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Original Article

Dynamic monitoring serum CEA and CYFRA21-1 during chemotherapy in patients with advanced lung adenocarcinoma and assessment of prognosis

Yanping Bei, Kaitai Liu, Miaozhen Lu

Department of Radiotherapy, Lihuili Hospital, Ningbo Medical Center, Ningbo, Zhejiang, China

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Abstract: Tumor markers contribute to lung cancer diagnosis, curative effect evaluation, and prognosis evaluation. CEA, CYFRA21-1, and NSE are commonly used for lung cancer in clinic. This study investigated serum CEA and CYFRA21-1 in advanced lung adenocarcinoma patient chemotherapy and assessed prognosis. 104 cases of advanced lung adenocarcinoma patients confirmed by pathology or cytology were enrolled. Serum CEA and CYFRA21-1 levels at different time were detected to analyze the correlation of CEA and CYFRA21-1 before and after chemotherapy with prognosis. Kaplan-Meier method was applied to calculate survival curve. Cox proportional hazard model was used for multivariate survival analysis. Serum CEA level before chemotherapy was higher in female than that in male ($P < 0.05$), while CYFRA21-1 showed no statistical difference with gender, age, and clinical stage. CEA was lack of significant difference among different age groups. Patients with partial remission showed markedly lower serum CEA and CYFRA21-1 after chemotherapy ($P < 0.05$). Serum CYFRA21-1 level obviously declined after two cycles of chemotherapy ($P < 0.05$). CEA and CYFRA21-1 levels in progressive stage were obviously higher after chemotherapy ($P < 0.05$). Kaplan-Meier curve showed that OS had statistical difference between different CEA and CYFRA21-1 levels ($P < 0.05$). Cox regression analysis presented that the prognostic risk factors of advanced lung adenocarcinoma patients were clinical stage IIIB~IV, serum CEA ≥ 20 ng/mL and CYFRA21-1 ≥ 5.0 ng/mL before chemotherapy. Dynamic monitoring serum CEA and CYFRA21-1 in advanced lung adenocarcinoma patients before and after chemotherapy was facilitated to prognosis evaluation.

Keywords: Lung adenocarcinoma, CEA, CYFRA21-1, prognosis

Introduction

Primary lung cancer is common in clinic with high incidence and mortality. It can be divided into small cell lung cancer and non-small cell lung cancer (NSCLC) according to the histopathological characteristics, while NSCLC accounts for 80-85% of total lung cancer. Its treatment strategy and prognosis are associated with early diagnosis and histological type [1, 2]. Serum tumor markers were widely applied in lung cancer diagnosis, curative effect evaluation, and prognostic evaluation along with the development of tumor molecular biology and genomics. Combined dynamic monitoring serum tumor markers facilitated tumor therapy surveillance [3, 4]. Currently, various serum tumor markers were used in clinic for lung cancer, including carcinoembryonic antigen (CEA), cytokeratin 19 fragment antigen (CYFRA21-1), neuronspecific enolase (NSE), squamous cell carcinoma antigen (SCC-Ag), pro-gastrin-releasing peptide (pro-GRP), and tissue polypeptide specific antigen (TPA) [5, 6]. CEA is a broad spectrum tumor marker that elevated in multiple tumors with low specificity, such as lung cancer, breast cancer, gastric cancer, and pancreatic cancer. Serum CEA level elevation followed with stage increasing which plays an important role in judging condition and prognosis assessment [7, 8]. CYFRA21-1 is a type of keratin with small molecular mass that firstly detected in squamous cancer cells. It has high sensitivity and specificity for NSCLC. Serum CYFRA21-1 has critical role for lung cancer diagnosis and prognosis assessment as its level increased with stage increasing [9, 10]. This study dynamically monitored serum CEA and CYFRA21-1 before

