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ORIGINAL ARTICLE

Analysis of clinical effects of neoadjuvant chemotherapy in advanced epithelial ovarian cancer

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Summary

Purpose: *To investigate the role and significance of neoadjuvant chemotherapy in advanced ovarian cancer.*

Methods: *128 patients clinically diagnosed with stage IIC-IV advanced epithelial ovarian cancer (EOC) were randomized into neoadjuvant chemotherapy (NACT) combined with interval cytoreductive surgery (ICS) group (n=66) and primary cytoreductive surgery (PCS) group (n=62). Chemotherapy in the PCS group was administered after cytoreductive surgery.*

Results: *Age, body mass index, clinical symptoms, clinical staging, histopathological grading and histopathological type had no differences between PCS and ICS groups (p>0.05). In NACT-ICS group, the mean operation time was shorter, the bleeding was less, the rate of optimal debulking surgery was higher and the total effective rate of clinical remission was higher, compared with those in PCS group (p<0.05). No significant differences were found in the survival rate, progression-free survival (PFS) and overall survival (OS) between the two groups.*

Conclusions: *In comparison to PCS, NACT-ICS can improve the intraoperative conditions, increase the cytoreductive rate, reduce the bleeding of operation, reduce the operation time and increase the clinical remission rate, but it has no impact on PFS and OS.*

Key words: *chemotherapy, ovarian cancer, primary cytoreductive surgery, prognosis, survival*

Introduction

The most common ovarian malignancy is the highly fatal EOC. As a result of the shortage in effective early screening methods, about 75% of EOC patients are diagnosed with already advanced disease stage (FIGO stages III/IV), so the therapeutic effect and prognosis are poor [1]. Despite the continuous development of surgery, chemotherapy and radiotherapy in recent years, the 5-year OS rate of EOC patients is just about 40% [2].

Nowadays, standard procedures for patients with advanced EOC is primary cytoreductive surgery (PCS) followed by postoperative platinum-based chemotherapy. Successful tumor resection is considered to be an important independent factor affecting the outcome of advanced EOC patients [3]. Clinically, a diameter of residual tumor lesions <1 cm in the abdominopelvic cavity after cytoreductive surgery or residual lesions not visible in the naked eye are defined as satisfactory cytoreductive surgery. However, for patients with advanced EOC (FIGO stages III/IV), the tumor volume is generally large or with extensive abdominal metastases, so it is difficult to completely remove the tumor and achieve a satisfactory cytoreductive surgery [4].

Therefore, in order to reduce the tumor burden and create favorable conditions for surgery, Griffiths et al. [3] proposed neoadjuvant chemotherapy

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(NAC) for advanced EOC patients in the 1970s. The application of NAC in advanced EOC patients includes the following two options: 1) With clear pathological EOC diagnosis, the patient receives the proper effective chemotherapy for finite-duration treatment, followed by cytoreductive surgery. 2) After PCS, EOC patients who fail to achieve satisfactory cytoreduction are treated with finite-duration chemotherapy after surgery, followed by interval cytoreductive surgery (ICS) [5].

In this study, the effects of NAC and PCS on PFS and OS of advanced EOC patients were compared and the clinical efficacy of NAC in advanced EOC was investigated, so as to offer a promising therapy for such patients.

Methods

General information

Study population: A total of 128 patients with advanced EOC (FIGO stages IIIC-IV) admitted at the Shanxi Cancer Hospital from January 2004 to December 2011 were retrospectively investigated. Inclusion criteria: patients pathologically diagnosed with primary advanced EOC for the first time (FIGO stages IIIC-IV), having no other malignancy. Exclusion criteria: patients with malignant ovarian cancer of other histological types, such as germ cell tumor, sex-cord stromal tumor as well as borderline ovarian tumors, patients with comorbidities (cardiac, pulmonary, CNS), patients with a history of other malignant tumor within 5 years and those with allergy to chemotherapeutic drugs.

This study was approved by the ethics committee of Shanxi Cancer Hospital and signed informed consent was obtained from all participants before the study entry.

Grouping method

Patients were randomly divided into NACT-ICS group (n=66) and PCS group (n=62). Participants in NACT-ICS group were given platinum-based chemotherapy for 2-3 courses before surgery, followed by ICS after the improvement of patients; ICS was performed after the last cycle of primary chemotherapy, followed by platinum-based chemotherapy for 6-8 courses on the basis of the general situations and intraoperative conditions of patients after surgery. Patients in PCS group were treated with cytoreductive surgery first, followed by chemotherapy for 6-8 courses after surgery.

Factors investigated

The general situation of patients in the NACT-ICS group and PCS group was assessed by estimating age and body mass index (BMI), intraoperative conditions, including the lesion size, operation time, intraoperative blood loss, residual lesions, postoperative pathology, and the clinical efficacy, i.e. PFS, and the 1-, 2-, 3- and 5-year OS of patients in the two groups were evaluated and compared.

Evaluation of prognosis

The study was terminated on December 31, 2011. Patient follow-up was performed by outpatient visits, telephone contacts and retrieval of medical records. Tumor size and changes in ascites and CA125 of survivors before and after treatment were assessed via clinical examination, B ultrasound and CT, so as to evaluate the remission extent and PFS.

Statistics

SPSS 19.0 software (Version X; IBM, Armonk, NY, USA) was used for data analyses. Quantitative data were presented as mean ± standard deviation and the independent sample t-test was used for quantitative data; chi-square test was applied for qualitative data. Kaplan-Meier method with log rank test were used for survival analysis. $P<0.05$ suggested that the difference was statistically significant.

