SCIREA Journal of Medicine

http://www.scirea.org/journal/PM

November 16, 2021

Volume 5, Issue 6, December 2021

The concentration of CEA and Cyfra 21-1 in patients with non-small cell lung cancer treated with tyrosine kinase inhibitors

Tong Quoc Dong[1], Ho Thi Long[2], Nguyen Thi Thu Hien[3], Doan Vu Nam[4], Pham Thai Binh[5], Pham Van Tran[2].

[1] Faculty of postgraduate education, Vietnam Military Medical University, Ha Dong, Ha Noi, Viet Nam

[2] Department of Biochemistry, 103 Military Medical Hospital, Ha Dong, Ha Noi, Viet Nam.

[3] Department of Biochemistry, K Tan Trieu Hospital, Thanh Tri, Ha Noi, Viet Nam.

[4] Department of internal medicine, Military Hospital 175, Go Vap, Ho Chi Minh, Viet Nam.

[5] Department of internal medicine, 103 Military Medical Hospital, Ha Dong, Ha Noi, Viet Nam.

The project received financial support from Military Hospital 103, Vietnam. We thank for that support.

Address for correspondence and reprint requests:

Tran PHAM VAN, Benh Vien Quan y 103, Phùng Hưng, Hà Đông, Hà Nội, Việt Nam

e-mail: phamvantransh@gmail.com Tel: (84) (9) 44030928

Abstract:

Objective: The purpose of this study was to determine CEA and Cyfra 21-1 concentrations in plasma of patients with non- small cell lung cancer before and after three months, six months of treatment with tyrosine kinase inhibitors.

Methods: 400 patients with non-small cell lung cancer were first treated with tyrosine kinase inhibitors (gefitinib or erlotinib). Before and after three months, six months of treatment, the patients were evaluated the clinical symptoms, chest computed tomography and quantified CEA, Cyfra 21-1 concentrations in plasma.

Results: In patients with non-small cell lung cancer, CEA and Cyfra 21-1 data followed an abnormal distribution with the median of 18.94 (range: 1.79 – 1553.0) and a median of 6.52 (range: 1.51 – 590.0), respectively. There was a strong positive correlation between CEA and Cyfra 21-1 concentrations ($r = 0.84$). CEA and Cyfra 21-1 concentrations decreased after treatment with tyrosine kinase inhibitors but the difference was not statistically significant ($p > 0.05$).

Conclusions: CEA and Cyfra 21-1 are significant markers for diagnosis and follow-up in patients with non- small cell lung cancer treated with tyrosine kinase inhibitors.

Keywords: CEA, Cyfra 21-1, erlotinib, gefitinib, non- small cell lung cancer

1. Introduction

Non-small cell lung cancer (NSCLC) is one of the worst prognostic cancers in the elderly[1]. Many studies have confirmed the role of tyrosine kinase inhibitors (TKIs) for NSCLC[2,3]. The Epidermal Growth Factor Receptor (EGFR) is the transmembrane tyrosine kinase receptor and its signaling pathway is closed related to the multiplication, invasion, metastasis, formation of blood vessels and apoptosis of cancer cells[4]. Patients with NSCLC and EGFR mutation are sensitive to TKIs. Randomized phase III trials have shown that TKIs could improve the survival rate and life quality of NSCLC patients with positive EGFR gene mutation. TKIs can inhibit the proliferation, invasion, metastasis of cancer cells and improve the effectiveness of chemotherapy[5].

Gefitinib and erlotinib are TKIs that specifically target EGFR and are currently approved by the Food and Drug Administration as a first-line treatment for patients with sensitive EGFR mutants[6]. CEA and Cyfra 21-1 are markers produced by cancer cells and related to tumor growth. Therefore, these markers play an important role in diagnosis, monitoring and evaluation of treatment effectiveness. In this study, we determined the CEA and Cyfra 21-1 concentrations of patients with NSCLC before and after TKI treatment.

2. Meterial and methods

2.1. Subjects

This study was carried out in 400 patients diagnosed with NSCLC according to the 2015 World Health Organization (WHO) Classification of Lung tumors[7], with EGFR mutation and had never been treated for cancer before.

