Prognostic value of serum IL-8 and IL-10 in patients with ovarian cancer undergoing chemotherapy

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Abstract. Prognostic value of serum interleukin-8 (IL-8) and interleukin-10 (IL-10) in patients with ovarian cancer undergoing chemotherapy was evaluated. The clinical data of ovarian tumor patients in Yidu Central Hospital of Weifang treated from January 2012 to December 2014 was retrospectively analyzed, 92 cases of which were malignant group, 64 cases were benign group, and 58 healthy subjects were selected as control group. Serum expression levels of IL-8 and IL-10 of the three groups were detected by enzyme-linked immunosorbent assay. Serum expression levels of IL-8 and IL-10 in benign and malignant groups both were higher than those in healthy control group (P<0.001). Serum expression levels of IL-8 and IL-10 of patients with ovarian cancer at III+IV stage were higher than that at I+II stage (P<0.001). Serum expression levels of IL-8 and IL-10 of patients with malignant ovarian tumors before chemotherapy were higher than those after chemotherapy (P<0.001). Serum levels of IL-8 and IL-10 of patients with malignant ovarian tumors in stable condition after chemotherapy were lower than those with recurrence and metastasis after chemotherapy (P<0.001). The median of serum expression levels of IL-8 and IL-10 was divided into low expression group and high expression group. The survival time of patients in high serum IL-8 and IL-10 expression group was significantly shorter than that in serum IL-8 and IL-10 low expression group (P<0.05). The survival time was negatively correlated with the expression levels of IL-8 and IL-10. Serum expression levels of IL-8 and IL-10 are closely related to the stages and prognosis of ovarian cancer. IL-8 and IL-10 may be involved in the occurrence and development of ovarian cancer. There are certain reference values on the changes of IL-8 and IL-10 levels, which may reflect the biological behavior and prognosis of ovarian cancer.

Introduction

Ovarian cancer has the highest mortality rate in gynecological malignancies at present (1). Due to the lack of typical clinical symptoms and occult onset at early stage, most patients with ovarian cancer have reached advanced stage by the time the diagnosis is confirmed, and even some have already metastasized (2). Clinically, ovarian cancer is mainly treated with cytoreductive surgery and adjuvant chemotherapy. However, for patients at advanced stage and with metastasis, even surgical treatment is difficult to stabilize the condition, and it easily relapse and metastasize (3,4). It shows that improving the early diagnosis rate of ovarian cancer, as early as possible to find the invasion and metastasis of cancer cells and to take measures have important significance. Although the mechanism of the disease is not yet fully understood, the research regarding this respect has been the focus of medical workers around the world (5).

Considerable research shows that the abnormal expression of cytokines plays a key role in the occurrence and development of ovarian cancer, which may be due to the expression imbalance of varieties of cytokines (6-8). Cytokines promote or inhibit the tumor cell differentiation through different secretory ways, thereby affect the angiogenesis and nutrient supply of the tumor, and regulate the immune response of tumor cells to affect their clinical treatment (9). Ovarian tumors are associated with many cytokines such as interleukin-8 (IL-8) and IL-10, and their abnormal expression affects the overall process of occurrence, development and metastasis of ovarian cancer. IL-8 is a cytokine which can accelerate cancer cells metastasis. IL-10 is a cytokine that can reduce and change the immune activity of the body (10). It has been reported that the expressions of IL-8 and IL-10 is enhanced in ovarian cancer patients, and the abnormal expression of these two cytokines is accompanied throughout the course of the disease (11).

The purpose of this investigation was to analyze the relationship between the expressions of IL-8 and IL-10 and patients with ovarian cancer undergoing chemotherapy, and to provide methods and references for early diagnosis, disease

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evaluation and treatment of ovarian cancer, which has certain clinical significance.

Materials and methods

General information. The clinical data of 156 patients with pathologically confirmed ovarian tumors who were treated at the Yidu Central Hospital of Weifang (Weifang, China) from January 2012 to December 2014 was retrospectively analyzed. The average age was 50.84±13.82 years, including 92 cases in malignant group and 64 cases in benign group, with 58 healthy subjects as control group, and the average age was 51.05±12.74 years. No significant differences were found between the two groups (P>0.05). None of the subjects were treated with endocrine therapy, biological therapy, chemical therapy and radiation therapy before operation, including 20 cases at stage I and II, and 72 cases at stage III and IV. Patients with ovarian epithelial tumor all received platinum-based chemotherapy after admission and were followed up for 36 months. None of the subjects had taken immunomodulators or hormone drugs in the past six months.

