DOI: 10.14744/ejmi.2020.60165
EJMI 2020;4(3):365–369

Research Article

The Clinical Importance of Fibroblast Growth Factor 23 on Advanced Non-small Cell Lung Cancer Patients Without Druggable Alterations in Genes as EGFR or ALK or ROS1 Fibroblast Growth Factor 23 and Non-small Cell Lung Cancer

Serdar Arici,[1] Ruhper Cekin,[1] Saban Secmeler,[1] Muhammed Mustafa Atci,[1] Birol Ocak,[2] Abdullah Sakin,[3] Sener Cihan[1]

[1]Department of Medical Oncology, Istanbul Okmeydani Training and Research Hospital, Istanbul, Turkey
[2]Department of Medical Oncology, Uludag University Faculity of Medicine, Bursa, Turkey
[3]Department of Medical Oncology, Yuzuncu Yil University Faculity of Medicine, Van, Turkey

Abstract

Objectives: We aimed to investigate the relation between serum fibroblast growth factor (FGF) 23 levels and clinicopathologic features of stage 3B and 4 non-small cell lung cancer (NSCLC) patients without druggable alterations in genes as epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) or c-ROS oncogene 1 (ROS1), by comparing healthy control group.

Methods: This was a prospective, single-center study. Newly diagnosed stage 3B and 4 NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1 and healthy control in similar age, without any chronic disease and vitamin D deficiency were enrolled in the study. Fibroblast growth factor 23 levels were compared between groups.

Results: Forty men newly diagnosed stage 3B and 4 patients and 24 healthy men were enrolled. The median age of patients and controls were 54.7 and 53.1 years. The number of patients were 22 (55.0%) and 18 (45.0%) in stage 3B and stage 4 groups respectively. The mean FGF 23 level was calculated as 87.7±58.0 pg/ml in patients group and 63.1±11.4 pg/ml in control group (p=0.045). Fibroblast growth factor 23 levels were 85.5±42.5 pg/ml and 89.6±69.1 in metastatic and non-metastatic patients respectively (p=0.532). The median FGF 23 levels were 91.1±58.4 pg/ml and 92.5±60.8 pg/ml in squamous cell carcinoma and adenocarcinoma groups respectively (p=0.926).

Conclusion: Our study suggests that high FGF-FGFR interaction may be causative for stage 3B and 4 NSCLC without druggable alterations in genes as EGFR, ALK or ROS1 and is important in terms of suggesting the FGF pathway as a new treatment target in NSCLC patients.

Keywords: Druggable alterations, fibroblast growth factor 23, non-small cell lung cancer

Cite This Article: *Arici S, Cekin R, Secmeler S, Atci MM, Ocak B, Sakin A, et al. The Clinical Importance of Fibroblast Growth Factor 23 on Advanced Non-small Cell Lung Cancer Patients Without Druggable Alterations in Genes as EGFR or ALK or ROS1 Fibroblast Growth Factor 23 and Non-small Cell Lung Cancer. EJMI 2020;4(3):365–369.*

Lung cancer is the most common cancer in the worldwide, and it is the most common reason for cancer-related mortality in women and men. Non-small cell lung cancer (NSCLC) constitutes 85% of all lung cancer cases.[1,2] The causes of NSCLC have not been fully elucidated. According to current consensus, smoking is the main cause of lung

Address for correspondence: Serdar Arici, MD. Istanbul Okmeydani Egitim ve Arastirma Hastanesi, Tibbi Onkoloji Klinigi, Istanbul, Turkey
Phone: +90 544 766 39 30 **E-mail:** serdararici@hotmail.com

Submitted Date: November 11, 2019 **Accepted Date:** February 20, 2020 **Available Online Date:** June 05, 2020

tumors, although not all patients with lung cancer have a history of smoking, suggesting that genetic variations are also involved in the development of this malignancy. Present research suggests that the occurrence of lung cancer is accounted for by the interaction between the environment and heredity.[3–5] To improve disease outcome, it is crucial to implement biomarkers into the clinics which assist physicians in their decisions regarding diagnosis, prognosis, as well as prediction of treatment response.[6]