Patients with contraindications to targeted therapy or who previously received cancer treatment were excluded from the study.

2.2. Methods

All subjects were taken gefitinib 250 mg or erlortinib 150 mg, once daily, at least once an hour before or two hours after eating. Subjects were treated for at least six months until they could not tolerate or progres the disease.

Subjects were checked and examined for clinical symptoms (including dry cough, hemoptysis, expectoration, chest pain and dyspnea), chest computed tomography (CT), CEA and Cyfra 21-1 concentrations in plasma before and after three months, six months of treatment with TKIs.

The response to treatment response was evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1), including complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)[8].

The stage of NSCLC was classified according to the 2015 WHO classification of lung tumors[7].

The concentration of CEA and Cyfra 21-1 in plasma were measured using an Electrochemilumiscence Immunoassay (ECLIA) in the Cobas E601 system (Roche, Hanoi,

Vietnam) with K2 EDTA-anticoagulated samples. The CEA and Cyfra 21-1 thresholds were 5.0 ng/ml and 3.3 ng/ml, respectively.

2.3. Calculation

Data were analyzed in Microsoft Excel 2013 and SPSS 20.0.

Data were present as number of patients, median, quartile 1, quartile 3, maximum, minimum. Differences between groups were tested with the T-test and the Mann-Whitney's test, according to distribution. The results were considered significant at $p<0.05$.

3. Results

3.1. Characteristics of subjects

The results showed that there were no differences in age and incidence between men and women. The average age of the subjects was 59.8 years. Patients over the age of 60 years had the highest incidence.

Common respiratory symptoms were dry cough and chest pain. All patients had adenocarcinoma, stage IIIB and IV (Table 1).

Table 1. Characteristics of the patients

Characteristics		Numbers	Percentages
Respiratory symptoms	Dry cough	200	50
	Hemoptysis	30	7.5
	Expectoration	30	7.5
	Chest pain	240	60
	Dyspnea	90	22.5
TNM stage	IIIB	180	45
	IV	220	55
Tumor size on CT	< 3 cm	190	47.5
	≥ 3 cm	210	52.5
Histopathology	Adenocarcinoma	400	100
EGFR mutation	Exon 19 mutation	280	70
	Exon 21 mutation	100	25

	Rare mutation	20	5

Note: CT: computed tomography; TNM: Tumor Node Metatasis; EGFR: Epidermal Growth Factor Receptor.

3.2. CEA and Cyfra 21-1 concentrations of patients before treatment.

The CEA and Cyfra 21-1 data of the patients before treatment followed an abnormal distribution and were presented in Table 2.

Table 2: CEA and Cyfra 21-1 concentrations before treatment

Markers	Min	Quartile 1 (Q1)	Median	Quartile 3 (Q3)	Max
CEA	1.79	6.44	18.94	58.07	1553.0
Cyfra 21-1	1.51	3.39	6.52	9.3	590.0

*Note: CEA: Carcinoembryonic antigen; * The concentration unit for CEA and Cyfra 21-1 was ng/mL.*

There was a strong postitive correlation between CEA and Cyfra 21-1 concentrations ($r = 0.84$, $p < 0.05$) (Figure 1)

