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Effects of changes in serum endostatin and fibroblast growth factor 19 on the chemotherapeutic sensitivity in acute myeloid leukemia patients

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ABSTRACT. The present study aimed to explore the changes in serum endostatin and fibroblast growth factor 19 (FGF-19) in acute myeloid leukemia patients, and to determine their effects on chemotherapeutic sensitivity. Sixty acute myeloid leukemia patients and 30 healthy controls were included in the study. Patient serum endostatin and FGF-19 levels were measured on admission, and then, standard chemotherapy was administered. The patients were divided into 2 groups according to chemotherapeutic effects: 21 patients in the chemotherapeutic sensitivity group (complete remission + partial remission) and 39 in the chemotherapeutic resistance group (no remission + degradation). A receiver operating characteristic (ROC) curve was used to analyze the relationship of serum endostatin and

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FGF-19 levels with chemotherapeutic sensitivity in acute myeloid leukemia patients. The levels of serum endostatin and FGF-19 in acute myeloid leukemia patients before chemotherapy were significantly higher than those in the control group. Moreover, these levels significantly decreased after chemotherapy ($P < 0.01$). The levels of serum endostatin and FGF-19 in the chemotherapeutic sensitivity group were lower than those in the chemotherapeutic resistance group, both before and after chemotherapy ($P < 0.05$ and $P < 0.01$, respectively). ROC curve analysis showed that the predictive values of endostatin and FGF-19 were good, and there was no significant difference between these results. In conclusion, serum endostatin and FGF-19 can be used as predictors of chemotherapeutic sensitivity for acute myeloid leukemia patients, and may be important for determining prognosis.

Key words: Acute myeloid leukemia; Fibroblast growth factor 19; Endostatin; Chemotherapeutic sensitivity

INTRODUCTION

Acute myeloid leukemia is a common malignant disease of the blood. It has a high incidence and accounts for approximately 60% of all leukemia; therefore, it is a serious threat to human health (Won et al., 2013; Bernal et al., 2014). Patients with acute myeloid leukemia often have a variety of diseases. Because of cytogenetic and other factors, complete remission after chemotherapy is low, patient prognosis is poor, the disease-free survival period is short, and the 5-year survival rate is only approximately 10% (Lin et al., 2013; Oberoi et al., 2014). Thus, early intervention is important for the treatment and prognosis of patients with acute myeloid leukemia. Serum endostatin is a potent endogenous vascular growth inhibitor; it can effectively inhibit the growth and transition of endothelial cells, and reduce primary tumor growth and the metastasis rate. No drug resistance or toxic side effects have been observed after its use. The level of endostatin has been correlated with the progression and prognosis of a variety of malignant tumors (Liu et al., 2012; Xia et al., 2012; Moiseev et al., 2013). Fibroblast growth factor 19 (FGF-19) belongs to the FGF family, and is often expressed in the terminal ileum, brain, skin, and other sites. It can be involved in the metabolism of bile acid, glucose, vitamin D, and can affect the transformation and prognosis of diseases to a certain extent (Rotschafer et al., 2013; Gacche and Meshram, 2014). To date, few studies have examined variations in serum endostatin and FGF-19 in patients with acute myeloid leukemia and those with chemotherapeutic sensitivity, and its effect on prognosis. This study focused on changes in serum endostatin and FGF-19 in patients with acute myeloid leukemia before and after chemotherapy, and analyzed the relationship with chemotherapeutic sensitivity.