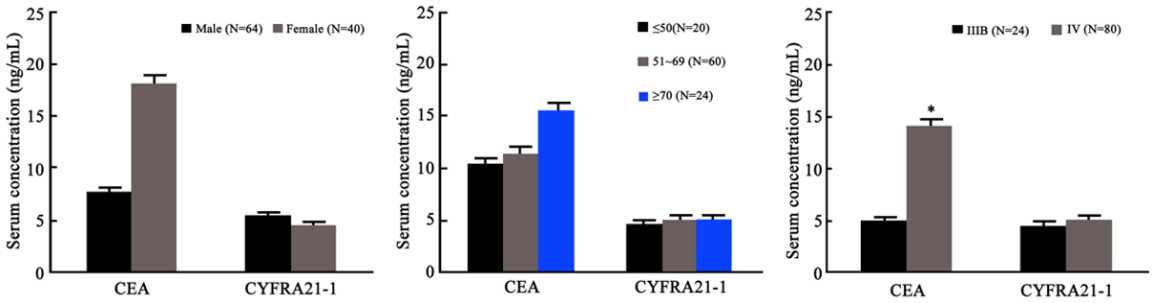

Figure 1. Correlation analysis of serum CEA and CYFRA21-1 with gender, age, and clinical stage. *$P < 0.05$, compared with male patients or stage IIIB.

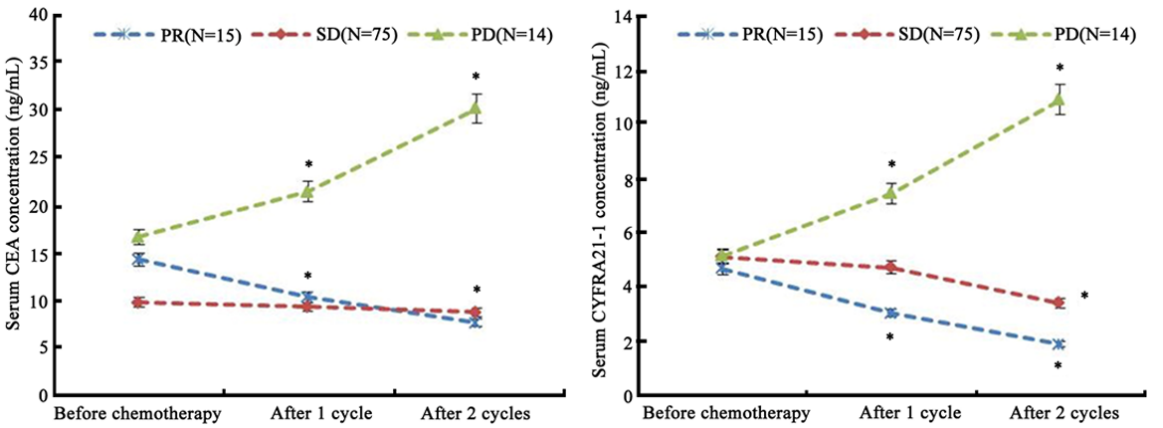

Figure 2. Correlation analysis of serum CEA and CYFRA21-1 with clinical curative effect. *$P < 0.05$, compared with before chemotherapy.

and after chemotherapy and assessed prognosis in 104 advanced lung adenocarcinoma patients, to provide reference for clinical lung cancer diagnosis and treatment.

Materials and methods

Clinical information collection

We select 104 cases of advanced lung adenocarcinoma patients between Jan 2009 and Jun 2014 in Ningbo medical center confirmed by pathology or cytology was enrolled. There were 64 males and 60 females with mean age 61.5 ± 6.7 (31~76) years old. 24 cases were in stage IIIB, and 80 cases were in stage IV. Inclusion criteria: all patients were confirmed by pathology or cytology (including percutaneous biopsy, lymph node biopsy, bronchial brush samples and biopsy, pleural effusion cytology, and sputumentum exfoliative cytology), complete clinical data, clear stage, received systemic treatment (intravenous chemotherapy, local treatment, targeted therapy), serum CEA and CYFRA21-1 detection before each cycle treatment. Exclusion criteria: combined the second primary malignant tumor, loss to follow-up.

Written consents have been obtained from all research objects. The protocol of this study has been pre-approved by the ethical committee in Ningbo medical center.

