type patients. The only significant factors improving platinum-based treatment results were concomittant RT and absence of bone metastasis at diagnose (p=0.004 and 0.046, respectively). Also some other studies evaluating platinum-based chemotherapy response from the perspective of EGFR gene mutation also declared ~30% treatment response, but no statistically significant difference was found in treatment response, PFS and OS between mutated and wild-type patients [13-15].

In the study published by Capuzzo et al. [2], 185 cases were examined and EGFR gene mutations were found in 24 cases (15 Exon 19 mutated, 2 Exon 20 mutated and 7 Exon 21 mutated). In patients who received platinum-based chemotherapy as frontline therapy, the response rates were 37% vs. 32.8% in EGFR-mutated and wild-type group, respectively (p=0.6). PFS and OS durations of EGFR-mutated and wild-type groups were also comparable (PFS: 8.1 vs. 4.1 mo., p=0.1; OS: 28.5 vs. 14.8 mo., p=0.07, respectively). But when EGFR subgroups were examined, it was observed that only patients with Exon 19 mutations responded to platinum-based chemotherapy (46.6%), while no treatment response was obtained in Exon 20 and 21 groups (p=0,02) [2].

In another article evaluating 162 lung adenocarcinoma patients [8], of which 40 were EGFR-mutated, platinum-based frontline therapy responses were comparable between EGFR- mutated and wild-type groups (43.5% vs. 23.9%, p=0.072). PFS and OS durations of EGFR- mutated and wild-type patients were also did not able to show significant difference between groups (p=0.69 and p=0.069, respectively). In this study only 9 patients were carrying classical EGFR mutations (exon 18, 19 and 21 mutations) while remaining 31 patients were positive for other EGFR mutations. Subanalysis of classical EGFR-mutated patients showed similar PFS duration (p=0.81) but better platinum-based therapy response (p=0.021) and improved OS duration (p=0.028) comparing wild-type patients. Although the small number of patients, the presence of EGFR gene mutation was declared as an independent favorable prognostic factor for platinum-based treatment response and overall survival [8].

EGFR gene mutation was found to be associated with brain, bone and pleural metastases in the REASON study [5] from Germany, which consisted of 432 EGFR gene mutation-positive cases. We also found a possible correlation between Exon 19, 20 and 21 mutations with liver, bone and pleural metastases, respectively. However, it was impossible to make a definitive interpretation due to the insufficient number of patients.

The presence of EML-4/ALK transfusion stands out as a negative factor for patients. In the study of Mayo Clinic [6], 266 EML-4/ALK negative non-small cell lung cancer cases compared to 34 EML-4/ALK-mutated patients and EML-4/ALK positivity declared as a negative predictive factor for progression/relapse-free survival [6]. Koh et al. [9] examined 221 lung adenocarcinoma patients, of which 45 were harboring EML-4/ALK transfusion and

46 were EGFR mutants, 170 cases were treated with platinum-based chemotherapy in frontline therapy. The treatment response rates were 18.8% in the EML-4/ALK group, 37.5% in the EGFR group and 40.4% in the EGFR and EML-4/ALK wild-type group (p=0.091). Progression-free survival durations were 6.2, 5.4 and 7.3 months, respectively (p=0.348). In patients treated with tyrosine kinase inhibitors (TKIs), the treatment response rate reached to 50% and PFS duration improved to 19.6 months in EGFR group. Due to low response rate to

platinum-based chemotherapy, EML-4/ALK transfusion gene positivity was declared as a poor prognostic factor [9].

Shaw et al. [7] obtained comparable results in response rates to platinum-based treatment in a cohort consisted of 19 EML-4/ALK positive, 31 EGFR positive and 91 WT/WT patients. But as expected, EGFR-mutated group's frontline TKI response rate was significantly superior than EML-4/ALK and WT/WT groups ($p<0.001$). PFS duration of EGFR group after TKI treatment was 16 months which was significantly longer than EML- 4/ALK-mutated (5 months) and WT/WT patients (6 months) ($p=0.004$). The presence of EML- 4/ALK transfusion gene was strongly related to TKI resistance [7].

Current guidelines recommend TKIs and ALK inhibitors as first-line therapy for patients with these mutations [1,3]. Although additional 20% increase in firstline therapy responses and approximately 12 months of PFS with targeted therapies for EGFR and ALK mutations, this improvement was not reflected in overall survival results.

First generation TKIs, gefitinib and erlotinib, were unable to show significant OS benefit with over platinum-based regimens but OR and PFS rates were significantly improved [1]. In the light of these results, and with their safe use even in patients with low performance scores, TKIs have become the backbone of EGFR-mutated lung adenocarcinoma patients. Following these agents, afatinib and dacomitinib emerged to the market as second generation TKIs. Osimertinib, third-generetion TKI, proved itself in the FLAURA study [11] with its PFS contribution against 1st generation TKIs and its superior response results in cases with CNS metastasis. Moreover, with the statistically significant contribution to OS (38.6 vs 31.8 months, $p=0.046$), the current guidelines are recommending asimertinib as preferred therapy in firstline treatment of patients with sensitizing EGFR mutations [1,3]. Crizotinib was the first targeted therapy improving OR and PFS rates of EML-4/ALK rearranged patients comparing platinum-based therapies. Ensuing ALK inhibitors, ceritinib, alectinib and brigatinib took these results to an even better point. In the ALTA-1L study [10], the estimated 1-year PFS rate for brigatinib was a remarkable success compared to crizotinib (67% vs 43%, $p<0,001$). Ensartinib and lorlatinib also stand out as ALK inhibitors whose phase 3 studies are ongoing and are expected to be included in daily clinical practice in the near future [1].