MATERIAL AND METHODS

General data

A total of 60 patients with acute myeloid leukemia admitted to our hospital and 30 healthy controls were included in this study. All patients did not undergo operative chemo-

therapy or targeted therapy, in accordance with the World Health Organization standards. Moreover, none of the patients had non-acute panmyelosis disease, bone marrow fibrosis, or myeloma. Of the patients with leukemia, 28 were men with an age range of 21-82 years, and a median age of 55.63 ± 24.18 years; 32 were women, with an age range of 23-80 years old, and a median age of 55.14 ± 25.61 years. Of the healthy controls, 14 were men with an age range of 22-73 years, and a median age of 53.24 ± 19.68 years; 16 were women with an age range of 20-81 years, and a median age of 56.42 ± 24.90 years. There were no significant differences in gender, age, or other general data between the two groups ($P > 0.05$). This study was conducted in accordance with the declaration of Helsinki and with the approval of the ethics committee of Yancheng Hospital affiliated to Southeast University. Written informed consent was obtained from all participants.

Detection methods

Serum endostatin and FGF-19 levels were analyzed in 30 controls and 60 leukemia patients after admission over the same time. The leukemia patients received neoadjuvant chemotherapy, and their serum endostatin and FGF-19 levels were reviewed after 2 weeks. On the second morning, 5 mL fasting venous blood was drawn from the elbow of all the subjects. After 2-week chemotherapy, 5 mL fasting venous blood was drawn from the elbow of leukemia patients, placed at room temperature for approximately 30 min, and centrifuged at 5000 revolutions/min for 10 min. The serum was separated and placed at a constant temperature of -20°C for preservation and future measurement. The detection of endostatin and FGF-19 levels were determined using kits and by following manufacturer protocols. The BIO-RAD Model 550 (Hercules, CA, USA) was also used. Endostatin levels were quantified using a human endostatin sandwich enzyme immunoassay kit (Chemicon International Inc., Temecula, CA, USA). FGF-19 levels were analyzed using a FGF-19 Quantikine® enzyme-linked immunosorbent assay kit (R&D Systems Inc., Minneapolis, MN, USA).

Treatment methods

All the leukemia patients received standard chemotherapy for at least 2 weeks by using the HA induction chemotherapy scheme (homoharringtonine, 2 mg/day, and cytarabine, 50 mg/day, for a total of 14 days) or the IA induction chemotherapy scheme (idarubicin, 6-8 mg/m^2 x 3 days and cytarabine, 100 mg/day x 7 days). Consolidation chemotherapy consisted of the DA scheme (daunorubicin, 40 mg/m^2, and cytarabine, 100 mg/day), HA scheme, or IA scheme. After chemotherapy, the curative effects were evaluated, and the patients' symptoms were observed.

Curative effect evaluation

Patients were divided into those who achieved complete remission (CR), partial remission (PR), no remission (SD), or degradation (PD) on the basis of their clinical profile and peripheral blood and bone marrow analysis, according to the third version of "Standard of diagnosis and curative effect for leukemia". CR + PR represented chemotherapeutic sensitivity and SD + PD, chemotherapeutic resistance.

Statistical analysis

All data were analyzed using the SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). The measurement data were compared using the *t*-test, and receiver operating characteristic (ROC) curves were drawn. The relationships between the serum endostatin and FGF-19 levels and the chemotherapeutic sensitivity were analyzed. P values < 0.05 were considered to be statistically significant.

RESULTS

Changes in serum endostatin and FGF-19 levels in leukemia patients before and after chemotherapy

The levels of serum endostatin and FGF-19 in leukemia patients were higher than those in the control group, and these levels significantly decreased after chemotherapy (P < 0.01; Table 1).

Table 1. Changes of serum endostatin and FGF-19 in patients with leukemia before and after chemotherapy.

Groups	Cases	Endostatin (μg /L)		FGF-19 (ng/L)	
		Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
Patients with leukemia	60	28.68 ± 15.26	18.14 ± 6.21	250.66 ± 45.81	140.24 ± 26.37
Control group	30	13.42 ± 5.74	13.42 ± 5.74	101.58 ± 34.65	101.58 ± 34.65
t		10.69	9.87	11.48	9.53
P		<0.01	<0.01	<0.01	<0.01

Comparison of serum endostatin and FGF-19 levels in the chemotherapeutic sensitivity and chemotherapeutic resistance groups after chemotherapy

Before and after chemotherapy, the levels of serum endostatin and FGF-19 in the chemotherapeutic sensitivity group were significantly lower than those in the chemotherapeutic resistance group, (P < 0.05 and P < 0.01, respectively; Table 2).