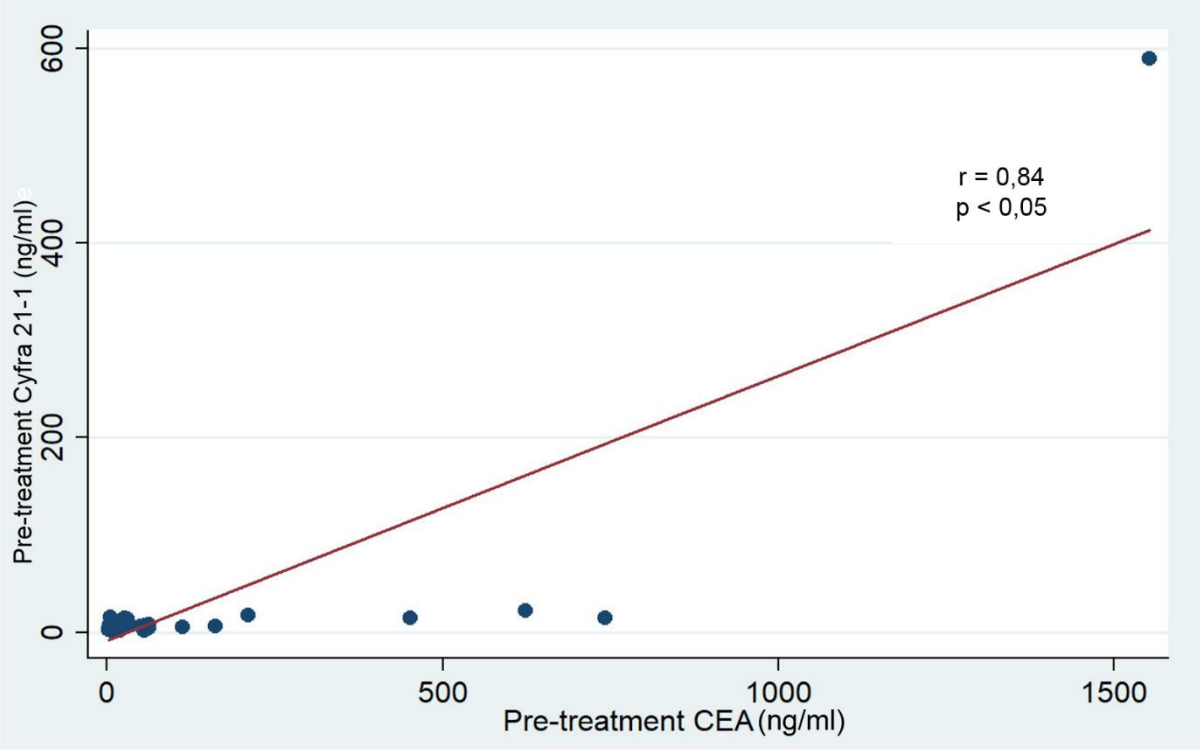

Figure 1: Correlation between CEA and Cyfra 21-1 concentrations. Cyfra 211 and CEA concentrations were quantified by Electrochemilumiscence Immunoassay (ECLIA) on Cobas E601 system. The correlation coefficient was calculated according to the program SPSS 20. There was a strong positive correlation between the concentrations of CEA and Cyfra 21-1 in the trial ($r = 0.84$, $p < 0.05$) before treatment.

3.3. CEA and Cyfra 21-1 concentrations of patients after treatment

The CEA and Cyfra 21-1 data of the patients after treatment followed abnormal distribution and were presented in Table 3.

Table 3: CEA and Cyfra 21-1 concentrations after treatment

Markers	After 3 months					After 6 months				
	Min	Q1	TV	Q3	Max	Min	Q1	TV	Q3	Max
CEA	1.05	3.08	4.77	12.72	298.9	1.06	3.04	4.66	10.53	38.59
Cyfra 21-1	1.27	1.68	2.41	3.37	6.65	1.09	1.55	2.13	2.74	13.29

Note: CEA: Carcinoembryonic antigen; Q1: Quartile 1; Q3: Quartile 3. CEA and Cyfra 21-1 were presented as median, Q1, Q3, min, max.

After being treated with TKI, CEA concentration of patients with NSCLC decreased; however, the differences were not statistically significant ($p > 0.05$) (Figure 2).