Follow-up

Electronic medical records query and telephone follow-up were both applied. Progression free survival (PFS) was determined from definite diagnosis time to progressive disease (PD). Overall survival (OS) was confirmed from definite diagnosis time to death or Jan 2015. Survivors were treated as censored data.

Indicators detection

Fasting venous blood was extracted at first admitted and before each cycle chemotherapy

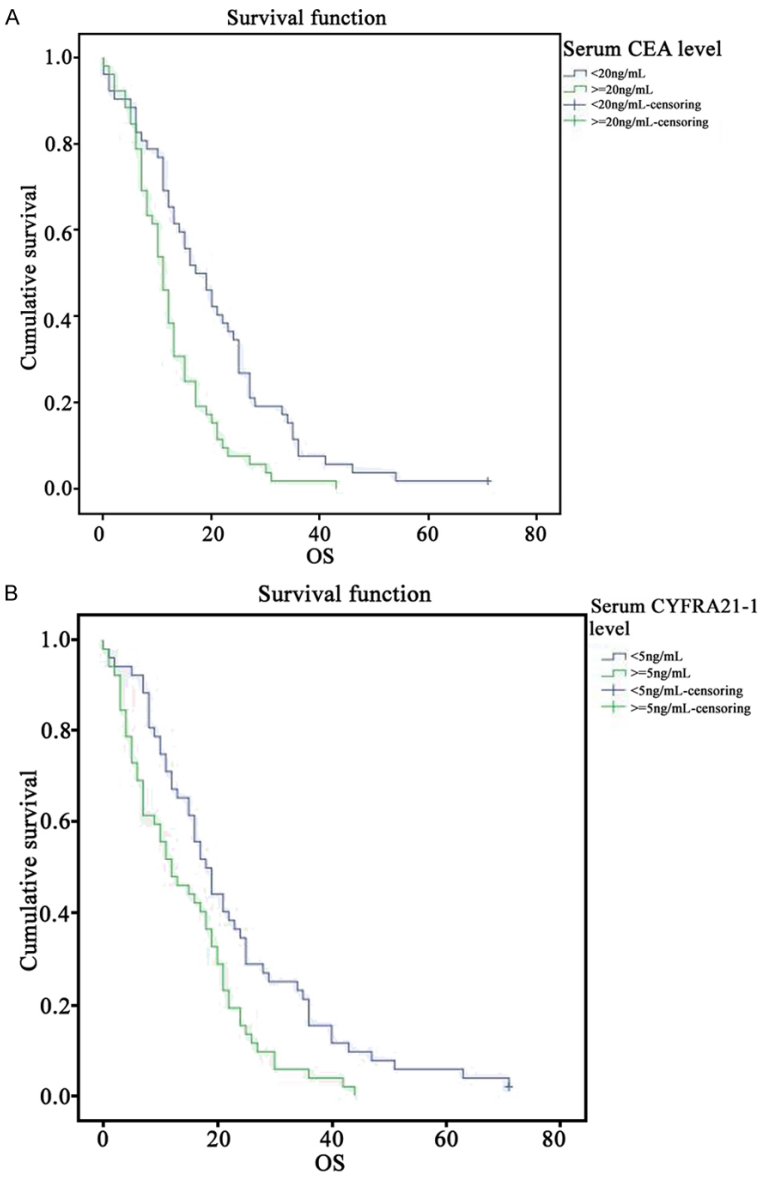

Figure 3. A. Correlation analysis between serum CEA before chemotherapy and prognosis. B. Correlation analysis between serum CYFRA21-1 before chemotherapy and prognosis.

(cycle 21 d~28 d). Serum was separated to detect CEA and CYFRA21-1 levels using electrochemiluminescence according to the kit (Nanjing Jiancheng Bioengineering Institute). Normal range: CEA, 0.0~4.7 ng/mL; CYFRA21-1, 0.1~3.3 ng/mL. Kaplan-Meier method was applied to calculate survival curve. Cox proportional hazard model was used for multivariate survival analysis.

