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Relationship between Expression of β-Tubulin-III Plus ERCC1 in Advanced Ovarian Cancer and Chemotherapy Sensitivity of Paclitaxel Plus Platin Chemotherapy

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Abstract

Objective: Ovarian cancer is one of the three major malignancies in the female reproductive system. Its histological types are numerous, and early diagnosis is difficult. Although surgery and radiotherapy and chemotherapy have made great progress, mortality still ranks first among female reproductive system malignancies, which seriously threatens gynecological cancer patient's life. To explore the expression of β-tubulin-III plus ERCC1 in advanced ovarian cancer and analyze its correlation with the chemotherapeutic effect of paclitaxel docetaxel plus cisplatin or carboplatin.

Patients and Methods: Sixty-four chemotherapy patients with advanced ovarian cancer were treated with paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) and cisplatinum (75 mg/m^2) or carboplatin (AUC5) days. Expression of β-tubulin-III and ERCC1 in 64 cases of ovarian cancer were detected by immunohistochemical method. According to the different expression of Tubulin III and ERCC1, the patients were divided into 2 groups, and then statistical analysis of the efficiency was conducted between the 2 groups. Efficiency rate, Progression Free Survival (PFS) and Overall Survival (OS) were analyzed. The effect of age, staging, and peritoneal metastasis on survival was analyzed using COX regression.

Results: Overall response rate is 76.6% (49/64), ERCC1+ group: Chemotherapy Overall Response Rate (ORR) is 50.0% (9/18). ERCC1- group: Chemotherapy ORR is 87% (40/46). The response rate between the two groups was significantly different and was statistically significant, P value <0.05. ERCC1+ group: Mean Progression Free Survival (PFS) is 12.3 ± 11.4 months. ERCC1- group: Mean Progression Free Survival (PFS) is 21.7 ± 23.3 months. There was significant difference between the two groups P value <0.05. ERCC1+ group: Overall Survival (OS) is 22.1 ± 16.1 months. ERCC1- group: Mean Overall Survival (OS) is 38.2 ± 34.6 months. The Overall Survival (OS) between the two groups was significantly different and was statistically significant, P value <0.05.

β-Tubulin III- group: Chemotherapy ORR is 89% (31/35), β-Tubulin III+ group: Chemotherapy ORR is 62% (18/29), the response rate between the two groups was significantly different and was statistically significant, P value <0.05. β-Tubulin III- group: Mean Progression Free Survival (PFS) is 27 ± 26 months. β-Tubulin III+: Mean Progression Free Survival (PFS) is 9.6 ± 5.3 months. The Progression Free Survival (PFS) between the two groups was significantly different and was statistically significant, P value <0.05. β-Tubulin III- group: Mean Overall Survival (OS) is 44.8 ± 37.6 months. β-Tubulin III+ group mean Overall Survival (OS) is 20.3 ± 12 months. The Overall Survival (OS) between the two groups was significantly different and was statistically significant, P<0.05.

Conclusion: Detection of the expression of β-tubulin-III and ERCC1 before chemotherapy may predict the sensitivity of ovarian cancer to paclitaxel and Platinum drugs.

Keywords: β-Tubulin-III and ERCC1; Ovarian cancer; Chemosensitivity; Chemotherapy

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Introduction

Ovarian cancer is one of the three major malignancies of the female reproductive system. Although surgery, radiotherapy and chemotherapy have made great progress, mortality still ranks first in terms of mortality among female reproductive system malignancies, the tumor's tissue

type (e.g. serous cystadenocarcinoma), stage, cell differentiation, sensitivity to chemotherapeutic drugs and the size of residual tumor after therapy, all have some impact on cancer recurrence [1-3]. The rapid development of pharmacogenetics and pharmacogenomics has made it possible to develop individualized chemotherapy regimens for different patients. This study reviewed the use of paclitaxel plus platinum in the treatment of advanced recurrent ovarian cancer, and explored the relationship between the tumoral expression of β-tubulin-III and ERCC1 and chemotherapy sensitivity of advanced ovarian cancer.

Patients and Methods

This retrospective study analyzed 64 patients with advanced ovarian cancer who had recurrence and metastasis after first-line treatment in our hospital from May 2007 to March 2016. The median age was 57 years; all cases were confirmed by pathological histological examination. 54 cases had multiple pelvic metastases, 48 cases had peritoneal metastases, 8 cases had lung metastases, and 18 cases had liver metastases. Before the treatment, the complete blood count was normal and there was no major organ dysfunction. The Karnofsky score ranged between 70 to 90. Patient characteristics are summarized in Table 1.

Table 1: Patient characteristics.

Age	Median age	57 y
	Average age	56.7 y
Karnofsky performance status	70 scores	n=13
	80 scores	n=16
	90 scores	n=35
Stage	I	n=4
	II	n=14
	III	n-38
	IV	n-8
Cycles of chemotherapy	2 cycle	n=7
	4cycles	n=15
	5cycles	n=4
	6 cycles	n=24
	8 cycles	n=9
	10 cycles	n=1
	12 cycles	n=3
	14cycles	n=1
Metastases	Lung	N=8
	Liver	N=18
	Pelvis	N=54
	Ascites	N=48

Test methods

Elivision two-step assay was used to detect the expression of ERCC1 and β-Tubulin III. One mouse anti-human monoclonal antibody was purchased from SANTA CRUZ Biological Inc., and two-step immunohistochemical kit was purchased from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd. Positive controls were known as positive controls and PBS was used as a negative control instead of primary antibody.

