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Original Article

The expression change and clinical significance of serum CEA, CYFRA21-1, ProGRP before and after IP regimen in the treatment of non small cell lung cancer

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Abstract: Objective: To investigate the expression change and their clinical significance of serum CEA, CYFRA21-1 and ProGRP before and after IP regimen in the treatment of non small cell lung cancer. Methods: 48 cases with NSCLC were selected as the observation group and 34 healthy people were selected as the control group. The serum levels of CEA, CYFRA21-1 and ProGRP in two groups were detected by electrochemiluminesecence immunoassay. The patients from the observation group received the IP regimen chemotherapy. According the curative effect, the patients in observation group were subdivided into two groups: the effective group and the deterioration group. The same methods were performed to detect the serum levels of CEA, CYFRA21-1 and ProGRP before and after chemotherapy in two groups. Results: The positive rate of serum CEA, CYFRA21-1 and ProGRP in the observation group were statistically higher than those in the control group, the difference was statistically significant ($P < 0.05$). After chemotherapy, in the effective group, the serum levels of CEA, CYFRA21-1 and ProGRP were significantly decreased. The difference was statistically significant, ($P < 0.05$). In the deterioration group, there was no significant difference between before and after thermotherapy for the expression of CEA, CYFRA21-1, and ProGRP ($P > 0.05$). Conclusion: The examination of serum CEA, CYFRA21-1, ProGRP before and after IP regimen chemotherapy was proved to be helpful for the prognosis for NSCLC patients.

Keywords: Non small cell lung cancer, IP regimen chemotherapy, tumor biomarkers

Introduction

As the incidence and mortality rate of lung cancer increasing year by year, lung cancer has become one of the most common malignant tumors that seriously threaten the lives of patients. Non-small cell lung cancer (NSCLC), as the main type of lung cancer, accounts for about 80% of the lung cancers, mainly including: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma; the cell proliferation and metastasis is slow that create conditions for local chemotherapy or radiotherapy in clinic [1, 2]. So far, IP chemotherapy is the main treatment for lung cancer at middle and late stages. It should not be overlooked that there are significant differences in overall survival time of patients after chemotherapy. Therefore, it is quite helpful to improve the survival rate of patients with lung cancer at middle/late stage if we can understand the prognosis after chemotherapy to intensively monitor the poor prognosis patients, and apply with appropriate anti-tumor treatment.

Many studies have shown that tumor markers can predict the prognosis of patients with NSCLC; at present, patients with elevated expression levels of tumor markers have a poorer prognosis than patients with normal levels [3-6]. The common focus of most previous studies was to highlight that the patients with tumor markers elevated in both pre-operation and post-operation would have the worst prognosis; they believed the serum carcinoembryonic antigen (CEA) is an independent risk factor for judging the prognosis of patients, and only studied CEA. Numerous studies revealed that cytokeratin fragment antigen (CYFRA21-1) and pro gastrin releasing peptide (ProGRP) also have predictive values for the prognosis of NSCLC patients [7, 8].

Table 1. Clinical databease of 48 patients with NSCLC

Clinical feature	*N* (%)
Age (year old)	
>60	29 (60.4)
≤60	19 (39.6)
Sex	
Male	32 (66.7)
Female	16 (33.3)
Cancer stage	
Stage I/II	8 (16.7)
Stage III/IV	40 (83.3)
PS scores	
0~1	22 (45.8)
≥2	26 (54.2)
Cancerous type	
SCC	21 (43.8)
Adenocarcinoma	27 (56.2)

To further precisely evaluate the effect of IP regiment chemotherapy in NSCLC, this study retrospectively investigated the expression levels of three tumor markers-CEA, CYFRA21-1, ProGRP, and the influence of these fluctuation on the efficacy and prognosis of NSCLC patients after IP chemotherapy by Cohor Study; the purpose of this study is to provide evidence for adjusting NSCLC chemotherapy.

