RESEARCH ARTICLE

Serum Tumor Markers, Hypoxia-Inducible factor-1α HIF-1α and Vascular Endothelial Growth Factor, in Patients with Non-small Cell Lung Cancer Before and after Intervention

Jun Liang[1]*, Ying Qian[1], Dan Xu[1], Qun Yin[2], Hui-Juan Pan[2]

Abstract

Objective: To explore changes in the serum tumor makers, hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) level and their relations in patients with non-small cell lung cancer (NSCLC) before and after intervention. Materials and Methods: Forty patients with NSCLC and 40 healthy individuals undergoing physical examination in our hospital provided the observation and control groups. HIF-1α and VEGF levels in serum were detected by enzyme-linked immuno-sorbent assay (ELISA) in the observation group before and after intervention and in control group on the day of physical examination, along with serum carcino-embryonic antigen (CEA), neuron-speci ic enolase (NSE) and squamous cell carcinoma antigen (SCC) levels in the observation group with a fully automatic biochemical analyzer. Clinical effects and improvement of life quality in the observation group were also evaluated. Results: The total effective rate and improvement of life quality after treatment in observation group were 30.0% and 32.5%, respectively. Serum HIF-1α and VEGF levels in the control group were lower than that in observation group ($p<0.01$), but remarkably elevatedafter intervention ($p<0.01$). In addition, serum CEA, NSE and SCC levels were apparently lowered by treatment ($p<0.01$). Serum HIF-1αdemonstrated a positive relation with VEGF level ($p<0.01$) and was inversely related with CEA, NSE and SCC levels ($p<0.01$). Conclusions: Significant correlations exist between marked increase of serum HIF-1α and VEGF levels and decrease of indexes related to hematological tumor markers in NSCLC patients after intervention.

Keywords: Intervention - non-small cell lung cancer - vascular endothelial growth factor - hypoxia-inducible factor-1α

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Introduction

At present, non-small cell lung cancer (NSCLC), a solid tumor accounting for 80% of lung cancer, has an infinite proliferation and uncontrolled growth, and becomes the first cause of cancer-related death. Microcirculation due to anoxia, the most common result of NSCLC, can improve the radiotherapy and chemotherapy tolerance as well as the invasiveness and distant metastasis of tumor cells (Li, et al., 2011; Wouters et al., 2011; Yan et al., 2011; Deacon et al., 2012; Li, et al., 2012; Liu et al., 2013; Lu et al., 2013). The tumor growth and metastasis mainly depend on tumor angiogenesis, in which vascular endothelial growth factor (VEGF) is the most powerful, and hypoxia-inducible factor 1 alpha (HIF-1α) is the core in regulating and controlling the expression of various target genes such as serum tumor markers and VEGF (Furrukh et al., 2013; Wang et al., 2013). The purpose of this study is to explore the serum tumor makers, HIF-1α and VEGF level changes and their relations in patients with NSCLC before and after intervention.

Materials and Methods

General Data

Forty patients diagnosed as NSCLC by pathology or cytology admitted in our hospital from Jul., 2010 to Aug., 2012 were selected as observation group, in which there were 15 males and 25 females. They were 46-82 years old, and the mean was (66.1±6.5) years old. Other 40 healthy people underwent physical examination at the same period were chosen as control group, in which 16 males and 24 females. They were 47-78 years old, and the mean age was (68.4±7.5) years old. There were no significant differences in general data like the age and gender, indicating that there was comparability between two groups ($p>0.05$). The general data of observation group was shown in Table 1.

Intervention

According to Seldinger technique, femoral artery puncture was performed on the patients in observation group under local anesthesia. 4-5Fcobra or Yashiro

*[1]Department of Oncology, [2]Nursing Department, Wuxi People's Hospital of Huishan District, Wuxi, Jiangsu, China *For correspondence: doctorliangjun@163.com*

Table 1. General Data of Observation Group(n=40)

Classifications	Number of cases
Disease location	
Left-side lung cancer	16
Right-side lung cancer	24
Disease types	
Central lung cancer	20
Peripheral lung cancer	20
Pathological types	
Squamous carcinoma	25
Adeno-carcinoma	15
Differentiation degrees	
High differentiation	11
Moderate differentiation	20
Low differentiation	9
Lymphatic metastasis	
Metastasis	30
Non-metastasis	10

