Pretreatment Serum Levels of Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor Binding Protein-3 in Men with Advanced Non-Small Cell Lung Cancer

İleri Evre Küçük Hücreli Dışı Akciğer Kanserli Erkeklerde, Tedavi Öncesi Serum İnsülin Benzeri Büyüme Faktörü 1 ve İnsülin Benzeri Büyüme Faktörünü Bağlayıcı Protein 3 Düzeyi

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ABSTRACT Objective: Insulin- like growth factor-1 (IGF-1) regulates a number of cellular functions such as proliferation and differentiation. On the other hand, insulin-like growth factor binding protein-3 (IGFBP-3) is a putative tumor suppressor and inhibits the proliferative activity of IGF-I. Therefore most studies report that IGF-I and IGFBP-3 may promote and inhibit tumor growth, respectively. In this study we aimed to evaluate the importance of IGF-1 and IGFBP-3 in advanced stage non-small cell lung cancer (NSCLC) and to find out whether they contribute to clinical evaluations. **Material and Methods:** We measured the pretreatment serum levels of IGF-1 and IGFBP-3 in 80 men between July 2007 and June 2008 by chemiluminescent immunometric assay. Serum samples were obtained from 50 patients with inoperable advanced stage NSCLC at Dr. Suat Seren Pulmonary Diseases Hospital and 30 healthy controls at Izmir Tepecik Research Hospital. All 80 men had a smoking history of minimum 20 pack/years. **Results:** Contrary to the results of many reports, the serum IGF-1 levels were lower in the patients and the difference between the groups reached a statistical significance (p=0.025). IGF-1/IGFBP-3 ratio was also significantly lower in lung cancer patients (p=0.016). The histological subtype of tumor was correlated with IGF-1 level (p=0.005). **Conclusion:** Our result showed that serum level of IGF-I/IGFBPs may be useful markers for diagnosing and identifying tumor subtypes in NSCLC. In addition, IGF-1 and IGFBP-3 levels in serum might serve a clinical significance in patients with advanced stage NSCLC. However, further studies comprising more cases are needed to investigate the clinical significance of IGF-1 and IGFBP-3 in NSCLC.

Key Words: Insulin- like growth factor-I (IGF-I); insulin-like growth factor binding protein-3 (IGFBP-3); lung neoplasms; Carcinoma, Non-Small-Cell Lung

ÖZET Amaç: İnsülin benzeri büyüme faktörü 1 (İGF-1), çoğalma ve farklılaşma benzeri birçok hücresel işlevi düzenler. İnsülin benzeri büyüme faktörünü bağlayıcı protein 3 (İGFBP-3) ise tersine tümör karşıtı özellikte olup, İGF-1'in tümör çoğaltıcı işlevini baskılar. Bu nedenle çoğu araştırmalarda İGF-1'nin tümör gelişimine desteklediği, İGFBP-3'ün ise tümör gelişimini önlediği bildirilmektedir. Bu çalışmanın amacı ileri evre küçük hücreli dışı akciğer kanserinde (KHDAK) İGF-1 ve İGFBP-3'ün rolünü irdelemek ve bu belirleyicilerin KHDAK'nin klinik değerlendirmesinde katkısı olup olamayacağını değerlendirmektir. **Gereç ve Yöntemler:** Dr. Suat Seren Göğüs Hastalıkları Hastanesinde tanı ve tedavisi yapılan ileri evre KHDAK'li 50 erkek olgunun serum İGF-1 ve İGFBP-3 düzeyleri kemilüminesans immün yöntem ile ölçülmüştür. Kontrol olgusu olarak Izmir Tepecik Eğitim ve Araştırma Hastanesi Biyokimya Laboratuarına başvuran gönüllü 30 sağlıklı erişkin erkek hasta serumu kullanılmıştır. Tüm olgular en az 20 paket/yıl sigara kullanımı öyküsüne sahiptir. **Bulgular:** Önceki birçok çalışmanın tersine, hasta grubundaki serum İGF-1 düzeyleri daha düşüktü ve fark istatistiksel olarak anlamlıydı (p=0,025). İGF-1/İGFBP-3 oranı da akciğer kanserli olgularda sağlıklı kontrollere göre belirgin düzeyde düşüktü (p=0,016). Ayrıca tümörlerin histolojik subtipi ile serum İGF-1 düzeyi arasında pozitif korelasyon saptandı (p=0,005). **Sonuç:** Bu çalışma, İGF-I/İGFBP oranı ölçümünün KHDAK'nin tanı ve histolojik subtipini belirlemede yararlı bir belirleyici olabileceğini düşündürmüştür. Ayrıca İGF-1 ve İGFBP-3 serum düzeyinin ölçümü ileri evre KHDAK değerlendirmesinde klinik olarak önem taşıyabilir. Ancak İGF-1 ve İGGFBP-3 serum düzeyinin ileri evre KHDAK'deki değişiminin daha geniş serilerde doğrulanıp, tedavi protokollerine etkisinin araştırılması gerekmektedir.