The study was approved by the Ethics Committee of Yidu Central Hospital of Weifang. Signed informed consents were obtained from the patients or the guardians. General information of the patients is shown in Table I.

Reagents and instruments. ELISA kit was purchased from Shanghai Xinran Biotechnology Co., Ltd. (Shanghai, China), and Antus PHOMO automatic microplate reader was purchased from Bio-Rad Laboratories, Inc., (Hercules, CA, USA).

Detection of serum IL-8 and IL-10. Peripheral venous blood (3 ml) was taken from study subjects following fasting in the morning as the first serum sample. The second serum sample was taken from the patients treated with chemotherapy on the second morning after the end of second stage, and was centrifuged at 2,600 x g for 8 min at 22℃. Serum IL-8, IL-10 and OD values at the wavelength of 450 nm were measured by ELISA method. The operation was carried out strictly according to the instructions.

Statistical analysis. The statistical software SPSS 19.0 (IBM Corp., Armonk, NY, USA) was used to carry out the analysis. The t-test was applied in data measurement, and the comparison was made before and after treatment with the paired t-test. The comparison among groups was performed with One-way ANOVA analysis, and least significant difference test, and Kaplan-Meier survival curves and the log-rank test was used to draw survival curve in survival analysis. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of serum levels of IL-8 and IL-10 among the three groups of patients. The expression level of serum IL-8 was 79.68±9.53 ng/l in benign group and 220.54±12.49 ng/l in malignant group, and both were higher than the 54.31±10.26 ng/l in healthy control group. The expression level of IL-10 was 7.05±2.37 ng/l in benign group and

Table I. General information.

Factors	Malignant group (n=92)	Benign group (n=64)	Control group (n=58)
	n (%)		
Age (years)			
≥50	48 (52.17)	34 (53.13)	30 (51.72)
<50	44 (47.83)	30 (46.87)	28 (48.28)
Tissue types			
Serous tumor	27 (29.35)		
Mucinous tumor	46 (50.00)		
Endometrioid tumors	19 (20.65)		
Tumor stages			
I+II	20 (21.74)		
III+IV	72 (78.26)		
Lymphatic metastasis			
Yes	52 (56.52)		
No	40 (43.48)		
Distant metastasis			
Yes	43 (46.74)		
No	49 (53.26)		
Tumor size			
<4 cm	35 (38.04)		
≥4 cm	57 (61.96)		
Differentiation degree			
Middle and low	42 (45.65)		
High	50 (54.35)		

17.35±4.02 ng/l in malignant group, and both were higher than the 3.81±0.52 ng/l in healthy control group. Serum expression levels of IL-8 and IL-10 in benign and malignant groups both were higher than those in healthy controls. The levels of IL-8 and IL-10 in malignant group were statistically significant higher than those in benign group (P<0.001) (Table II).

Comparison of serum IL-8 and IL-10 levels of patients with malignant ovarian tumors at clinical stages. The IL-8 level of ovarian cancer I+II was 181.37±13.54 ng/l, and the level of IL-10 was 13.52±2.16 ng/l. The IL-8 level of ovarian cancer III+IV was 228.41±6.79 ng/l, and the level of IL-10 was 20.16±4.84 ng/l. The serum expression levels of IL-8 and IL-10 at ovarian cancer III+IV stage were higher than those at I+II stage (P<0.001) (Table III).

Changes of serum levels of IL-8 and IL-10 of malignant ovarian tumor patients before and after chemotherapy. Serum levels of IL-8 and IL-10 in malignant ovarian tumor patients were respectively 220.54±12.49 and 17.35±4.02 ng/l before chemotherapy, and were respectively 159.82±8.77 and 11.48±1.74 ng/l after chemotherapy. Serum levels of IL-8 and IL-10 of malignant ovarian tumor patients before chemotherapy both were statistically significant higher than those after chemotherapy (P<0.001) (Table IV).

Table II. Comparison of IL-8 and IL-10 levels in serum of patients among the three groups (ng/l).

Items	Control group	Benign group	Malignant group	F-value	P-value
Case number	58	64	92		
IL-8	54.31±10.26	79.68±9.53[a]	220.54±12.49[b]	50.970	<0.001
IL-10	3.81±0.52	7.05±2.37[a]	17.35±4.02[b]	55.570	<0.001

[a]$P<0.001$ vs. control group, [b]$P<0.001$ vs. control group. IL-8, interleukin-8.

