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ORIGINAL ARTICLE

Neoadjuvant chemotherapy combined with interval cytoreductive surgery in ovarian cancer

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Summary

Purpose: *This study aimed to explore the value and prognosis-influencing factors for neoadjuvant chemotherapy combined with interval cytoreductive surgery in patients with advanced ovarian cancer.*

Methods: *178 patients were divided into the research group and control group. The research group was treated with neoadjuvant chemotherapy combined with interval cytoreductive surgery, while the control group underwent primary cytoreductive surgery alone. Postoperative situation, efficacy, progression-free survival (PFS) and overall survival (OS) were compared between the two groups of patients, and the postoperative influencing factors for the patients were analyzed.*

Results: *The operation time, intraoperative blood loss and ascites volume in patients in the research group were shorter and lower than those in the control group ($p<0.05$). Univariate Cox regression analysis showed that the size of residual lesions after cytoreductive surgery, age, the International Federation of Gynecology and Obstetrics (FIGO) stage, the maximum primary tumor diameter and results of ascites cytological examination were the influencing factors for the OS of patients in the research group. The size of residual lesions after cytoreductive surgery, age and FIGO stage were independent factors affecting the postoperative OS of patients in the research group.*

Conclusion: *Administering neoadjuvant chemotherapy combined with interval cytoreductive surgery for patients with advanced ovarian cancer can reduce the operation time, intraoperative blood loss and ascites volume. Besides, the size of residual lesions after cytoreductive surgery, age and FIGO stage are independent factors affecting the postoperative OS of patients.*

Key words: *advanced stage, ovarian cancer, neoadjuvant chemotherapy, cytoreductive surgery*

Introduction

Ovarian cancer, a malignant tumor frequently occurring in females, has become the first killer among gynecological malignant tumors [1,2]. However, ovarian cancer is characterized by difficult identification in the early stages and a trend for abdominal dissemination, the result of which is that approximately 70% of patients are already in advanced stage when they are definitely diagnosed with ovarian cancer so that they have lost the best time to completely remove the tumor [3]. Currently, primary cytoreductive surgery combined with postoperative paclitaxel- and platinum-based adjuvant chemotherapy is the primary clinical treatment for ovarian cancer. However, systemic or abdominal metastasis, poor constitution and a variety of complications in patients with advanced ovarian cancer result in reduced tolerance of patients to the primary cytoreductive surgery and unsatisfactory postoperative results [4]. Neoadjuvant chemotherapy is a relatively new treatment method for ovarian cancer that has been proposed in recent years. It can be applied to treat ovarian cancer in patients with poor tolerance to the primary cytoreductive surgery and poor postoperative results, so as to im-

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prove the therapeutic effect of ovarian cancer [5]. In this study, a retrospective analysis was conducted for the efficacy of neoadjuvant chemotherapy combined with interval cytoreductive surgery in the treatment of ovarian cancer, and the factors affecting the therapeutic effect were analyzed, thus providing a scientific basis for reasonable treatment of ovarian cancer in clinical practice.

Methods

Patients

A total of 178 patients with advanced ovarian cancer who were admitted to Linyi Women's and Children's Hospital from January 2011 to January 2014 were selected. They were aged 40-77 years (mean 57.3±8.9). According to the patient's treatment methods (neoadjuvant chemotherapy combined with interval cytoreductive surgery or primary cytoreductive surgery alone), the patients were divided into the research group (n=94) and the control group (n=84).

Inclusion criteria

(1) Patients whose case data were complete, (2) patients diagnosed with ovarian cancer by imaging, cytology, pathology, etc., and those whose ovarian cancer was in stage IIIC or IV according to the International Federation of Gynecology and Obstetrics (FIGO) staging, (3) patients who had no severe systemic dysfunctions, and (4) patients with no history of malignant tumors or no history of neoadjuvant chemotherapy.