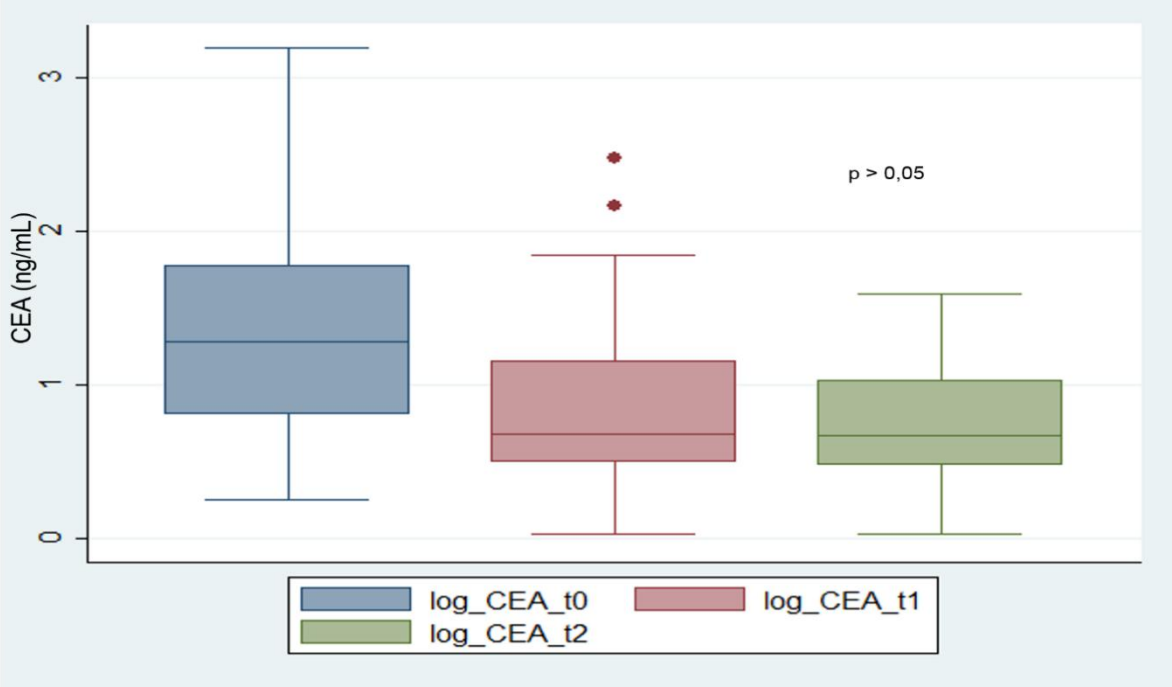

Figure 2: The change of CEA concentration after treatment. t0, t1, t2: before, after 3 and 6 months of treatment. Comparison CEA concentrations before and after treatment by T student test. CEA concentration decreased after 3 months and 6 months of treatment, $p > 0.05$.

Cyfra 21-1 concentration of patients with NSCLC decreased after treatment, however, the differences were not statiscally significant ($p > 0.05$) (Figure 3)