Materials and methods

General material

48 patients with NSCLC treated in our hospital from May, 2012 to May, 2015 were selected as observation group and 34 healthy volunteers in the same period were selected as control group; among the 48 cases in observation group, there were 32 males and 16 females, aged from 38-80 years with a median age of 61 (60.28 ± 10.81) years, in which 29 patients > 60 years and 19 patients ≤ 60 years; cancer staging: 8 cases of Stage I or II and 40 cases of Stage III or IV; cancerous type: 27 cases of SCC and 21 cases of adenocarcinoma; Performance Score (PS): 22 cases scored 0-1 and 26 cases scored ≥ 2, see in **Table 1**; 34 cases of control groups included 17 males and 17 females, aged from 39 to 81 years with a median age of 60 (59.35±10.21) years, in which 17 patients > 60 years and 17 patients ≤ 60 years; the inclusion criteria: all patients were diagnosed and confirmed by histopathology; the imaging examination confirmed there was a cancerous lesion, and could be used for quantitative examination of the target lesion; clinical data were complete, and patients did not receive surgical treatment or chemoradiotherapy treatment; the exclusion criteria: co-exist with cardiovascular and cerebrovascular diseases; tumors in other organs; diseases of respiratory, immune and endocrine system; the staging and type of cancer was not confirmed; patients had history of operation and chemoradiotherapy.

The overall survival time (OS) refers to the period from the first day after IP regiment chemotherapy to the time of death of patients or the last follow-up date. 48 patients were followed up; the follow-up period was 6 months to 42 months with an average period of 20 months. The follow-up was mainly telephone follow-up and outpatient follow-up.

Treatment programs

Patients in observation group were treated with IP chemotherapy, IP chemotherapy dose: irinotecan 90 mg/m^2, intravenously dripped on D1and D8; cisplatin 20 mg/m^2, intravenously dripped from D1 to D3; the observation group was subdivided into effective group and deterioration group according to treatment efficacy.

Detection of serum CEA, CYFRA21-1, ProGRP

5 ml peripheral venous blood was collected from all experimental subjects one week before IP chemotherapy, and 1 week after the 2nd cycle of IP chemotherapy; then the blood was centrifuged at 4000 r/min, the serum was used for direct detection, the expression levels of CYFRA21-1 and ProGRP were detected by ECLIA, using Roche electrochemical analyzer (Roche). CEA levels were detected by CLIA. The kits were purchased from Abbott US. The normal levels of CEA, CYFRA21-1 and ProGRP are 0~4.3 ng/ml, 0~3.3 ng/ml, and 0~46 pg/l respectively.

Efficacy evaluation criteria

According to 1979 WHO criteria, the efficacy can be divided into four grades: complete remission, partial remission, stable disease and disease progression; complete remission: no cancerous lesions, the levels of tumor mark-

Table 2. The comparison of positive rate of tumor markers between the observation group and the control group (n (%))

Group	*N*	CEA positive rate	CYFRA21-1 positive rate	ProGRP positive rate
Control group	34	2 (5.88)	3 (8.82)	1 (2.94)
Observation group	48	38 (79.16)	44 (91.67)	41 (85.42)
χ^2		12.658	15.652	14.324
P		0.046	0.026	0.037

Table 3. Comparison of the levels of tumor markers in patients of effective group before and after chemotherapy

Time	CEA (ng/ml)	CYFRA21-1 (ng/ml)	ProGRP (pg/l)
Before chemotherapy	5.91±1.42	8.29±3.92	38.7±8.62
After chemotherapy	1.52±0.52	1.04±0.35	12.6±2.75
χ^2	15.325	14.965	17.362
P	0.029	0.36	0.015

Table 4. Comparison of the levels of tumor markers in patients of deterioration group before and after chemotherapy