Treatment methods in the research group

Patients in the research group underwent neoadjuvant chemotherapy combined with interval cytoreductive surgery. They were subjected to relevant examinations after admission, and the attending doctor carried out neoadjuvant chemotherapy for patients according to one of the following conditions, followed by cytoreductive surgery: (1) The large solid mass in the pelvic cavity of the patients had invaded the pelvic wall, (2) the tumor resection was found to be difficult to be performed after the abdomen was opened, (3) imaging examinations revealed that the malignant tumor had metastasized to the lungs, spleen, liver and other organs, (4) a large amount of effusion existed in the thoracic cavity and abdominal cavity, so that the patients could not put up with the surgical process, and (5) it was difficult to define the diameter of the patient's residual lesion below 1.0 cm through the primary cytoreductive surgery.

All patients completed the examinations and received chemotherapy after excluding the contraindications of chemotherapy. Neoadjuvant chemotherapy lasted for 3 courses and each course lasted 3 weeks. Paclitaxel (175 mg/m^2) combined with carboplatin (AUC=5) or cisplatin (70 mg/m^2) was given. Pretreatment with 20 mg dexamethasone was given 12 h and 6 h respectively before chemotherapy, and symptomatic supportive treatment with stomach protection and antiemetic therapy were given during chemotherapy. After 3 courses of treatment, the patients were treated with cytoreductive surgery and continued to receive 6-8 courses of chemotherapy after operation. The chemotherapy regimen was the same as before.

Treatment methods in the control group

If the diameter of the tumor was <1.0 cm, the patients were subjected to primary cytoreductive surgery and paraaortic lymph node dissection of the abdomen and the pelvic cavity. Then, the patients received 6-8 courses of postoperative chemotherapy.

Observational indexes

The postoperative condition, efficacy, PFS and OS of patients were compared between the research group and the control group, and the postoperative influencing factors of the patients were analyzed.

Evaluation criteria for the efficacy: 1) Complete remission: No tumor lesions were found in patients according to magnetic resonance imaging (MRI), B-ultrasound and other imaging examinations after operation. 2) Partial remission: MRI, B-ultrasound and other imaging examinations revealed that the reduction of the baseline length of tumor lesions was >50% compared with that before treatment. 3) Improvement: MRI, B-ultrasound and other imaging examinations after operation manifested that the reduction of the baseline length of tumor lesions was >25% but <50% compared with that before treatment. 4) Stability: MRI, B-ultrasound and other imaging examinations after operation demonstrated that the reduction of the baseline length of tumor lesions was <25% compared with that before treatment. 5) Progression: MRI, B-ultrasound and other imaging examinations after operation manifested that the baseline length of tumor lesions showed growth before treatment. Total effective rate = the number of cases of (complete remission + partial remission) / total number of cases × 100.00%

Statistics

SPSS 19.0 software was used for the statistical analyses of the data in this study. Measurement data were expressed as mean±standard deviation, and count data were expressed as percentages. Statistical analyses were conducted for the difference in measurement data between groups using the *t*-test, and the chi-square test was used to statistically analyze the difference in count data between groups. Cox proportional hazards regression model was used to analyze the factors affecting the postoperative OS. P<0.05 suggested that the difference between groups was statistically significant.

Results

Comparisons of intraoperative conditions between the two groups of patients

The operation time, intraoperative blood loss and ascites volume were compared between the two groups of patients. The results illustrated that the operation time and intraoperative blood loss

and ascites volume in the research group were remarkably shorter and lower than those in the control group (p<0.05) (Table 1).

Comparison of the postoperative efficacy between the two groups of patients

The postoperative efficacy was compared between the two groups of patients. It was found that there were no cases of complete remission in the two groups, and there were no significant differences in the partial remission rate, improvement rate, stability rate, progression rate and the total effective rate between the two groups of patients (p>0.05) (Table 2).

Comparisons of postoperative PSF and postoperative OS between the two groups of patients

The postoperative PFS and postoperative OS were compared between the two groups of patients, which revealed that there were no significant differences in the postoperative PFS and postoperative OS of patients in the research group compared with those in the control group (p>0.05) (Table 3).