The results of immunohistochemical determination criteria: ERCCI positive brownish yellow particles in the nucleus, TUBB3 positive brownish yellow staining in the cytoplasm. Randomized double-blind method for reading, 200 specimens randomly counted in a 400-fold field of view for each specimen. The cells were observed for positive staining intensity and percentage of positive cells. Dyeing intensity: No color 0 point 1 point for coloring to light yellow; 2 points for coloring to yellow; 3 points for coloring to dark brown. Percentage of positive cells: <10% for 0 points, 10% to 25% for 1 point, 26% to 50% for 2 points, >50% for 3 points. At present, most pathologists use the method of integral measurement, the calculation method is: (+)% × 1+(++)% × 2+(+++)% × 3; if the total value is less than 1.0, (+), 1.0-1.5 are (++), >1.5 is (+++). At least 5 to 10 high power fields were randomly observed.

Treatment method

The choice of chemotherapy regimen: paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) plus carboplatin (AUC5) or cisplatin (75 mg/m^2), depending on the patient's specific liver and kidney function and age and general conditions.

Efficacy evaluation

The effect was evaluated after 2 cycles of treatment and re-evaluation was performed every 2 cycles. The baseline of the tumor lesions was based on measurable lesions. CT or MRI was used to judge the target lesions. The remission criteria were determined by response evaluation criteria in solid tumors RECIST Version 1.1 (RECIST) method: Complete Response (CR): All target lesions disappeared and maintained for 4 weeks, Partial Response (PR): The sum of the maximum diameter of baseline lesions was reduced by ≥ 30% for 4 weeks; the Progression (PD): The sum of the maximum diameter of the baseline lesions increased by ≥ 20% or new lesions appeared; the stable (SD): The sum of the maximum diameters of the baseline lesions was reduced but not reached PR or increase but not reach PD. The effective rate (RR) was calculated as CR+PR, and the Disease Control Rate (DCR) was calculated as CR+PR+SD. Adverse reactions were judged according to the toxicity of WHO anticancer drugs and they were divided into 5 grades. I: Mild adverse reactions; II: Moderate adverse reactions; III: Serious adverse reactions; IV: Life-threatening or declining adverse reactions; V: Death associated with adverse reactions.

Statistical methods

Using SPSS18 Statistical Software Package for Statistical Analysis. SPSS18.0 Software Manufacturer: International Business Machines Corporation. We apply chi-square test, Kaplan-Meier method and t test of comparing the mean of two samples, P<0.05 was statistically significant.

Result

Response data

Overall response rate is 76.6% (49/64), ERCC1+ group: Chemotherapy Overall Response Rate (ORR) is 50.0% (9/18), Figure 1. ERCC1- group: Chemotherapy ORR is 87% (40/46). The response rate between the two groups was significantly different and was statistically significant, P value <0.05. ERCC1+ group: Mean Progression Free Survival (PFS) is 12.3 ± 1.4 months. ERCC1- group: Mean Progression Free Survival (PFS) is 21.7 ± 23.3 months. There was significant difference between the two groups P value <0.05. ERCC1+ group: Overall Survival (OS) is 22.1 ±16.1 months. ERCC1- group: Mean Overall Survival (OS) is 38.2 ± 34.6 months. The Overall

Table 2: Number of patients by ERCC+ and ERCC-.

ERCC1	PR+CR+SD	PD	SUM	X2	p	OR
Positive	9	9	18			
Negative	40	6	46	3.873	0.049<0.05	0.15
Sum	49	15	64			

Table 3: Number of patients by β-tubulin III+ and β-tubulin III–.

β-Tubulin III	PR+CR+SD	PD	SUM	X2	p	OR
Positive	18	11	29			
Negative	31	4	35	6.208	0.013<0.05	0.21
Sum	49	15	64			

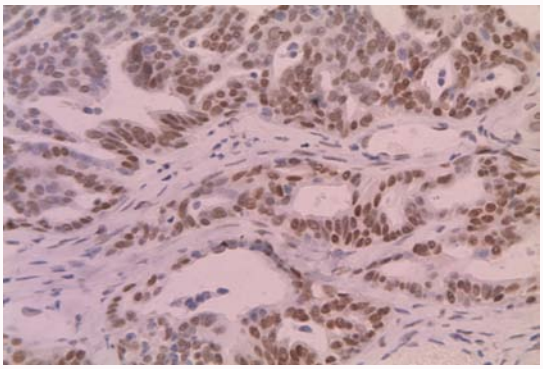

Figure 1: ERCC1(+) x400.