Table 2. Changes of HIF-1α and VEGF levels in Two Groups ($\overline{\chi}\pm s$)

Groups	Number of cases	HIF-1α/ng·L^{-1}	VEGF/pg·mL^{-1}
Control Group	40	37.21±4.33	596.45±60.24
Observation Group	40		
Before Treatment	40	50.66±6.54**	724.56±76.42**
After Treatment	40	60.82±6.71**$^{\#\#}$	965.22±98.41**$^{\#\#}$

Compared with control group, **p<0.01; Compared with treatment before, $^{\#\#}p$<0.01

catheter was adopted and transferred to the level of 4-7th thoracic vertebra under the monitoring of X ray scan or digital subtraction angiography (DSA) to search for bronchial artery ostia. Once the catheter entered the bronchial artery, 3-6 mL contrast medium was injected to observe the entrance of the target artery under the X ray. After tumor vessels were confirmed, 1.0 g cyclophosphamide, 1.0g 5-flourouracil (5-FU), 50 mg oxaliplatin and 50 mg adriamycin were diluted into 40-60 mL solution with normal saline respectively, and injected gradually through the catheter in 30 min. Gelatin sponge was used to stuff the tumor blood vessels if there was no common stem between bronchial artery and spinal or intercostal artery. The vertebra was extracted after injection, and local compression hemostasis was made for 15 min before pressure bandaging. Immobilization was made for 12 h for the punctured limb, and then staying in bed was 24 h.

Observation indexes

In the morning, 5 mL blood was taken from the fasting patients in control group on the day of physical examination and observation group 1-2 d and 1 d before and after intervention, respectively. The blood was centrifuged for 10 min at speed of 5 000 r/min, followed by serapheresis and preserved in freezer at -20°C. HIF-1α and VEGF levels were detected with ELISA, and relevant serum tumor markers were observed by fully automatic biochemical analyzer. Clinical effect of observation group was evaluated. Evaluation criterions for the therapeutic effect were as follows: complete remission (CR), complete disappearance of tumor over 4 weeks; partial remission (PR), shrank tumor >50%; normal control (NC), shrank tumor >25%; progressive disease (PD), increased tumor >25% or appearance of new lesions. Total effective rate= [(CR+PR)/total cases]×100%. The quality of life was evaluated according to Karnofsky performance status (KPS) score. After treatment, the patients with increased KPS≥10 scores after treatment was regarded as improvement, those with reduced ≥10 scores as decrease, while the level between the above two was considered as stabilization.

Table 3. Changes of Serum Tumor Markers in Observation Group ($\overline{\chi}\pm s$, ng/mL)

Groups	Number of cases	CEA	NSE	SCC
Before Treatment	40	40.23±4.21	33.78±4.06	38.45±4.06
After Treatment	40	28.54±3.04**	19.56±2.14**	22.47±2.36**

Compared with treatment before, **p<0.01

Table 4. Relations between Serum HIF-1α and VEGF and Expression of Tumor Markers Before and after Intervention in Observation Group

	VEGF	CEA	NSE	SCC
r	0.512	-0.426	-0.468	-0.307
p	<0.01	<0.01	<0.01	<0.01

Statistical data analysis

SPSS 13.0 statistical software and t test were applied to compare the means of two groups with as the standard deviation. p<0.05 was represented differences had statistical significance.

Results

Clinical effective rate in observation group

Of 40 cases in observation group, 0 was CR, 12 were PR, 15 were NC and 13 were PD. The total effective rate reached 30% (12/40). KPS score was improved by different degrees in patients with NSCLC after intervention, and the improvement rate was obtained as 32.5% (13/40).

Changes of serum HIF-1α and VEGF levels before and after intervention in two groups

Serum HIF-1α and VEGF levels in control group were evidently lower than that in observation group, being(37.21±4.33) ng/L and (596.45±60.24) pg/mL, respectively, and the difference was statistically significant (p<0.01). Serum HIF-1α and VEGF levels in observation group after intervention were remarkably higher than that treatment before (p<0.01). The changes of serum HIF-1α and VEGF levels before and after intervention in two groups were shown in Table 2.

Changes of tumor markers before and after intervention in observation group

Serum tumor markers CEA, NSE and SCC levels detected in observation group decreased apparently after treatment (p<0.01) (Table 3).