Statistical analysis

All statistical analysis was performed on SPSS-19.0 software. Measurement data was tested by Kolmogorov-Smirnov test, and skewed distribution was presented as median ± quartile range (M ± Q). Mean value was compared using ANOVA and t test. Kaplan-Meier method was applied to calculate survival curve. Cox proportional hazard model was used for multivariate survival analysis. $P < 0.05$ was considered as statistically significant.

Results

Serum CEA and CYFRA21-1 levels and clinical characteristics

Serum CEA and CYFRA21-1 expression levels were detected during first admission. Serum CEA level was higher in female than that in male ($P < 0.05$), while CYFRA21-1 showed no statistical difference with gender ($P > 0.05$). CEA and CYFRA21-1 were lack of significant difference among different age groups ($P > 0.05$). CEA level in stage IV was obviously higher than that in stage IIIB ($P < 0.05$). CYFRA21-1 presented no statistical difference with clinical stage ($P > 0.05$) (**Figure 1**).

Correlation analysis of serum CEA and CYFRA21-1 with clinical curative effect

Serum CEA and CYFRA21-1 levels at admission were treated as base line. Imagological examination was applied after two cycles of chemotherapy to evaluate the curative effect [11]. No case achieved complete remission (CR) (0.00%), 15 cases reached partial response (PR) (14.42%), 75 cases showed stable disease (SD) (72.12%), and 14 cases appeared progressive disease (PD) (13.46%). Correlation between serum tumor markers level and clinical curative effect was analyzed. It was found that PR patients showed markedly lower serum CEA and CYFRA21-1 after chemotherapy ($P < 0.05$). CEA level in SD stage presented no statistical changes ($P > 0.05$). Serum CYFRA21-1 level obvi-

Table 1. Cox regression analysis of prognosis risk factor in advanced lung adenocarcinoma

Relative factor	β	$S_{\bar{x}}$	Wald χ^2	*P* value	OR value	95% CI	
Clinical stage IIIB~IV	0.839	0.354	5.610	0.019	2.314	1.156	4.633
CYFRA21-1 before chemotherapy	0.623	0.292	4.548	0.035	1.865	1.052	3.305
CEA before chemotherapy	0.677	0.313	4.689	0.034	1.968	1.066	3.632

ously declined after two cycles of chemotherapy ($P < 0.05$). CEA and CYFRA21-1 levels in PD stage were obviously higher after chemotherapy ($P < 0.05$) (**Figure 2**).

Correlation analysis of serum CEA and CYFRA21-1 with prognosis

Follow-up was end till Jan 2015. 103 patients died and only one case was still alive. Overall survival (OS) was 15 months (95% CI: 13.176~17.088). Median level of serum CEA in patients before chemotherapy was 17.62 ng/mL, while CYFRA21-1 was 4.93 ng/mL. Critical value of CEA was selected as 20 ng/mL, whereas CYFRA21-1 was chose as 5.0 ng/mL. OS in patients with CEA ≥ 20 ng/mL (11.0 months) was significantly shorter than that in patients with CEA < 20 ng/mL (17.0 months) (P < 0.05). OS in patients with CYFRA21-1 ≥ 5.0 ng/mL (12.0 months) was obviously shorter than that in patients with CYFRA21-1 < 5.0 ng/mL (18.0 months) (P < 0.05) (**Figure 3**).

Cox regression analysis

Cox regression analysis was used for multivariate survival analysis. It presented that the prognostic risk factors of advanced lung adenocarcinoma patients were clinical stage IIIB~IV, serum CEA ≥ 20 ng/mL and CYFRA21-1 ≥ 5.0 ng/Ml before chemotherapy (**Table 1**).

Discussion

Primary lung cancer is characterized as fast progress and high malignancy. It is the first cause of cancer death with 5-year survival rate at 10~15% [12, 13]. Following the aging of population and the environmental pollution aggravation, its incidence showed an increasing trend year by year [14, 15]. Since it lack of specific symptoms in early stage, most patients were in locally advanced stage when diagnosed and lost the optimal timing of treatment. Early diagnosis and treatment play important roles for improving the prognosis. Serum tumor markers are bioactive substance produced by oncogene abnormal expression in tumor tissue that can reflect cancerous tumor growth in a certain extent. They showed great significance in early phase screening, differential diagnosis, and curative effect evaluation [16-18]. This study discussed serum CEA and CYFRA21-1 expression in advanced lung adenocarcinoma before and after chemotherapy to analyze their role in prognosis.