Table 2. Comparison of the levels of serum endostatin and FGF-19 in two groups after chemotherapy.

Groups	Cases	Endostatin (μg /L)		FGF-19 (ng/L)	
		Before chemotherapy	After chemotherapy	Before chemotherapy	After chemotherapy
Sensitivity group	21	23.18 ± 9.64	14.61 ± 4.42	210.74 ± 36.48	120.64 ± 24.12
Resistance group	39	31.15 ± 7.14	20.13 ± 5.71	281.14 ± 41.63	158.14 ± 25.51
t		8.25	7.48	8.06	8.14
P		<0.01	<0.01	<0.01	<0.01

Predictive value of serum endostatin and FGF-19 levels for the chemotherapeutic sensitivity of acute myeloid leukemia patients

ROC curve analysis of serum endostatin and FGF-19 levels before chemotherapy showed that the sensitivity predicting chemotherapeutic sensitivity was 92.16% and the speci-

ficity was 65.43% when endostatin reached 30.285 μg/L (Figure 1). When FGF-19 reached 276.140 ng/L, the sensitivity predicting chemotherapeutic sensitivity was 94.43% and the specificity was 69.38%. There was no significant difference between these two results (Table 3).

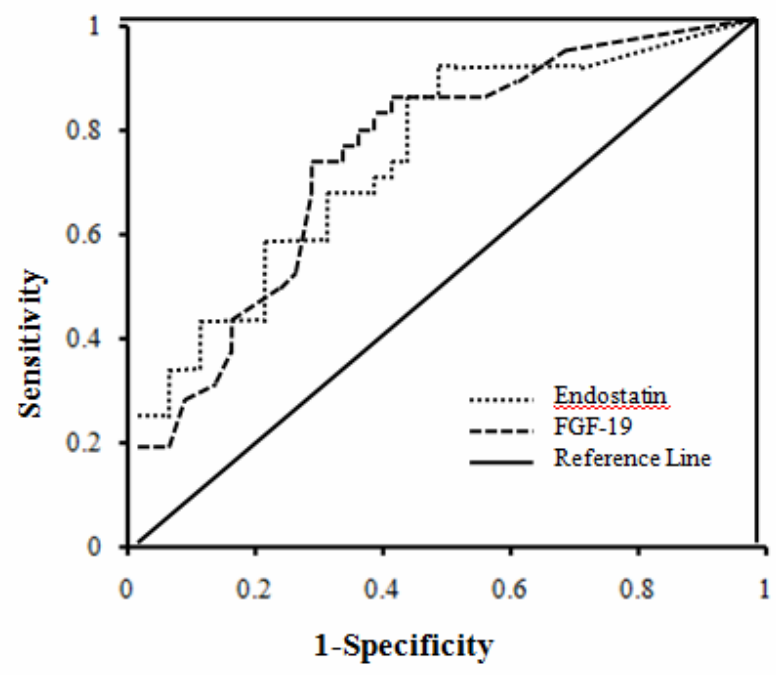

Figure 1. ROC curve of predictive value of the levels of serum endostatin and FGF-19 on chemotherapeutic sensitivity before chemotherapy.

Table 3. Predictive value of the levels of serum endostatin and FGF-19 on chemotherapeutic sensitivity of the patients with acute myeloid leukemia.