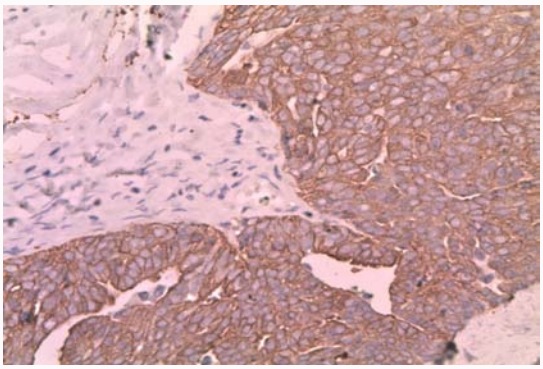

Figure 2: β-Tubulin III(+) x400.

Survival (OS) between the two groups was significantly different and was statistically significant, P value <0.05. OR (odds ratio): 0.15. Table 2 β-Tubulin III+ group Chemotherapy ORR is 62% (18/29) Figure 2, the response rate between the two groups was significantly different and was statistically significant, P value <0.05. β-Tubulin III- group: Mean Progression Free Survival (PFS) is 27 ± 26 months. β-Tubulin III+: Mean Progression Free Survival (PFS) is 9.6 ± 5.3 months. The Progression Free Survival (PFS) between the two groups was significantly different and was statistically significant, P value <0.05. β-Tubulin III- group: Mean Overall Survival (OS) is 44.8 ± 37.6 months. β-Tubulin III+ group: Mean overall survival (OS) is 20.3 ± 12 months. The Overall Survival (OS) between the two groups was significantly different and was statistically significant, P<0.05. OR (Odds Ratio): 0.21 Table 3.

Data assumptions

Variable "effect" describes chemotherapy response, where "CR", "PR" and "SD" defines response (49 patients) and "PD" no response

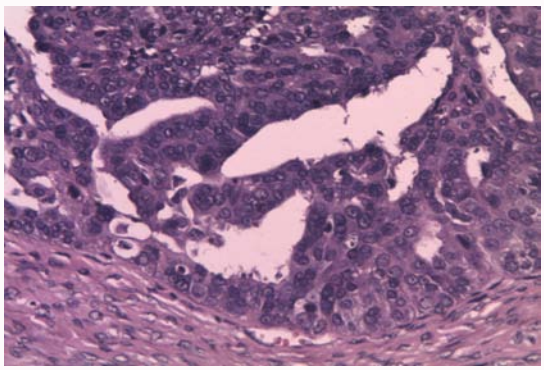

Figure 3: Ovarian cancer HE staining.

(15 patients). All patients progressed; time to progression is given in the variable "PFS". Variable "State" describes survival state at end of follow-up, where "1" defines death (59 patients) and "0" no death during follow-up (5 patients). Time to death is given in the variable "OS".

Multivariable analyses with stage

In multivariable analysis with stage, ERCC1 did not predict progression (Hazard Ratio [HR] 1.71, 95% Confidence Interval [CI] 0.91-3.20; p=0.097) nor overall survival (HR 1.56, 95% CI 0.87-2.78; p=0.14); corresponding univariate analyses gave a HR of 1.70 (95% CI 0.97-2.98; p=0.051) and 1.88 (95% CI 1.06-3.32; p=0.022). However β-tubulin III did predict progression (HR 2.67, 95% CI 1.44-4.96; p=0.002) and death (HR 2.36, 95% CI 1.29-4.32; p=0.005) in multivariable analysis with stage; corresponding univariate analyses gave a HR of 3.01 (95% CI 1.67-5.42; p<0.001) and 2.86 (95% CI 1.59-5.15; p<0.001).

Discussion

There is some evidence to suggest that platinum-based drug resistance is related to the expression of ERCC1 gene. ERCC1 is found in all tumor cells and its expression level varies greatly. ERCC1 mRNA levels are prognostic indicators of survival in completely resected NSCLC patients who have not undergone perioperative chemotherapy or radiotherapy [4].

Several studies have shown that ERCC1 levels can be used to predict the efficacy of platinum-based chemotherapy in the treatment of NSCLC; "high levels" are resistant, and "low levels" are sensitive. Therefore, the detection of ERCC1 gene expression levels can be used to predict the efficacy of platinum drugs in cancer patients [5,6]. A: As the main component of the cytoskeleton and spindle, β-tubulin plays an important role in cell mitosis, organelle composition and transportation and signal transmission. Not only the role of paclitaxel chemotherapeutic drugs, but also the acquired resistance to paclitaxel is also closely related. A large number of clinical trials have shown that TUBB3 mRNA expression levels are closely related to the efficacy of anti-microtubule drugs, and the degree of β-tubulin III expression affects the sensitivity of cancer tissues to paclitaxel. Patients with low expression received better chemotherapy with paclitaxel or vinblastine and a longer median survival. However, patients with high expression of TUBB3 have low response rate to anti-microtubule drugs [7-11].

Conclusion

This preliminary study suggests that β-tubulin III and ERCC1 may indicate response to chemotherapy in ovarian cancer patients and

perhaps also subsequent progression and survival, but verification in much larger cohorts is needed as well as further study of the relation to established tumor characteristics.

The main limitation is the small number of patients. Here we have only conducted preliminary studies. Next, we will expand the sample size and carry out multi-center research.

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