Anahtar Kelimeler: İnsülin-benzeri büyüme faktörü-1 (İGF-1); insülin benzeri büyüme faktörünü bağlayıcı protein -3 (IGFBP-3); akciğer tümörleri; karsinom, küçük hücreli olmayan

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The incidence of lung cancer is declining following a drop in smoking rates, but it is still the leading cause of cancer- related deaths Worldwide and survival rates are poor everywhere.[1] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[1] The etiology of most lung cancers strongly related to cigarette smoking.[2] For patients with early-stage NSCLC, surgical resection with adjuvant chemo-radiotherapy is considered as the standard of care.[2,3] Unfortunately, most of the tumors are considerable size when they are first detected and approximately 80% are inoperable due to advanced disease. Only 5% of people with NSCLC survive for 5 years and nearly all of these patients are in an early stage.[1-4]

Insulin- like growth factor 1 (IGF-1) is a single chain polypeptide involved in the regulation of a number of cellular functions including proliferation and differentiation. It has mitogenic effect in many tissues and inhibits apoptosis. Its effects are mediated primarily through its interaction with the IGF-1 receptor.[5] Insulin-like growth factor binding protein-3 (IGFBP-3) is a putative tumor suppressor and inhibits the mitogenic and anti-apoptotic activity of insulin-like growth factor (IGF) by blocking its binding to its receptors or by an IGF-independent manner.[4] IGF-1 and IGFBP-3 are produced mainly in the liver, but they are also produced locally in many tissues such as bronchial epithelial cells.[5] The interaction of IGF-1 and IGFBP-3 is thought to be a potential risk factor for malignancies. Several studies suggest that higher blood level of IGF-1 and/or lower blood levels of IGFBP-3 associated with an increased risk of various cancers including the lung cancers.[2,6-13]

The aim of this study was to investigate the clinical significance of IGF-1 and IGFBP-3 serum levels by comparing advanced NSCLC patients with healthy controls and to evaluate whether the levels of IGF-1 and IGFBP-3 would predict the outcome in these patients.

MATERIAL AND METHODS

A total of 80 men aged between 40 and 79 years (60.1±10.7) were included in this study. All 80 cases had smoking histories of ≥ 20 pack/years. Thirty of them who applied to the department of clinical biochemistry, Izmir Tepecik Research Hospital constituted the healthy control group, while 50 patients with advanced stage (Stage 3B and stage 4) non-small cell lung cancer who were diagnosed and treated at the Dr. Suat Seren Pulmonary Diseases Hospital between July 2007 and June 2008 constituted the study group. Serum samples of the patients were obtained before therapy. A systemic examination was performed and a detailed medical story was obtained to identify the cases with chronic disorders. Patients with prior myocardial infarction, diabetes mellitus, systemic hypertension, cerebrovascular disease, vasculitis, renal or hepatic dysfunction, gastrointestinal malabsorption, obesity, and/or chronic alcohol abuse were excluded from the study. The study was designed according to the Helsinki Declaration and approved by the institutional ethics committee. Informed consents were obtained from the patients and the volunteers.

For biochemical analyses, all the serum samples were drawn into gel separator tubes (Vacutainer SST , Beckton Dickinson, France) between 08.00 and 08.30 a.m. after 12 hours of fasting. The blood samples were allowed to clot and then centrifuged at 1500 rpm for 10 min at room temperature. The serum samples were immediately separated and stored at -70^{0}C until analysis. All biochemical analyses were performed simultaneously. IGF-1 and IGFBP-3 levels were measured by solid-phase, enzyme-labeled chemiluminescent immunoassay with an Immulite 2000 immunoassay analyzer (Siemens, Llanberis, United Kingdom) according to standard procedures. The intra-assay and inter-assay precisions were between 2.3-3.9% and 3.7-8.1% for the IGF-1 assay, between 4.1-4.8% and 5.2-7.2% for the IGFBP-3 assay by data sheets. IGF-1/ IGFBP-3 ratio of all cases were calculated.

For statistical analyses, Student's t-test was performed for comparison of groups and Mann Whithey U test for comparison of tumor subtypes. Relationships between variables were determined by Pearson's correlation coefficient. A one-way analysis of covariance with age as covariates was

performed for IGF-1 and IGFBP-3. In addition, Kaplan Meier test was performed to analyze survival-time data. P values less than 0.05 were considered as statistically significant. Analyses were performed using SPSS program (version 9.05) for Windows.