Univariate analysis of the prognosis of patients in the research group

The univariate analysis was conducted for the size of residual lesions after cytoreductive surgery, FIGO stage, the patient's age and gender, the maximum primary tumor diameter and results of ascites cytological examination of patients in the research group. The results revealed that the size of residual lesions after cytoreductive surgery, age, FIGO stage, maximum primary tumor diameter and results of ascites cytological examination of patients were the factors affecting the OS of the research group (Table 4).

Multivariate analysis of the prognosis of patients in the research group

The influencing factors in the univariate analysis, including the size of residual lesions after cytoreductive surgery, age, FIGO stage, maximum primary tumor diameter and results of ascites cytological examination, were introduced into the multivariate Cox regression model. The results showed that the size of residual lesions after cytoreductive surgery, age and FIGO stage were independent factors affecting the OS of patients in the research group (Table 5).

Discussion

Neoadjuvant chemotherapy refers to the chemotherapeutic treatment prior to cytoreductive surgery in patients if they can tolerate cytoreductive

Table 1. Comparisons of intraoperative conditions between the two groups of patients

Group	*n*	*Operation time (min)*	*Intraoperative blood loss (mL)*	*Ascites volume (mL)*
Control group	84	243.4±40.5	878.9±22.4	652.4±78.9
Research group	94	132.5±30.4*	494.5±14.5*	302.6±49.7*

*p<0.05 vs. control group

Table 2. Comparison of the postoperative efficacy between the two groups of patients (n/%)

Group	*n*	*Complete remission rate*	*Partial remission rate*	*Improvement rate*	*Stability rate*	*Progression rate*	*Total effective rate*
Control group	84	0/0.00	32/38.10	40/47.62	7/8.33	5/5.95	32/38.09
Research group	94	0/0.00*	35/37.23*	44/46.81*	8/8.51*	7/7.45*	35/37.23*

*p>0.05, compared with control group

Table 3. Comparisons of postoperative progression-free survival and postoperative overall survival between the two groups of patients

Group	*n*	*Postoperative progression-free survival (months)*	*Total postoperative survival (months)*
Control group	84	10.3±2.1	24.5±3.5
Research group	94	11.4±2.3*	25.3±3.4*

*p>0.05, compared with control group

Table 4. Univariate analysis of the prognosis of patients in the research group

Factor	*β*	*Standard deviation*	*Relative risk (RR) value*	*95% confidence interval (CI)*	*p*
Size of residual lesions after cytoreductive surgery (cm)	0.037	0.013	1.038	1.011-1.065	0.007
<1.0					
≥1.0					
FIGO stage	0.682	0.334	2.228	1.190-4.405	0.013
IIIC					
IV					
Age, years	0.762	0.310	2.142	1.156-3.934	0.014
<60.0					
≥60.0					
Gender	0.042	0.327	1.043	0.549-1.981	0.897
Male					
Female					
Maximum primary tumor diameter (cm)	1.033	0.362	2.809	1.381-5.732	0.004
<5.0					
≥5.0					
Results of ascites cytological examination	1.773	0.527	5.890	2.097-10.546	0.002
Positive					
Negative					

Table 5. Multivariate analysis of the prognosis of patients in the research group

Variables	*β*	*Standard deviation*	x^2	*RR value*	*95% CI*	*p*
Size of residual lesions after cytoreductive surgery	0.076	0.015	6.933	1.041	1.070-1.098	0.008
Age	0.087	0.028	7.404	1.079	1.022-1.140	0.007
FIGO stage	1.323	0.539	6.025	3.765	1.306-7.098	0.014
Maximum primary tumor diameter	0.170	0.097	3.055	1.185	0.980-1.435	0.080
Results of ascites cytological examination	0.221	0.134	3.890	1.241	0.948-2.375	0.108