Time	CEA (ng/ml)	CYFRA21-1 (ng/ml)	ProGRP (pg/l)
Before chemotherapy	5.87±1.39	8.34±3.87	38.6±8.74
After chemotherapy	5.62±1.14	8.56±3.63	36.5±8.33
χ^2	5.632	4.257	6.053
P	0.075	0.083	0.068

ers were normal, and maintained for more than four weeks; partial remission: cancer lesion diameter, compared to baseline levels, reduced ≥ 30%, and maintained for more than four weeks; stable disease: cancerous lesion diameter, compared to baseline level, reduced but did not reach partial remission level or increased but did not reach the level of disease progression, and maintained for more than four weeks; disease progression: cancerous lesion diameter, compared to baseline, increased ≥ 25% or new cancerous lesions appeared. In this study, the patients in effective group had complete remission, partial remission, or stable disease; patients in deterioration group had disease progression.

Data processing

SPSS12.0 software was used to deal with experimental data, measurement data was represented by (x ± s), T test was used to compare the data between groups; count data was tested by χ^2; Cox proportional hazards regression model was used to analyze risk factors associated with prognosis. P <0.05 was considered statistically significant.

Results

The comparison of positive rate of tumor markers between observation group and control group

Before the IP chemotherapy treatment, the positive rates of serum CEA, CYFRA21-1, ProGRP in patients of the observation group were significantly higher than those of the control group (P <0.05); see **Table 2**.

Comparison of the levels of tumor markers in patients of effective group before and after chemotherapy

Compared with pre-chemotherapy, the levels of serum CEA, CYFRA21-1, and ProGRP were significantly decreased after chemotherapy (P <0.05); see **Table 3**.

Comparison of the levels of tumor markers in patients of deterioration group before and after chemotherapy

The levels of serum CEA, CYFRA21-1, and ProGRP in patients of deterioration group showed no significant difference before and after the chemotherapy (P >0.05); see **Table 4**.

Univariate analysis on the factors affecting the prognosis of patients with NSCLC after IP chemotherapy

Sex (HR = 4.698, 95% CI: 1.402-13.556), cancer stage (HR = 1.793, 95% CI: 1.091-2.776), CYFRA21-1 (HR = 1.018, 95% CI: 1.005-1.036) and ProGRP (HR = 2.132, 95% CI: 1.106-1.723) were the prognostic risk factors affecting overall survival time of patients; see **Table 5**.

Discussion

Occult onset, unspecific symptoms in the early stage of NSCLC results in missing the best opportunity of diagnosis and treatment for patients. Epidemiological studies show, more

Table 5. Results of the univariate analysis of prognostic factors in NSCLC patients after IP chemotherapy treatment

Parameter	Overall survival time	
	HR (95% CI)	P
Age	1.055 (0.486-2.203)	0.924
Sex	4.698 (1.402-13.556)	0.013
Types of cancer	1.036 (0.478-2.182)	0.923
Cancer stage	1.793 (1.091-2.776)	0.021
CEA	1.005 (1.000-1.008)	0.062
CYFRA21-1	1.018 (1.005-1.036)	0.022
ProGRP	2.132 (1.106-1.723)	0.030

than 80% NSCLC patients have extrathoracic metastasis after diagnosis; these patients usually lost indications for surgery, or have reoccurrence or cancer metastasis after surgery [9-11]. In this regard, chemotherapy, as one of the primary treatments for NSCLC, combined with surgery/radiotherapy, can significantly improve the treatment efficacy of NSCLC. Currently, cisplatin-based combination chemotherapy is still used clinically as one of the main chemotherapies in NSCLC treatment, IP regimen chemotherapy, with irinotecan and cisplatin, is beneficial for specifically killing NSCLC tumor cells. However, exploring a method to predict the prognosis of patients, and then aggressively treat those patients with poor prognosis to improve their long-term survival, is one of the major challenges we currently face.

So far, a lot of biomarkers have been shown to predict the prognosis of NSCLC patients, such as P53, Bcl-2, K-ras mutant, erbB2/Neu etc. However, these biomarkers are often obtained from the specimen surgically removed; This is highly cost. Also, some scholars believe that BVI staging, PT staging, VPI staging and tumor heterogeneity can predict the prognosis of NSCLC patients. However, compared with the previously mentioned indicators, tumor markers are the best indicators for predicting the prognosis of NSCLC patients [12-14] due to its simple detection method, repeatability, low cost and accuracy.