RESULTS

A total of 50 men with NSCLC were treated with chemotherapy and radiotherapy according to individual features in Dr. Suat Seren Pulmonary Diseases Hospital between October 2007 and September 2008. Thirty heavy smokers were included in the study as the control group. Two groups had similar features. For example, all cases were males and they had been smoking history of more than 20 pack/years. In this study, a one-way analysis of covariance (ANCOVA) was also used to adjust variables for the age, because the control group was younger than the patient group (p=0.011). This test revealed that age had no interaction with IGF-1 and IGFBP-3 (p=0.117 and p=0.662, respectively). On contrary, IGF-1/ IGFBP-3 ratio was affected by age (p=0.07). The mean ages, smoking history and the levels of IGF-1 and IGPBP-3 of patients and the control cases are listed in Table 1. The mean age of all participants was 59.9±11.5 years (40-79). The mean age of the patients was 62.48 years (± 9.8), ranging from 40 to 78. Total follow-up time was 40 months. The mean survival was 8.78±8.85 months for the patient group. It was 12.7±10.33 (1-36) for the patients with stage 3B disease, while it was 5.12±5.1 (1-19) for the patients with stage 4 disease. In the lung tumor group, 6 cases (12%) were alive, 33 cases (66%) were died and 11 cases (22%) were lost from follow up. When the lost patients were censored, the mean and median survivals were found as 13 (95% CI: 9-17) and 6 months (95% CI: 2-10) by the Kaplan-Meier Survival Analyses. All 50 patients with lung cancer had advanced stage disease. Twenty-four cases were stage IIIB (48%) and 26 cases were stage IV (52%). Sixteen (32%) were diagnosed as adenocarcinoma while 34 tumors (68%) were diagnosed as squamous cell cancer (SCC). The distributions of patients' features according to the tumor subtypes are presented in Table 2.

TABLE 1: The distribution of serum IGF-1 and IGFBP-3 levels in the groups studied.

	Control cases (n=30)	Patients (n=50)	P
Age	55.7± 11.1	62.48± 9.8	**0.011**
Cigarettes/day (mean/range)	18.2± 4.7 (10- 25)	52.08± 11.09 (20- 100)	**<0.001**
IGF-1 (ng/ml),	132.4± 63.6	104.7± 44.7	**0.025**
IGFBP3 (ng/ml)	3128.2± 1422.6	2607.3± 1036.8	**0.036**
IGF-1/IGFBP3	0.049±0.03	0.041±0.013	**0.016**

TABLE 2: The distribution of patients' mean ages, the number of cigarettes smoked per day, mean IGF-1 and IGFBP-3 levels, disease stage and survival according to the tumor subtypes.

	Squamous cell carcinomas (n=34)	Adenocarcinomas (n=16)	P
Percent	68%	32%	-
Age	62.09±11.56	63.3± 10.3	0.910
Cigarettes/ day (mean/range)	48.68± 19.18 (20-100)	57.5± 25.5 (25-100)	0.346
IGF-1	115.6± 42.6	81.4± 41.09	**0.005**
IGFBP-3	2826.7±1061.44	2141.3±832.1	0.058
IGF-1/IGFBP-3	0.042±0.013	0.038±0.013	0.608
Stage (3/4)	14/ 20	10/ 6	-
Status (alive/ exitus/ lost)	2/ 26/ 6	4/ 7/ 5	-
Survival (months)	8.88± 9.4	8.56±7.7	0.725

Serum levels of IGF-1 and IGFBP-3 were 104.7±44.7 ng/ml and 2607.3±1036.8 ng/ml, respectively in the patient group; while they were 132.4±63.6 ng/ml and 3128.2±1422.6 ng/ml,, respectively in the control group. Both IGF-1 and IGFBP-3 levels were lower in lung cancer patients and the difference between the groups reached a statistical significance (p=0.025 and p=0.036). Similarly, IGF-1/ IGFBP-3 ratios were also significantly lower in lung cancer patients (p=0.016). On contrary, serum IGF-1 (p=0.007) and IGFBP-3 (p=0.077) levels were determined to be significantly higher in patients with distant metastasis. The mean levels of IGF-1 and IGFBP-3 were 87.2± 33 ng/ml and 2337.4±977 ng/ml, respectively in patients with non-metastatic disease, while these values were 120.8±48.4 ng/ml and 2856.5±1045.9 ng/ml, respectively in patients with metastatic disease. The mean survival was 10.46±9.67 months for the patients with low serum IGF-1 levels, while it was 6.64±7.35 for the patients with high serum IGF-1 levels. IGF-1 levels were found to be negatively correlated with the survival rates by the Pearson's correlation analysis (p=0.025, r=-0.250). The histological subtype of tumor was correlated with IGF-1 level as well (p=0.005). IGF levels were lower in patients with adenocarcinoma and the mean level of IGF-1 was 81.4±41.09 (25-163).