Although targeted therapies have considerably increased the OR and PFS results compared to platinum-based therapies, there is still a need for new agents to prolong the duration of OS.

Conclusion

The presence of EGFR and ALK mutations does not effect the treatment response of platinum-based regimens according to current literature and our study. Retrospective study design and low numbered subgroups in EGFR and EML-4/ALK mutated patients are the limitations of our study. Although these limitations, the association of EGFR exon subsets with metastasis points is worth investigating, as demonstrated in REASON study [5].

Disclosure

The study was not supported by any individual, institution or organization. It does not contain any conflict of interest.

References

1. Planchard D, Popat S, Kerr K et al. ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow- up. Ann Oncol. 2018 Oct 1;29(Suppl 4): iv192-iv237. doi: 10.1093/annonc/mdy275. Erratum in: Ann Oncol. 2019 May;30(5):863-870. PMID: 30285222.
2. Cappuzzo F, Ligorio C, Toschi L et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2007 May;2(5):423-9. doi: 10.1097/01.JTO.0000268676.79872.9b. Erratum in: J Thorac Oncol. 2007 Jul;2(7):676. Ligorio, Claudio [corrected to Ligorio, Claudia]. PMID: 17473658.
3. Ettinger DS, Wood DE, Aisner D L et al. NCCN Guidelines® Insights: Non–Small Cell Lung Cancer, Version 2.2023: Featured Updates to the NCCN Guidelines. J Natl Compr Canc Netw., 21(4), 340-350.
4. Mitsudomi T, Kosaka T, Yatabe Y. Biological and clinical implications of EGFR mutations in lung cancer. Int J Clin Oncol. 2006 Jun;11(3):190-8. doi: 10.1007/s10147- 006-0583-4. PMID: 16850125.
5. Schuette W, Schirmacher P, Eberhardt WE et al. EGFR mutation status and first-line treatment in patients with stage III/IV non-small cell lung cancer in Germany: an observational study. Cancer Epidemiol Biomarkers Prev. 2015 Aug;24(8):1254-61. doi: 10.1158/1055-9965.EPI-14-1149. Epub 2015 Jun 12. PMID: 26070531.
6. Yang P, Kulig K, Boland JM et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. J Thorac Oncol. 2012 Jan;7(1):90-7. doi: 10.1097/JTO.0b013e31823c5c32. PMID: 22134072; PMCID: PMC3931519.
7. Shaw AT, Yeap BY, Mino-Kenudson M et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009 Sep 10;27(26):4247-53. doi: 10.1200/JCO.2009.22.6993. Epub 2009 Aug 10. PMID: 19667264; PMCID: PMC2744268.

8. Kalikaki A, Koutsopoulos A, Hatzidaki D et al. Clinical outcome of patients with non- small cell lung cancer receiving front-line chemotherapy according to EGFR and K-RAS mutation status. Lung Cancer. 2010 Jul;69(1):110-5. doi: 10.1016/j.lungcan.2009.09.010. Epub 2009 Oct 24. PMID: 19854533.

9. Koh Y, Kim DW, Kim TM et al. Clinicopathologic characteristics and outcomes of patients with anaplastic lymphoma kinase-positive advanced pulmonary adenocarcinoma: suggestion for an effective screening strategy for these tumors. J Thorac Oncol. 2011 May;6(5):905-12. doi: 10.1097/JTO.0b013e3182111461. PMID: 21358343.

10. Camidge DR, Kim HR, Ahn MJ et al. Brigatinib versus Crizotinib in ALK-Positive Non- Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2027-2039. doi: 10.1056/NEJMoa1810171. Epub 2018 Sep 25. PMID: 30280657.

11. Ramalingam SS, Vansteenkiste J, Planchard D et al.; FLAURA Investigators. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med. 2020 Jan 2;382(1):41-50. doi: 10.1056/NEJMoa1913662. Epub 2019 Nov 21. PMID: 31751012.

12. SEER*Stat Databases: November 2022 Submission [cited 2023 Aug 18]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html

13. Wu M, Zhao J, Song SW et al. EGFR mutations are associated with prognosis but not with the response to front-line chemotherapy in the Chinese patients with advanced non- small cell lung cancer. Lung cancer. 2010; 67(3), 343-347. PMID: 19477549.

14. Dziadziuszko R, Holm B, Skov BG et al. Epidermal growth factor receptor gene copy number and protein level are not associated with outcome of non-small-cell lung cancer patients treated with chemotherapy. Ann Oncol. 2007;18(3), 447-452. PMID: 17082511.

15. Hotta K, Kiura K, Toyooka S et al. Clinical significance of epidermal growth factor receptor gene mutations on treatment outcome after first-line cytotoxic chemotherapy in Japanese patients with non-small cell lung cancer. J Thorac Oncol. 2007;2(7), 632-637. PMID: 17607119.