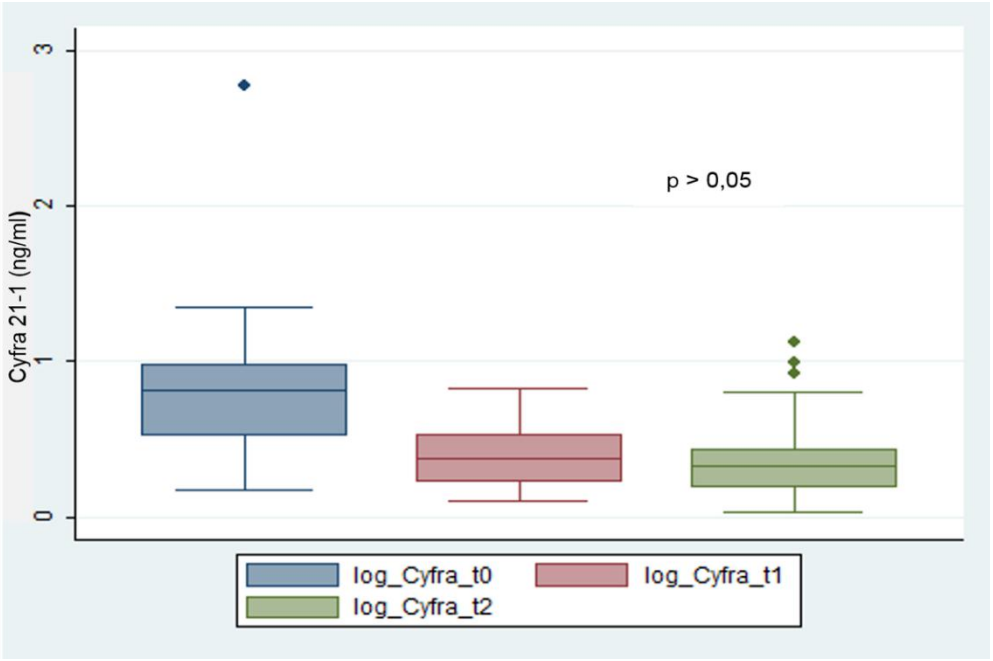

Figure 3: The change of Cyfra 21-1 concentration after treatment. t0, t1, t2: before, after 3 and 6 months of treatment. Comparison Cyfra 21-1 concentrations before and after treatment by T student test. Cyfra 21-1 concentration decreased after 3 months and 6 months of treatment, $p > 0.05$).

After 3 months and 6 months of treatment, no patients had CR on CT. Most of the patients with PR and SD had decreased concentrations of CEA and Cyfra 21-1 (Table 4).

Table 4: CEA and Cyfra 21-1 concentrations according to the response to treatment on CT

Marker change \ Treatment response		After 3 months (n, %)				After 6 months (n, %)			
		CR	PR	SD	PD	CR	PR	SD	PD
CEA	Decrease	0 (0)	350 (87.5)	20 (5)	10 (2.5)	0 (0)	70 (17.5)	290 (72.5)	10 (2.5)
	Increase	0 (0)	20 (5)	0 (0)	0 (0)	0 (0)	0 (0)	10 (2.5)	20 (5)
Cyfra 21-1	Decrease	0 (0)	300 (75)	10 (2.5)	0 (0)	0 (0)	70 (17.5)	280 (70)	20 (5)
	Increase	0 (0)	70 (17.5)	10 (2.5)	10 (2.5)	0 (0)	0 (0)	20 (5)	10 (2.5)

Note: CEA: Carcinoembryonic antigen; CR: complete response; CT: computed tomography; PR: partial response; PD: progressive disease; SD: stable disease. The data was presented as numbers and percentages.

The difference in CEA and Cyfra 21-1 concentrations after treatment between stages IIIB and IV was not statistically significant ($p > 0.05$) (Table 5).

Table 5: CEA and Cyfra 21-1 concentrations after treatment according to stages

Marker change \ Stages		After 3 months (n, %)		After 6 months (n, %)	
		Stage IIIB	Stage IV	Stage IIIB	Stage IV
CEA	Decrease	170 (94.4)	220 (100)	160 (88.9)	200 (90.1)
	Increase	10 (5.6)	0 (0)	20 (11.1)	20 (9.9)
p		> 0.05		> 0.05	
Cyfra 21-1	Decrease	170 (94.4)	220 (100)	160 (88.9)	200 (90.1)
	Increase	10 (5.6)	0 (0)	20 (11.1)	20 (9.9)
p		> 0.05		> 0.05	

Note: CEA: Carcinoembryonic antigen. The data was presented as numbers and percentages. Comparison of CEA and Cyfra 21-1 concentrations between stages using the chi-square test.

4. Discussion

The average age of the subjects was 59.8 years. Patients over the age of 60 years had the highest incidence. Cancer is considered an age - related disease because it increases exposure and accumulation time to carcinogens that cause DNA mutations and disorders in cell regulatory mechanisms[9].

Men were found to have a higher risk of lung cancer associated with smoking compared to women[10]. However, in this study, the difference was not statistically significant, which may be related to a small sample size.

The most respiratory symptoms were dry cough (60%) and chest pain (50%). With NSCLC, clinical symptoms often appear in the early stages. All subjects were in stages IIIB and IV, so many patients appeared with respiratory symptoms.

Adenocarcinoma was the most common histological subtype of lung cancer. This result was consistent with the study by Nanda Horeweg et al. (2013)[11].

The results of CEA and Cyfra 21-1 concentrations were consistent with some authors such as Sone K et al. (2017)[12], Okamura et al. (2013)[1]. The studies concluded that CEA and Cyfra 21-1 were reliable tumor markers that contribute to the diagnosis of lung cancer, especially when combined with CT.