Indexes	Critical value	Area under curve	Sensibility (%)	Specificity (%)
Endostatin	30.285 μg/L	0.701	92.16	65.43
FGF-19	276.140 ng/L	0.712	94.43	69.38

DISCUSSION

Acute myeloid leukemia is a heterogeneous malignant disease of the blood and includes acute leukemia originating from non-lymphocytes (Trifilio et al., 2013). Although hematopoietic stem cell transplantation can help acute myeloid leukemia patients achieve long-term disease-free survival or even a cure, it is an expensive treatment, and hence, is not desired by all patients. Chemotherapy is still the main treatment for acute myeloid leukemia (Wu et al., 2012; Champlin, 2013; Martner et al., 2013). There is continuous in-depth research into the cytogenetics of this disease, its mechanism of occurrence and development, and the effectiveness of chemotherapeutic drugs. Consequently, the remission and overall survival

rates after chemotherapy are increasing for these patients; some patients with acute myeloid leukemia can obtain long-term disease-free survival (Penack, 2013; Cagnetta et al., 2014). In addition, the prognosis of some patients was good, but did not correspond with the clinical response to therapy; also, the treatment effect was poor, the symptoms were difficult to relieve, and symptoms recurred easily (Chromik et al., 2014). Therefore, it is important to identify effective methods to evaluate curative effects and prognosis after chemotherapy. Endostatin was discovered in 1997, and was considered one of the most active angiogenesis inhibitors. It can effectively inhibit the growth of endothelial cells, and has been associated with the development and prognosis of malignant tumor diseases (Fung et al., 2013; Watts et al., 2014). FGF-19 belongs to an endocrine subfamily, and it is expressed in the terminal ileum, brain, cartilage, kidney, and other organs; it is important for the metabolism of nutrients. Studies showed that its expression was altered in leukemia patients (Cojoc et al., 2014; Haley and Kim, 2014). Endostatin is currently considered one of the most effective endogenous vascular growth inhibitors. Research has shown that endostatin was associated with the onset and progression of leukemia (Mittal et al., 2014). Changes in serum endostatin and FGF-19 in patients with acute myeloid leukemia may affect chemotherapeutic sensitivity and prognosis; however, few studies have examined this. It is important to clarify any changes in serum endostatin and FGF-19 levels in these patients, and to determine their effects on remission rates and survival time.

The results of this study showed that the levels of serum endostatin and FGF-19 in acute myeloid leukemia patients were increased compared with the normal population. The levels of serum endostatin and FGF-19 in the chemotherapeutic sensitivity group were significantly lower than that in the chemotherapeutic resistance group, which suggested that chemotherapy based on cytarabine over a certain time period can reduce these levels in patients with acute myeloid leukemia. Therefore, the levels of serum endostatin and FGF-19 may be associated with the pathogenesis of acute myeloid leukemia and treatment effects. ROC curve analysis showed that when endostatin reached 30.285 μg/L, the sensitivity predicting chemotherapeutic sensitivity was 92.16% and the specificity was 65.43%, and when FGF-19 reached 276.140 ng/L, the sensitivity was 94.43% and the specificity was 69.38%. There was no significant difference between the two results, which confirmed that the levels of serum endostatin and FGF-19 in patients with acute myeloid leukemia could be used as predictors of chemotherapeutic sensitivity. These levels may be associated with treatment effects and the prognosis of the patients with acute myeloid leukemia, and this supports the hypothesis that serum endostatin and FGF-19 in patients with acute myeloid leukemia may affect chemotherapeutic sensitivity and prognosis. For patients with higher levels of serum endostatin and FGF-19, options include comprehensive treatment or hematopoietic stem cell transplantation depending on their clinical characteristics. Preoperative analysis of serum endostatin and FGF-19 levels may help predict the chemotherapeutic effect and the selection of a treatment plan for acute myeloid leukemia patients. In this study there were small sample sizes, short chemotherapy duration and observation time. Clarifying the effects of changes in serum endostatin and FGF-19 levels on chemotherapeutic sensitivity in acute myeloid leukemia patients will require long-term observation and in-depth research with a larger sample size.

In conclusion, the levels of serum endostatin and FGF-19 were higher in patients with acute myeloid leukemia. Serum endostatin and FGF-19 in patients with acute myeloid leukemia can be used as predictors of chemotherapeutic sensitivity, and may be important for determining the prognosis.

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