The human fibroblast growth factor (FGF) family consists of 22 members. Fibroblast growth factor 23 (FGF 23), is a peptide hormone member of the FGF 15/19 subfamily, which is differentiated from the larger FGF family by virtue of its lacking the conventional FGF heparin-binding domain and by exhibiting endocrine function.[7] Klotho is an essential cofactor for binding of FGF 23 to the FGF receptor (FGFR), it modulates bFGF signaling, inhibits the insulin and the insulin-like growth factor (IGF)-1 pathways, and regulates the activity of the transient receptor potential vanilloid type 5 calcium channel.[8–11] It was shown that FGF 23 level was increased in hematologic malignancies, prostate cancer, breast cancer and ovarian cancer.[12–15]

Fibroblast growth factor pathway is a new treatment target for urotelhial cancer.[16] In NSCLC patients without druggable alterations in genes as epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) or c-ROS oncogene 1 (ROS1), prognosis remains adverse with a median survival time of about 18 months.[17] New treatment agents are needed in the specific population. There is no study investigated the relation between NSCLC and FGF 23.

We aimed to investigate the relation between serum FGF 23 levels and clinicopathologic features of stage 3B and 4 NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1, by comparing healthy control group.

Methods

Study Population

This was a prospective, single-center study. Medical information was obtained from the archived files of newly diagnosed stage 3B and 4 NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1 in the medical oncology clinic of Okmeydani Training and Research Hospital, in 2019. A total of 97 NSCLC patients older than 18 years were scanned. Patients without pathology reports and laboratory test results and 18 fluorodeoxyglucose (18-FDG) positron emission tomography/computed tomography (PET/CT) were excluded. Also, we excluded patients with EGFR, ALK or ROS1 positive NSCLC, chronic kidney disease and vitamin D deficiency. Disease staging was performed according to the Tumor, Node, Metastasis eighth edition (TNM 8) staging system. We also enrolled healthy control in similar age, without any chronic disease and vitamin D deficiency in the study. The study was performed in accordance with the declaration of Helsinki. The ethical approval was received. The patients give a written informed consent before the study.

Fibroblast Growth Factor 23

Venous blood samples required for laboratory examination were taken in the morning following a 12-hour fasting. The samples were transported to the laboratory on an ice mold and the serum sample was separated by centrifuging at 4000 rpm, 5 minutes, and the samples were stored at -80° C. Human Fibroblast Growth Factor 23 ELISA (Enzyme-Linked-ImmunoSorbentAssay) Kit (Catalog No: YLA-1509HU, YL Biotech Co. Ltd., Shanghai China) was used by ELISA method for intact FGF23 measurement. The readings were made spectrophotometrically with a 450 nm wavelength scanning device. Results are given in pg/ml.

Statistical Methods

SPSS 15.0 for Windows was used for the statistical analysis. Descriptive statistics were given as number and percentage for the categorical variables, average, standard deviation, minimum, and maximum for the numeric variables. The relations between the numerical variables were made using the Spearman Correlation Analysis since the parametric test condition could not be met. Two independent group comparisons of the numerical variables were made using the Mann–Whitney U test when normal distribution conditions were not achieved. The statistical significance level of alpha was accepted as $p<0.05$.

Results

In this study, 40 men newly diagnosed stage 3B and 4 NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1 and 24 healthy men were enrolled. All of patients had smoking history. The median age of patients and controls were 54.7 and 53.1 years. Histologic subtypes were squamous cell carcinoma in 22 (55.0%) patients, adenocarcinoma in 18 (45.5%) patients. The median tumor diameter was 5.3 cm. The number of patients with N1, N2 and N3 according to TNM 8 staging system were, 12 (30.0%), 20 (50.0%) and 8 (20.0%) respectively. The number of patients were 22 (55.0%) and 18 (45.0%) in stage 3B and stage 4 groups respectively. The most common metastasis sites were liver, bone and brain respectively (Table 1).