There was a strong postitive correlation between CEA and Cyfra 21-1 concentrations. CEA and Cyfra 21-1 are tumor markers produced by cancer cells, so tumor growth will increase the production of two markers. In this study, all patient were adenocarcinoma. Some studies around the world showed that CEA and Cyfra 21-1 often increased greatly in patients with lung adenocarcinoma[14].

The concentration of CEA and Cyfra 21-1 decreased after treatment with TKI but the differences were not statistically significant. The decrease in these markers demonstrated the therapeutic efficacy of EGFR − TKI. This study was conducted in a short period of time, most of the patients have not completed treatment. All patients were in the pre-stage, so there was no difference. EGFR-targeted drugs that have been shown to benefit selected patients with NSCLC belong to a class of drugs known as tyrosine kinase inhibitors (TKIs). Drugs enter the cell and interfere with EGFR from within. Gefitinib and erlotinib are first generation EGFR-TKIs and their working mechanism is to block the activation of downstream signaling induced by EGFR through binding to the ATP-binding sites. These drugs improved progression-free survival, with acceptable toxicity compared to standard chemotherapy[15]. However, the effectiveness of treatment depends on many factors. Therefore it is necessary to have methods to monitor and evaluate treatment response and the uses of tumor markers is a simple and effective method.

When comparing the change in CEA and Cyfra 21-1 concentrations after treatment, we found that the proportion of patients who decreased the Cyfra 21-1 concentration was higher than that of the CEA concentration, but the difference was not statistically significant. The study showed that Cyfra 21-1 changed more markedly than CEA. This result was similar to the conclusion of Pang L et al. (2013)[16]. This study suggested that Cyfra 21-1 is an early prognostic factor after treatment.

No patients had CR on CT. Most of the patients with PR and SD had decreased concentration of CEA and Cyfra 21-1. This result was consistent with studies of some authors such as Yang L. et al. (2012)[17], Pang L. et al. (2013)[16]. Thus, in addition to CT, quantification of CEA and Cyfra 21-1 concentrations is an effective method of monitoring patients after treatment with TKIs.

In our study, there were no differences in the change in CEA and Cyfra 21-1 concentrations between stage IIIB and stage IV. In the research by Xu Y et al. (2015), mortality risk in the

group with stage IIIB – IV and Cyfra 21-1 > 3.3 ng/ml was 2.1 times higher than in the group with stage I- IIIA and Cyfra 21-1 < 3.3 ng/ml[18]. The study by Pang L (2012) concluded that the CEA concentration of patients with stage III- IV was higher than that of patients with stage I- II[16]. This difference was a result of the subgroup of patients. Other studies compared early-stage patients to advanced-stage patients while all patients in our research were in stage IIIB- IV.

Conclusions

CEA and Cyfra 21-1 are significant markers that contribute to diagnosis and follow-up in patients with NSCLC treated with TKIs. Larger population studies or multicenter studies are required to clarify the value of two markers.

Authors Contribution

Tong Quoc Dong, Nguyen Thi Thu Hien processed the research data, performed the analysis. Pham Thai Binh, Ho Thi Long drafted the manuscript and designed the figures, performed the calculations, Dang Vu Nam, Pham Van Tran research design, assisted in interpreting the results, and worked on the manuscript. All authors discussed the results and commented on the manuscript.

Ethical Approval

The study was approved by the Ethics Committee of the K Hospital Tan Trieu, Vietnam.

Statement of Human Rights

The study was carried out following the ethical standards of the responsible committee for human experimentation (institutional and national).

Statement of Informed Consent

Informed consent was obtained from the participants on the Internet at the end of the e-questionnaire to publish their anonymized information in this article.

Declaration of Conflict of Interests

The authors declared that they had no potential conflicts of interest in the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article. This work was supported by Military Hospital 103, Vietnam.

References

[1] Parkin DM. International variation. Oncogene. 2004;23(38):6329-40. doi:10.1038/sj.onc.1207726.