CEA was first found in colon cancer, and later its high expression was also found in esophageal cancer, lung cancer and other malignant tumors. At present, the reasons for the rise of CEA are not consistent, but it is more accurate that CEA expression level increased in patients with poor prognosis. There are studies [15, 16] believe that CEA, as a tumor marker, has high sensitivity and specificity in NSCLC diagnosis. By detecting serum CEA level, it is beneficial to monitor and accurately diagnose the disease, as well as detect the efficacy of treatment. Research has confirmed that CEA was a risk factor for postoperative prognosis of patients with NSCLC. Further subgroup analysis showed that CEA was an independent risk factor for the prognosis of NSCLC patients [17]. In addition, the change of CEA level has a certain value in predicting the curative effect and prognosis of patients with advanced lung cancer. Study has indicated that increasing or decreasing of serum CEA level in patients with only 1 chemotherapy regimen can predict their response to therapy. In this study, CEA levels of NSCLC patients after IP regimen chemotherapy were significantly lower than those of pretreatment; and compared with the control group, there was no significant difference; however, univariate factor analysis showed that the level of CEA was not one of the risk factors for the prognosis of NSCLC patients after IP regimen chemotherapy.

As acidic protein, CYFRA21-1 is highly expressed in cancer cells; after cancer cell apoptosis, it enters into blood circulation [19]; due to the low level in serum of healthy organism, and negative reaction, CYFRA21-1 has a week effect in screening patients with early stage lung cancer. After NSCLC lesion formation, serum CYFRA21-1 levels were abnormally elevated, with specificity more than 87%; combined with CEA detection, the sensitivity of the diagnosis of NSCLC can be increased to more than 80%. In addition, in the chemotherapy treatment of NSCLC, the half-life of CYFRA21-1 is very short, and adversely related with the treatment response of patients, proving that under inhibition circumstance, cancer cells release less cell keratin fragments that directly reduce CYFRA21-1 from entering into the blood circulation; however, elevated preoperative CYFRA21-1 levels are closely related with T stage and N stage in tumor staging; the higher the expression level is, the higher the T staging will be, and so does the tumor size, which further suggesting that CYFRA21-1 can be used as a tumor marker of NSCLC to evaluate the effect and prognosis of NSCLC treatment. The results of this study showed that the change of CYFRA21-1 expres-

sion level was one of the important factors to predict the prognosis of NSCLC patients after IP chemotherapy.

ProGRP, as the precursor of gastrin releasing peptide, is highly expressed in the tumor lesions of NSCLC; it can enter into blood circulation during the process of tumor cell proliferation and metastasis. A large number of studies [20, 21] showed that ProGRP used as a tumor marker, has higher specificity and sensitivity than CEA in diagnosing NSCLC. The serum ProGRP highly expressed in patients with NSCLC. Under the circumstance of effective chemotherapy, serum ProGRP was significantly decreased; however, with the reoccurrence of NACLC, the serum ProGRP level significantly elevated. By detecting the level of serum ProGRP, especially when the level is higher than 46 pg/l, we can accurately diagnose NSCLC to avoid missing the best treatment time of NSCLC. The results of this study showed that the change of ProGRP expression level is also an important factor for predicting the prognosis of NSCLC patients after chemotherapy.

In summary, serum levels of CEA, CYFRA21-1 and ProGRP in patients of observation group were significantly higher than those of control group, especially CYFRA21-1 and ProGRP; NSCLC patients, who had elevation in both CYFRA21-1 and ProGRP after surgery, had significantly poor prognosis. The detection of ProGRP, CYFRA21-1 and CEA before and after chemotherapy is beneficial to the prognosis of NSCLC patients. But there are some limitations in this study: a retrospective study, the sample size is too small etc.

Disclosure of conflict of interest

None.

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