The mean SUVmax was 14.1±6.1 in patients group. The mean phosphor level was 3.61±0.43 mg/dl and 3.7±0.38 in patients and control groups respectively. The mean FGF 23

Table 1. Patients characteristics

	n	%
Gender		
Male	40	100.0
Histology		
SCC	22	55.0
Adenocarcinoma	15	37.5
Tumor diameter (cm)	5.3±2.8 (1.5-1.3)	
SUV max	14.1±6.1 (2.1-26.1)	
T stage		
1	7	17.5
2	14	35.0
3	10	25.0
4	9	22.5
N stage		
1	12	30.0
2	20	50.0
3	8	20.0
M stage		
0	22	55.0
1	18	45.0
Prognostic stage		
3B	22	55.0
4	18	45.0
Distant metastasis		
No	22	55.0
Yes	18	45.0
Site of metastasis		
Liver	6	15.0
Brain	5	12.5
Bone	6	15.0

FGF: Fibroblast growth factor; N: Lymph node; M: Metastasis; SCC: Squamous cell carcinoma; SUV: Standard uptake value; T: Tumor.

Table 2. FGF-23 levels in patients and controls

	Patient	Control
SUV max	14.1±6.1	–
Phosphor	3.61±0.43	3.7±0.38
FGF 23	87.7±58.0	63.1±11.4

FGF: Fibroblast growth factor; SUV: Standard uptake value.

level was calculated as 87.7±58.0 pg/ml in patients group and 63.1±11.4 pg/ml in control group (p=0.045) (Table 2). Fibroblast growth factor 23 levels were 85.5±42.5 pg/ml and 89.6±69.1 in metastatic and non-metastatic patients respectively (p=0.532). The median FGF 23 levels were 91.1±58.4 pg/ml and 92.5±60.8 pg/ml in squamous cell carcinoma and adenocarcinoma groups respectively (p=0.926) (Table 3).

Table 3. FGF-23 levels in subgroups

	FGF-23 (pg/ml)	
	Mean±SD	Median
Histology		
SCC	91.1±58.4	81.9
Adenocarcinoma	92.5±60.8	69.6
Metastasis		
Yes	89.6±69.1	68.01
No	85.5±42.5	73.145

FGF: Fibroblast growth factor; SCC: Squamous cell carcinoma; SD: Standard deviation.

In the correlation analysis, there was no any statistical significant correlation between FGF 23 and prognostic factors such tumor diameter, lymph node status, stage and SUVmax (rho=0.006 p=0.971, rho=-0.127 p=0.440, rho=0.029 p=0.858 and rho=0.299 p=0.090 respectively). There were the statistical significant correlation between FGF 23 and alanine aminotransferase and aspartate aminotransferase (rho=0.359 p=0.027 and rho=0.362 p=0.025 respectively) (Table 4).

Discussion

We planned this study to detect the clinical importance of serum FGF 23 in newly diagnosed NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1. We found that serum FGF 23 levels were higher in patients with NSCLC than healthy controls but there was no significant difference of FGF 23 levels in different prognostic groups. There are some trials focused on the relation between FGF 23 and cancer, in different tumor types. Firstly, in a study, FGF 23 level was evaluated in ovarian cancer and was found that serum FGF 23 concentrations are significantly higher in women with advanced-stage ovarian cancer compared with concentrations in women with early-stage ovarian cancer or benign disease or in healthy women.[15] In a trial published in 2015 was found that FGF 23 is expressed in prostate cancer at increased levels but FGF 23 is not correlated with clinical or pathological parameters. Also in this study, exogenous FGF 23 has been shown to increase proliferation and invasion of prostate cancer.[13] In another trial published in 2019, circulating FGF 23 level was evaluated in patients with urothelial carcinoma and was found that FGF 23 is significantly higher in patients group than control group but FGF 23 levels are similar in, different grades, tumor sites and stages.[18] Also, FGFs genomic alterations were shown in many solid tumors. Fibroblast growth factor genomic alterations were found 46% in squamous cell lung carcinoma and 39% in lung adenocarcinoma.[19–21] Fibroblast growth factor 23 interacts with FGFR 1,2,3,4 and