Table III. Comparison of IL-8 and IL-10 levels in serum of malignant ovarian tumor patients at different clinical stages (ng/l).

Clinical stages	Case number	IL-8	IL-10
I+II	20	181.37±13.54	13.52±2.16
III+IV	72	228.41±6.79	20.16±4.84
t value		21.620	8.308
P-value		<0.001	<0.001

IL-8, interleukin-8.

Table IV. Changes of IL-8 and IL-10 levels in serum of malignant ovarian tumor patients before and after chemotherapy (ng/l).

Groups	Case number	IL-8	IL-10
Before chemotherapy	92	220.54±12.49	17.35±4.02
After chemotherapy	92	159.82±8.77	11.48±1.74
t value		38.16	12.85
P-value		<0.001	<0.001

IL-8, interleukin-8.

Changes of serum levels of IL-8 and IL-10 of malignant ovarian tumor patients before and after chemotherapy. Serum levels of IL-8 and IL-10 were, respectively 184.52±11.47 and 18.24±3.05 ng/l in malignant ovarian tumor patients with recurrence and metastasis after chemotherapy, and serum levels of IL-8 and IL-10 were, respectively 151.08±9.38 and 9.46±1.08 ng/l in malignant ovarian tumor patients in stable condition after chemotherapy. The serum levels of IL-8 and IL-10 in malignant ovarian tumor patients in stable condition after chemotherapy both were statistically significant lower than those in malignant ovarian tumor patients with recurrence and metastasis after chemotherapy ($P<0.001$) (Table V).

The median of serum expression level of IL-8 of ovarian cancer patients after chemotherapy was 167.43 ng/l and 46 were in the low expression and the high expression group, respectively. The median of serum expression level of IL-10 of ovarian cancer patients after chemotherapy was 13.54 ng/l and 46 were in the low expression group and the high

Table V. Comparison of IL-8 and IL-10 levels in serum of malignant ovarian tumor patients with stable state or recurrent and metastasis after chemotherapy (ng/l).

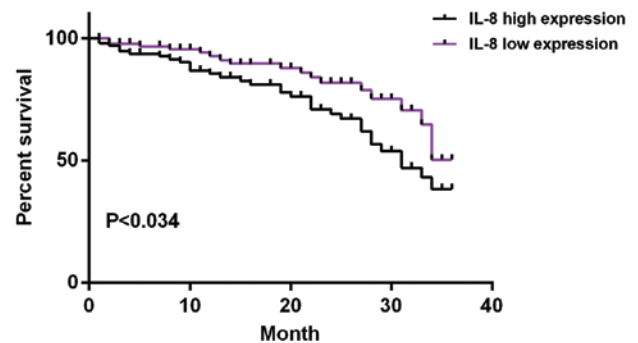| Groups	Case number	IL-8	IL-10
Recurrence and metastasis after chemotherapy	59	184.52±11.47	18.24±3.05
Stable condition after chemotherapy	33	151.08±9.38	9.46±1.08
t value		11.16	14.81
P-value		<0.001	<0.001

IL-8, interleukin-8.

Figure 1. Relationship between IL-8 and survival of ovarian cancer patients after chemotherapy. Kaplan-Meier survival curve showed that the survival time of patients with high expression of IL-8 was significantly shorter than that with low expression of IL-8 ($P<0.034$). IL-8, interleukin-8.
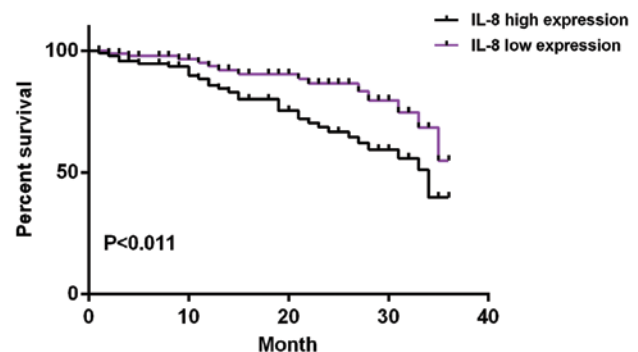

Figure 2. Relationship between IL-10 and survival of ovarian cancer patients after chemotherapy. Kaplan-Meier survival curve showed that the survival time of patients with high expression of IL-10 was significantly shorter than that with low expression of IL-10 ($P<0.011$). IL-10, interleukin-10.

expression group, respectively. The average survival time of IL-8 low expression group was 33.12±1.08 months and that of IL-8 high expression group was 28.82±2.84 months. The average survival time of IL-10 low expression group was 32.16±1.88 months and that of IL-10 high expression group was 29.86±2.02 months. Survival analysis showed that the survival time of patients with high expression of IL-8 and IL-10 was significantly shorter than that of patients with low expression of IL-8 and IL-10 (P<0.05) (Figs. 1 and 2).