CEA is acids glycoprotein with low level in normal adult serum. It can be detected in fetus in 3~6 months and decreased after the birth. Cancer cells can secrete CEA to increase serum level, while benign disease seldom causes serum CEA over 10 ng/mL [19, 20]. Prospective study about serum CEA in advanced NSCLC and chemotherapy curative effect showed that [21, 22] serum CEA level was significantly lower than the baseline value 10 ng/mL in effective patients after two cycles of chemotherapy. Serum CEA reduction represented progression-free survival extension, and it showed high sensitivity for curative effect evaluation in advanced NSCLC. In SCLC and lung adenocarcinoma, CEA level was related to chemotherapeutic response. Serum CEA was an independent risk factor for NSCLC death. Resectable NSCLC in stage I showed 5-year survival rate decline with elevated serum CEA. Unresectable advanced lung cancer patient showed significantly shorter PFS and OS with CEA increasing [21, 23]. Our results revealed that serum CEA in female was higher than in male before treatment, while it was lack of statistical difference among different ages. Patients in stage IV showed obviously higher serum CEA level than in stage IIIB, suggesting that female patients were more in advanced lung adenocarcinoma. Serum CEA was related to clinical stage. Dynamic monitoring CEA showed that its level decreased markedly in PR patients but was lack of changes in SD, while increased in PD after treatment, indicating that serum CEA level before treatment was associated with curative effect. Kaplan-Meier curve showed that serum CEA level before treatment was related to prog-

nosis. OS in patients with CEA ≥ 20 ng/mL was significantly shorter than that in patients with CEA < 20 ng/mL, suggesting that serum CEA before chemotherapy had a correlation with curative effect and prognosis. High serum CEA before treatment may be with poor prognosis.

CYFRA21-1 is a cytoskeleton marker that expressed in epithelial cell derived malignant tumor. Its level elevated obviously in NSCLC serum. CYFRA21-1 is sensitive to lung squamous carcinoma, and its serum concentration is associated with cancer severity. Study showed that CYFRA21-1 can be used as a predictor for recurrent NSCLC second-line chemotherapy efficacy [21, 23, 24]. It can predict different chemotherapies curative effects. Serum CYFRA21-1 elevation before treatment is a relevant factor of poor prognosis in local advanced and metastatic NSCLC [25, 26]. This study analyzed serum CYFRA21-1 level correlation with therapeutic effect and prognosis through dynamic monitoring its level before and after treatment in advanced lung adenocarcinoma. The results showed that serum CYFRA21-1 level before treatment presented no significant correlation between gender, age, and clinical stage. Serum CYFRA21-1 level decreased obviously in PR and SD patients after two cycles of chemotherapy, while increased in PD after treatment. Kaplan-Meier curve showed that serum CYFRA21-1 level before treatment was related to prognosis. OS in patients with CYFRA21-1 ≥ 5.0 ng/mL was obviously shorter than that in patients with CYFRA21-1 < 5.0 ng/mL. Cox regression analysis presented that the prognostic risk factors of advanced lung adenocarcinoma patients were clinical stage IIIB~IV, serum CEA ≥ 20 ng/mL and CYFRA21-1 ≥ 5.0 ng/mL before chemotherapy. It demonstrated that monitoring CEA and CYFRA21-1 can predict therapeutic efficacy.

In conclusion, dynamic monitoring serum CEA and CYFRA21-1 in advanced lung adenocarcinoma patients before and after chemotherapy was facilitated to prognosis evaluation.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yanping Bei, Department of Radiotherapy, Lihuili Hospital, Ningbo Medical Center, 57 Xingning Road, Ningbo 315000, Zhejiang, China. Tel: +86-13456130499; E-mail: beiyanpingl@126.com

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