DISCUSSION

IGF-1 is an important mitogen required by some cell types to progress from the G1 phase to the S phase of the cell cycle.[14] IGF binding proteins (IGFBPs) can have opposing actions, by binding IGF-1 or by direct inhibitory effects on target cells. As mitogens and anti-apoptoticagents, IGFs may be important in carcinogenesis, possibly by increasing the risk of cellular transformation by enhancing cell turnover.[14-16] Indeed, many types of neoplastic cells express or overexpress IGF-I receptors, which stimulate mitogenesis when activated by IGF-1 in vitro.[14] Because determinants of tissue IGF bioactivity appear to be regulated in parallel with circulating IGF-1 level, tissue IGF bioactivity can be evaluated by only circulating IGF-1 and IGFBP levels. In recent epidemiologic studies, relatively high plasma IGF-1 and low IGFBP-3 levels have been independently associated with greater risk of several malignancies including prostate cancer in men, breast cancer among premenopausal women, and colorectal neoplasms.[13,15,16] However it has been reported that the pattern of this association differs smoking-related cancers and the others.[13] Over the past decade, many studies have also provided evidence for relationship between IGF system and lung cancers.[13,17-21] In some of them, elevated IGF-1 and depressed IGFBP-3 levels were reported in lung cancers.[13,17-19] On the other hand, some authors reported that mean serum levels were not significantly different between the case and the control groups.[20] In the present study, we found depressed IGF-1 and IGFBP-3 levels in the patients. However, lower IGF-1 and IGFBP-3 levels were determined in stage 3B disease when compared to stage 4 disease among the patients. We found the higher IGF-1 and IGFBP-3 levels in metastatic disease. In a previous study, Unsal et al. reported a similar result for the patients and the control group.[21] However, higher levels were found in lower stage disease unlike our results. We could not explain the cause of this discrepancy. However we thought that the balance between IGF-1 and IGFBP-3 could be affected in the patients with NSCLC, and this balance might be important for growth of lung cancer. In addition, because of mitogenic effect, IGF-1 may provoke the tumor dissemination and aggressiveness.

It is known that serum levels of IGF-1 and IGFBP-3 depend on age, smoking history and nutritional status.[21] The effects of the cigarette smoking on the serum levels of IGF-1 are unclear.[13] A number of studies showed a declining trend for IGF-1 concentrations with increased smoking.[18] In the present study, the mean number of cigarettes smoked per day was 18.2±4.7 in the control group and 52.08±22.03 in patients with NSCLC. All cases (despite the difference in terms of the number of daily smoked cigarettes in patients and the controls) had smoking history of 20 pack/years and all of them were defined as "heavy smokers". For this reason, the effect of smoking was not analyzed statistically. We thought that the depressed IGF-1

and IGPBP-3 levels could depend on smoking history in our series. In recent studies, usually there was a between the patients and the controls for smoking history. Therefore we selected the healthy heavy smokers as controls and we thought that our different results occurred due to smoking status.

Lee et al. showed that the histological type of lung tumor was related to IGF system and lower IGF-1 levels were reported in NSCLC compared to small cell lung cancer (SCLC).[17] Low levels of IGF-1 and IGFBP-3 in lung cancers could be due to decreased synthesis or increased catabolism of IGF-1. However, the reason for different IGF-1 levels in the subtypes of lung cancers are unclear. Reave et al. reported that decreased serum IGF-1 concentrations might be associated with an abnormal glucose tolerance in SCLC.[22] They suggested that these findings may indicate that increased serum IGFBPs disrupt IGF-I regulation of GH secretion and glucose homeostasis. In the present study, lower IGF levels were determined in patients with adenocarcinoma and higher levels were in SCC. We thought this difference might be caused from an imbalanced insulin and IGF system.

In conclusion, we have demonstrated that the pretreatment serum levels of IGF-1 and IGFBP-3 are associated with advanced NSCLC. We also identified low plasma levels of IGF-1 and IGFBP-3 in advanced NSCLC. On the other hand, higher levels of IGF-1 and IGFBP-3 might be useful for identifying patients with high risk of metastases. Naturally high IGF-levels do not represent evidence of the presence of metastatic lung cancer, but rather may reflect host characteristics that may indicate a relatively favorable environment for neoplastic progression. With rare exceptions, insulin is not produced by cancer cells. In contrast, IGF-1 is locally produced by neoplastic tissues and this provides a source of these ligands supplementary to the classical endocrine production by the host liver. We are aware of limitations of this study, the sample size is small and follow-up time is insufficient. Therefore larger-scale studies are needed to verify the clinical significance of IGF system in patients with lung cancer.

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