Discussion

The pathogenesis of ovarian cancer is not yet clear and there is a lack of appropriate and accurate early diagnosis. Therefore, the 5-year survival rate of ovarian cancer does not exceed 30% (12). According to statistics, >120,000 people worldwide die of this disease every year (13). The process of cancer cell growth and diffusion is extremely complex, and the possible influencing factors are various, but mainly tumor angiogenesis (14). IL-8 can accelerate tumor angiogenesis and promote the progress of ovarian cancer. It has been widely accepted that IL-8 plays an important role in tumor angiogenesis (15). When a person is healthy and in good condition, the IL-10 content in the body is extremely low, but if someone is sick or stimulated by external environmental factors, such as pregnancy, tumor and infectious disease the IL-10 content will increase rapidly, and it only affects the human body. The reason is that there is no homologous sequence in other organism cells (16).

This study shows that serum expression levels of IL-8 and IL-10 in benign ovarian disease group and malignant ovarian tumor group both were statistically significantly higher than those in healthy control group (P<0.001). The serum expression levels of IL-8 and IL-10 at ovarian cancer III+IV stage were statistically significantly higher than those at ovarian cancer I+II stage (P<0.001). The results of Charbonneau *et al* (11) are consistent with ours. The expression of IL-8 and IL-10 in ovarian cancer was positively correlated with clinical stages, and the occurrence and development of ovarian cancer was closely related to IL-8 which is a special marker (17). The high expression of IL-10 in tumor microenvironment inactivate the cell lesion, however, tumor cells cannot be effectively eliminated. Therefore, the measurement of IL-8 and IL-10 levels has an important reference value in judging the malignant degree and staging of ovarian cancer (17-19). Serum levels of IL-8 and IL-10 in malignant ovarian tumor patients before chemotherapy both were statistically significant higher than those after chemotherapy (P<0.001). Serum levels of IL-8 and IL-10 of malignant ovarian tumor patients in stable condition after chemotherapy were statistically significantly lower than those in patients with recurrence and metastasis after chemotherapy (P<0.001). Our results are similar to those of Matte *et al* (20). Studies show that polyphenols can enhance the sensitivity of ovarian cancer cell CAOV-3 to cisplatin. The cells produce high levels of IL-8, IL-10, and have poor sensitivity to cisplatin. Polyphenols can inhibit CAOV-3 cells to produce IL-8 and IL-10. Therefore, the patients with metastasis and recurrence after chemotherapy may be due to the high levels of IL-8 and IL-10 *in vivo* reducing the sensitivity of cancer cells to chemotherapy, thus leading to recurrence and metastasis. The average survival time of IL-8 in low expression

group was 33.12±1.08 months, and that of IL-8 in high expression group was 28.82±2.84 months. The average survival time of IL-10 in low expression group was 32.16±1.88 months and that of IL-10 in high expression group was 29.86±2.02 months. Survival analysis showed that the survival time of patients with high expression of IL-8 and IL-10 was significantly shorter than that of patients with low expression of IL-8 and IL-10 (log-rank, P<0.05). The results of follow-up were consistent with the results of Table V. Serum expression of IL-8 and IL-10 in patients with poor chemotherapy effect and those in deceased patients were higher, which indicated that the expressions of IL-8 and IL-10 played a certain role in predicting and evaluating the survival prognosis of ovarian cancer patients after chemotherapy.

However, the study has some limitations. Although the follow-up results of ovarian cancer patients after chemotherapy are consistent with the results of our study, which shows that the high expression of IL-8 and IL-10 can shorten the survival time of patients. Nevertheless, there may be still other factors which need to be further studied.

In conclusion, serum high expression of IL-8 and IL-10 is involved in the occurrence and development of ovarian cancer, and also have an effect on sensitivity to chemotherapy. The changes of IL-8 and IL-10 levels indirectly reflect the biological behavior and prognosis of ovarian cancer, which has certain clinical significance.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

LZ drafted the manuscript. LZ and WL were mainly devoted to collecting and interpreting the general data. XinboW and XiaoliW performed ELISA. LZ and HS were responsible for statistical analysis. All authors read and approved the final study.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Yidu Central Hospital of Weifang (Weifang, China). Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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