Relations between serum HIF-1α and VEGF and expression of tumor markers before and after intervention in observation group

Serum HIF-1α was in positive relation with VEGF

level (p<0.01), but was negatively related to the levels of CEA, NSE and SCC (p<0.01) (Table 4).

Discussion

Lung cancer, a malignant tumor derived from pulmonary bronchial mucosal epithelium, becomes the leading cause of death in all caners. With the development of industrialization, lung cancer is paid more and more attention due to its annually rising morbidity (Falchook et al., 2013; Pallis et al., 2013). As an emerging therapeutic method, intervention with less invasiveness, small trauma and no operation is more superior in treating lung cancer than medical and surgical therapies. Local anesthesia is needed to reduce adverse reactions to a minimum (Frechen et al., 2011; Lee et al., 2012) and inhabit the drug actions to local lesions in order to reduce damage to other organs. Moreover, intervention is widely applied in clinic to treat lung cancer due to its incomparable advantages (Tanabe et al., 2010).

The proliferation and spread of cancer cells are closely related with its environment, so anaerobic condition can improve the drug resistance and invasiveness of cancer cells (Kim et al., 2005). Neo-vascularization is the main cause of the spread and metastasis of cancer cells, in which VEGF, the main factor of angiogenesis, is in close correlation with its spread and HIF-1α plays an important role in overall regulation and control (Deacon Ket al., 2012; Nakajima et al., 2012). Considerable researches have shown that serum VEGF level is evidently higher in patients with lung caner than in healthy control group, and is in positive relation with TNM staging of lung cancer with no significant difference in NSCLC patients with different genders, differentiated degrees and pathological types (Ramlau et al., 2012; Sandler et al., 2012; Siejka et al., 2012). As VEGF is important in the occurrence, development and metastasis of lung cancer, the change of serum VEGF level can be used as a significant index to evaluate the early diagnosis, effectiveness and prognosis of lung cancer (Kausar et al., 2012).

HIF, a transcription factor and important substance in maintaining oxygen homeostasis, is widely found in human and mammal bodies. It is a hetero-dimer including HIF-1α and HIF-1β, the subunits of oxygen conditioning and structure, respectively (Andersen et al., 2011). The former is an sub-gene regulating HIF-1 activity with over 100 target genes including VEGF, erythropoietin, glycolytic enzyme, TGF-β and transferrin factor that can improve the tumor growth and metastasis. Previous studies demonstrated that HIF-1α expression level was closely associated with angiogenesis, progression, metastasis and invasiveness, and could effectively evaluate the prognosis of malignant tumors (Jackson et al., 2010; Singh-Gupta et al., 2011). The high expression level of HIF-1α in patients with NSCLC was associated with clinical differentiation and metastasis, but there ass no expression in healthy pulmonary tissue 15-20 cm away from tumor tissue, indicating that HIF-1α plays an important role in the occurrence, development, distal metastasis and local infiltration of NSCLC (Choi et al., 2009; Jacoby et al., 2010). The results of this study showed that serum HIF-1α and VEGF levels in observation group were evidently higher than that in control group, and increased remarkably in both groups after intervention, showing no difference with other researches.

As the antigens and bio-activators produced by tumor tissues and cells due to the abnormal expression of oncogenes and their products, hematological tumor markers have the crucial research value in early detection and diagnosis of lung cancer. CEA, VEGF, SCC and NSE are the common markers for lung cancer, which are closely connected with tumor burden and will increase in advanced cancer. Some studies revealed that SCC level at phases III and IV was evidently higher than at phases I and II, suggesting that SCC level runs parallel with TMN staging of lung cancer and the increased CEA and NSE (Lazarev et al., 2010; Ma et al., 2011-2012). This study showed that serum CEA, NSE and SCC levels in patients with NSCLC decreased significantly after intervention, and serum HIF-1α level was proportional to VEGF, CEA, NSE and SCC levels.

In conclusion, HIF-1α, VEGF and tumor markers are relevant and of great importance in predicting the occurrence, development, metastasis and prognosis of tumors. The joint detection of serum HIF-1α, VEGF and tumor markers in patients with NSCLC before and after intervention can reflect the degree of angiogenesis, and positively guide the clinical judgment on intervention response, organic tumor burden, growth, metastasis and prognosis of tumors.

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