[2] Hsieh Y-Y, Fang W-T, Lo Y-W, Chen Y-H, Chien L-N. Comparing the effectiveness of different EGFR-TKIs in patients with EGFR mutant non–small-cell lung cancer: A retrospective cohort study in Taiwan. International journal of cancer. 2020;147(4):1107-16. doi:10.1002/ijc.32841.

[3] Goss GD, Spaans JN. Epidermal Growth Factor Receptor Inhibition in the Management of Squamous Cell Carcinoma of the Lung. The oncologist. 2016;21(2):205-13. doi:10.1634/theoncologist.2015-0209.

[4] Wieduwilt MJ, Moasser MM. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci. 2008;65(10):1566-84. doi:10.1007/s00018-008-7440-8.

[5] Metro G, Crinò L. Advances on EGFR mutation for lung cancer. Translational lung cancer research. 2012;1(1):5-13. doi:10.3978/j.issn.2218-6751.2011.12.01.

[6] Lee E, Keam B, Kim DW, Kim TM, Lee SH, Chung DH et al. Erlotinib versus gefitinib for control of leptomeningeal carcinomatosis in non-small-cell lung cancer. Journal of

thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2013;8(8):1069-74. doi:10.1097/JTO.0b013e318294c8e8.

[7] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2015;10(9):1243-60. doi:10.1097/jto.0000000000000630.

[8] Nishino M, Jackman DM, Hatabu H, Yeap BY, Cioffredi L-A, Yap JT et al. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. AJR Am J Roentgenol. 2010;195(3):W221-W8. doi:10.2214/AJR.09.3928.

[9] White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med. 2014;46(3 Suppl 1):S7-S15. doi:10.1016/j.amepre.2013.10.029.

[10] Kabir Z, Connolly GN, Clancy L. Sex-differences in lung cancer cell-types? An epidemiologic study in Ireland. Ulster Med J. 2008;77(1):31-5.

[11] Horeweg N, van der Aalst CM, Thunnissen E, Nackaerts K, Weenink C, Groen HJ et al. Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial. American journal of respiratory and critical care medicine. 2013;187(8):848-54. doi:10.1164/rccm.201209-1651OC.

[12] Sone K, Oguri T, Nakao M, Kagawa Y, Kurowaka R, Furuta H et al. CYFRA 21-1 as a Predictive Marker for Non-small Cell Lung Cancer Treated with Pemetrexed-based Chemotherapy. Anticancer research. 2017;37(2):935-9. doi:10.21873/anticanres.11402.

[13] Okamura K, Takayama K, Izumi M, Harada T, Furuyama K, Nakanishi Y. Diagnostic value of CEA and CYFRA 21-1 tumor markers in primary lung cancer. Lung cancer (Amsterdam, Netherlands). 2013;80(1):45-9. doi:10.1016/j.lungcan.2013.01.002.

[14] Matsuoka K, Sumitomo S, Nakashima N, Nakajima D, Misaki N. Prognostic value of carcinoembryonic antigen and CYFRA21-1 in patients with pathological stage I non-small cell lung cancer. European Journal of Cardio-Thoracic Surgery. 2007;32(3):435-9. doi:10.1016/j.ejcts.2007.05.014.

[15] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. The New England journal of medicine. 2010;362(25):2380-8. doi:10.1056/NEJMoa0909530.

[16] Pang L, Wang J, Jiang Y, Chen L. Decreased levels of serum cytokeratin 19 fragment CYFRA 21-1 predict objective response to chemotherapy in patients with non-small cell lung cancer. Exp Ther Med. 2013;6(2):355-60. doi:10.3892/etm.2013.1171.

[17] Yang L, Chen X, Li Y, Yang J, Tang L. Declines in serum CYFRA21-1 and carcinoembryonic antigen as predictors of chemotherapy response and survival in patients with advanced non-small cell lung cancer. Exp Ther Med. 2012;4(2):243-8. doi:10.3892/etm.2012.570.

[18] Xu Y, Xu L, Qiu M, Wang J, Zhou Q, Xu L et al. Prognostic value of serum cytokeratin 19 fragments (Cyfra 21-1) in patients with non-small cell lung cancer. Scientific Reports. 2015;5(1):9444. doi:10.1038/srep09444.