surgery, or the expected efficacy cannot be achieved based on the preoperative evaluation [6-8]. The clinical symptoms of ovarian cancer in the early stage are mild and unclear, so that most patients are already in advanced stage when they are diagnosed with ovarian cancer [9]. Moreover, cancer metastasis and infiltration may occur in ovarian cancer in the advanced stage, resulting in failure to achieving the expected effects in the primary cytoreductive surgery [10]. With the research and development of chemotherapeutics and the maturity of clinical studies, neoadjuvant chemotherapy exerts an increasingly crucial effect in the treatment of advanced ovarian cancer. In particular, it enhances the patient's ability to tolerate cytoreductive surgery so as to achieve the expected effects [11]. In this study, there were no significant differences in the postoperative efficacy, postoperative PFS and postoperative OS between patients undergoing neoadjuvant chemotherapy combined with interval cytoreductive surgery and those receiving primary cytoreductive surgery. However, the operation time, intraoperative blood loss and ascites volume in patients who underwent neoadjuvant chemotherapy combined with interval cytoreductive surgery were evidently shorter and lower than those in patients who were subjected to primary cytoreductive surgery. The above results indicate that neoadjuvant chemotherapy has no significant superiority in improving the efficacy of cytoreductive surgery, postoperative PFS and postoperative OS. Nevertheless, the analysis in this study revealed that neoadjuvant chemotherapy played the following roles in the treatment of ad-

vanced ovarian cancer: (1) Preoperative neoadjuvant chemotherapy could effectively kill metastatic lesions around the tumor lesions, lower the adhesion between tumor tissues and surrounding normal tissues, reduce the tumor volume and stage, and make the tumor lesions that are not suitable for cytoreductive surgery applicable. (2) Preoperative neoadjuvant chemotherapy could effectively control the ascites, reduce its volume and improve the patient's tolerance to cytoreductive surgery. (3) Since neoadjuvant chemotherapy effectively reduces the adhesion between tumor and surrounding normal tissues as well as the volume and stage of tumors, the difficulty in cytoreductive surgery, operation time and intraoperative blood loss were reduced. Analyses of other researchers in China and foreign countries reveal that neoadjuvant chemotherapy for patients with advanced ovarian cancer has the following advantages: (1) Preoperative neoadjuvant chemotherapy can enable a tumor cell to be in a dormant state, reduce or avoid tumor cell proliferation and migration caused by stimuli in the process of cytoreductive surgery, and lower the postoperative recurrence rate [12]. (2) Preoperative neoadjuvant chemotherapy reduces tumor cell proliferation and migration triggered by postoperative coagulation mechanisms or intensive immunosuppression after operation [13].

Neoadjuvant chemotherapy has been broadly applied in treating advanced ovarian cancer, but the factors influencing neoadjuvant chemotherapy combined with interval cytoreductive surgery for advanced ovarian cancer have not been uniformly identified. Six clinical or pathological factors were selected in this study. It was found from the univariate and multivariate Cox regression analysis that the size of residual lesions after cytoreductive surgery, age and FIGO stage were independent factors affecting the OS. The specific proliferation mode of ovarian cancer cells makes the residual lesions small after cytoreductive surgery, and a large number of exfoliated cells will be produced. These exfoliated cells will form new tumor lesions, and the larger the postoperative residual lesions, the more the exfoliated tumor cells will be [14]. The patient's body's resistance is notably reduced, and the postoperative recovery ability is also reduced with age. Patients with ovarian cancer are often in advanced stage when definitely diagnosed. In advanced ovarian cancer with the increase of age, the degree of decrease of normal body functions is more obvious [15,16]. As for FIGO stage, the tumor volume, metastasis, and infiltration degree in stage IV are greater than those in stage IIIC, indicating that the efficacy of neoadjuvant chemotherapy combined with interval cytoreductive surgery for advanced ovarian cancer will be decreased with the increase of FIGO stage [17].

In conclusion, applying neoadjuvant chemotherapy combined with interval cytoreductive surgery for patients with advanced ovarian cancer can reduce the operation time, intraoperative blood loss and ascites volume, but it does not significantly improve the efficacy of cytoreductive surgery, postoperative PFS and the postoperative OS. Besides, the size of residual lesions after cytoreductive surgery, age and FIGO stage are independent factors affecting the postoperative OS of patients.

Conflict of interests

The authors declare no conflict of interests.

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