Table 4. The analysis of correlation between FGF-23 and clinicopathologic features of patients

	FGF-23 (pg/ml) Rho
Tumor features	
Diameter	0.070
SUV max	0.299
T stage	0.006
N stage	-0.127
M stage	0.088
Prognostic stage	0.029
CBC	
WBC	0.071
Neu	0.100
Lym	0.131
Hgb	0.100
MPV	0.303
PDW	0.183
Plt	-0.070
Biochemistry	
BUN	-0.006
Creatinin	0.203
GFR	-0.244
AST	0.362
ALT	0.359
Lactate dehidrogenaz	0.489
Sedimentation	0.288
C- reactive protein	-0.439
Sodium	-0.081
Potassium	0.028
Calcium	-0.031
Phosphor	0.420

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CBC: Complete blood count; GFR: Glomerular filtration rate; FGF: Fibroblast growth factor; Hgb: Hemoglobin; LDH: Lactate dehydrogenase; Lym: Lymphocyte; M: Metastasis; MPV: Mean platelet volume; N: Lymph node; Neu: Neuthrophil; PDW: Platelet distribution width; Plt: Platelet; SUV: Standard uptake value; T: Tumor; WBC: White blood cell.

α-Klotho co-factor.[19] Fibroblast growth factor receptor genomic alterations were analysed in many solid tumors and FGFR1, FGFR3 and FGFR4 gene amplifications were found in NSCLC patients.[22] In a study published in 2019, the interaction between FGFR signaling and EGFR was investigated, when the cells were stimulated with the FGFR4 specific factor FGF 19, the activation of both FGFR4 and EGFR was observed. Also this cooperation was found independent of EGFR activating mutations.[23]

In our study, serum FGF 23 levels were higher in patients with NSCLC than healthy controls but there was no significant difference of FGF 23 levels in different prognostic groups. Considering high FGFR alteration rates and FGFR related EGFR activation in patients with lung cancer, our study suggests that high FGF-FGFR interaction may be causative for EGFR, ALK or ROS1 wild type non-small cell lung cancer.

This is the first prospective study focused on the clinical impact of serum FGF 23 levels in newly diagnosed NSCLC patients without druggable alterations in genes as EGFR, ALK or ROS1. There are some limitations in our study. Firstly, patients outcomes still are not mature to determine the prognostic impact of FGF 23 on lung cancer. Secondly, the patients number was not enough for subgroup analysis.

Conclusion

Our study suggests that high FGF-FGFR interaction may be causative for stage 3B and 4 NSCLC without druggable alterations in genes as EGFR, ALK or ROS1 and is important in terms of suggesting the FGF pathway as a new treatment target in NSCLC patients. There are needed the studies focused on the FGF-FGFR interaction as a target for this specific cohort.

Disclosures

Informed Consent: The patients give a written informed consent before the study.

Ethics Committee Approval: The Okmeydani Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 08.10.2019, number: 48670771-514.10).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

Authorship Contributions: Concept – S.A., R.Ç.; Design – S.A., A.S.; Supervision – Ş.C., A.S., S.A.; Materials – B.O., M.M.A., Ş.S.; Data collection and/or processing – S.A., Ş.C., A.S., R.C.; Analysis and/or interpretation – S.A., B.O., R.C., Ş.S.; Literature search – S.A., M.M.A.; Writing – S.A., R.C.; Critical review – S.A., A.S.

Financial Disclosure: There is no grant funding for this study.

References

1. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero-Luna G, et al. Cancer Statistics for Hispanics/Latinos, 2018. CA Cancer J Clin 2018;68:425–45.
2. Sakin A, Secmeler S, Arici S, Geredeli C, Yasar N, Demir C, et al. Prognostic Significance of Mean Platelet Volume on Local Advanced Non-Small Cell Lung Cancer Managed with Chemoradiotherapy. Sci Rep 2019;9:3959.
3. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 2008;452:638–42.
4. Chen G, Hu C, Lai P, Song Y, Xiu M, Zhang H, et al. Associa-

tion between TGF-beta1 rs1982073/rs1800469 polymorphism and lung cancer susceptibility: An updated meta-analysis involving 7698 cases and controls. Medicine (Baltimore) 2019;98:e18028.
5. Sakin A, Sahin S, Atci MM, Sakin A, Yasar N, Geredeli C, et al. The effect of different treatment modalities on survival in elderly patients with locally advanced non-small cell lung cancer. Pulmonology. 2019.
6. Muller S, Janke F, Dietz S, Sultmann H. Circulating MicroRNAs as Potential Biomarkers for Lung Cancer. Recent Results Cancer Res 2020;215:299–318.
7. Marsell R, Jonsson KB. The phosphate regulating hormone fibroblast growth factor-23. Acta Physiol (Oxf) 2010;200:97–106.
8. Wolf I, Levanon-Cohen S, Bose S, Ligumsky H, Sredni B, Kanety H, et al. Klotho: a tumor suppressor and a modulator of the IGF-1 and FGF pathways in human breast cancer. Oncogene 2008;27:7094–105.
9. Abramovitz L, Rubinek T, Ligumsky H, Bose S, Barshack I, Avivi C, et al. KL1 internal repeat mediates klotho tumor suppressor activities and inhibits bFGF and IGF-I signaling in pancreatic cancer. Clin Cancer Res 2011;17:4254–66.
10. Cha SK, Ortega B, Kurosu H, Rosenblatt KP, Kuro OM, Huang CL. Removal of sialic acid involving Klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1. Proc Natl Acad Sci U S A 2008;105:9805–10.
11. Chang Q, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG. The beta-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. Science 2005;310:490–3.
12. Stewart I, Roddie C, Gill A, Clarkson A, Mirams M, Coyle L, et al. Elevated serum FGF23 concentrations in plasma cell dyscrasias. Bone 2006;39:369–76.
13. Feng S, Wang J, Zhang Y, Creighton CJ, Ittmann M. FGF23 promotes prostate cancer progression. Oncotarget 2015;6:17291–301.
14. Parish A, Schwaederle M, Daniels G, Piccioni D, Fanta P, Schwab R, et al. Fibroblast growth factor family aberrations in cancers: clinical and molecular characteristics. Cell Cycle 2015;14:2121–8.
15. Tebben PJ, Kalli KR, Cliby WA, Hartmann LC, Grande JP, Singh RJ, et al. Elevated fibroblast growth factor 23 in women with malignant ovarian tumors. Mayo Clin Proc 2005;80:745–51.
16. Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2019;381:338–48.
17. D'Angelo SP, Janjigian YY, Ahye N, Riely GJ, Chaft JE, Sima CS, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol 2012;7:1815–22.
18. Li JR, Chiu KY, Ou YC, Wang SS, Chen CS, Yang CK, et al. Alteration in serum concentrations of FGF19, FGF21, and FGF23 in patients with urothelial carcinoma. BioFactors 2019;45:62–8.
19. Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. Cancer metastasis reviews 2015;34:479–96.
20. Cancer Genome Atlas Research N. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519–25.
21. Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543–50.
22. Helsten T, Elkin S, Arthur E, Tomson BN, Carter J, Kurzrock R. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. Clinical cancer research: an official journal of the American Association for Cancer Research 2016;22:259–67.
23. Quintanal-Villalonga A, Molina-Pinelo S, Yague P, Marrugal A, Ojeda-Marquez L, Suarez R, et al. FGFR4 increases EGFR oncogenic signaling in lung adenocarcinoma, and their combined inhibition is highly effective. Lung cancer 2019;131:112–21.