Results

General data

Age, body mass index, clinical symptoms, clinical staging, histopathological grading and histopathological type had no differences between the 2 groups ($p>0.05$). The general patient situations in both groups were similar (Table 1).

Surgery

The operation time of NACT-ICS group ranged from 70 to 380 min (mean 215.65±68.48), while that of PCS group was 125-460 min (mean 275.94±70.84) ($p<0.05$). The intraoperative blood loss of NACT-ICS group ranged from 100 to 1400 mL (mean 467.84±220.14), while that of PCS group it was 250-3100 mL (mean 794.94±250.16) ($p<0.05$). The rate of optimal debulking surgery was 60.6% in the NACT-ICS group and 38.7% in the PCS group ($p<0.05$) (Table 2).

Clinical efficacy

The response rate was 72.7% (48/66) in the NACT-ICS group and 53.2% (33/62) in the PCS group, favoring significantly the former ($p<0.05$) (Table 3).

Survival

The survival of the two groups was compared (Table 4) and the mean follow-up time was 61.3 months (range 24-119). There were 28 (42.4%) deaths in the NACT-ICS group and 32 (51.6%) deaths in the PCS group ($p>0.05$). The 1-year survival rate was 93.9% (62/66) in the NACT-ICS group and 95.2% (59/62) in the PCS group ($p>0.05$). The 2-year survival rate was 87.9% (58/66) in the NACT-ICS group and 87.1% (54/62) in the PCS

Table 1. Comparison of general clinicopathological characteristics of the two groups

Characteristics	*Neoadjuvant chemotherapy (n=66) Patients, n*	*Primary debulking surgery (n=62) Patients, n*	*t/x²*	*p value*
Age, years, mean±SD	54.28±7.84	55.76±8.26	t=0.302	0.752
BMI (kg/m²), mean±SD	22.77±2.57	22.12±2.56	t=0.128	0.336
Clinical symptoms			x²=2.379	0.795
Abdominal pain	14	15		
Abdominal distention	22	18		
Menstrual disorder	5	8		
Vaginal bleeding	8	9		
Physical examination	12	7		
Others (wheezing or tightness in chest, fatigue/ weakness, weight loss, frequency or urgency of urination)	5	5		
Clinical stage			x²=1.373	0.241
III C	45	48		
IV	21	14		
Histopathological grade			x²=1.086	0.781
Well differentiated	9	8		
Moderately differentiated	22	16		
Poorly differentiated	32	34		
Unknown	3	4		
Histopathological types			x²=0.218	0.999
Serous carcinoma	43	42		
Mucinous carcinoma	7	6		
Clear-cell carcinoma	5	4		
Endometrioid adenocarcinoma	4	3		
Undifferentiated carcinoma	4	4		
Mixed carcinoma	3	3		

Table 2. Comparison of surgical data between the two groups

Surgical data	*NACT-ICS group*	*PCS group*	*t/x²*	*p value*
Duration of operation(min), mean±SD	215.65±68.48	275.94±70.84	t=-2.719	0.005
Blood loss (mL), mean±SD	467.84±220.14	794.94±250.16	t=-3.623	0.00
Residual lesions (cm), n (%)			x²=6.131	0.013
<1	40 (60.6)	24 (38.7)		
≥1	26 (39.4)	38 (61.3)		

Table 3. Comparison of clinical efficacy between the two groups

	CR	*PR*	*SD*	*PD*
NACT-ICS group	22	26	8	10
PCS group	13	20	18	11
p value	0.022			

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease

Table 4. Comparison of survival rates between the two groups

Survival rates	*NACT-ICS group n (%)*	*PCS group n (%)*	*p value*
Death			0.298
Yes	28 (42.4)	32 (51.6)	
No	38 (57.6)	30 (48.4)	
1-year survival	62/66 (93.9)	59/62 (95.2)	0.761
2-year survival	58/66 (87.9)	54/62 (87.1)	0.894
3-year survival	52/66 (78.8)	45/62 (73.6)	0.413
5-year survival	11/24 (45.8)	15/32 (46.9)	0.938
Median PFS (months)	18.5	17.9	0.783
Median OS (months)	47.5	46.3	0.284

group (p>0.05). The 3-year survival rate was 78.8% (52/66) in the NACT-ICS group and 73.6% (45/62) in the PCS group (p>0.05). The 5-year survival rate was 45.8% (11/24) in the NACT-ICS group and 46.9% (15/32) in the PCS group (p>0.05).

Median PFS and OS of the NACT-ICS group were 18.5 months (range 5.5-41.3) and 47.5 months (range 6.2-110.3), respectively, and those of the PCS group were 17.9 months (range 4.0-88.5) and 46.3 months (range 9.1-110.2) (p>0.05).

Discussion

In this retrospective cross-sectional study, patients with EOC (FIGO stages IIIB or less) were not included, and only patients with stages IIIC-IV were studied, because in patients with earlier stages, optimal treatment is excision of all visible lesions. The preferred therapeutic method of advanced EOC patients is cytoreductive surgery, followed by chemotherapy, but NACT can be applied to patients with large tumors in advanced stage who cannot be subjected to surgery [6]. Currently the recognized NACT indications include [7]: (1) Tumors confirmed to be pathologically malignant by biopsy or pleural effusion exfoliative cytologic examination; (2) Tumors with extensive intraperitoneal metastases via clinical manifestations, physical examination, imaging and laparoscopy, and the residual lesions cannot be reduced below 1 cm with surgery, or the lesion site is special and difficult to remove with primary surgery; (3) Patients having other serious diseases, weakness and unfit for surgical operation; (4) No acute intestinal obstruction and other indications of emergency surgery.

At present, the National Comprehensive Cancer Network (NCCN) Guidelines suggest that the satisfactory cytoreductive surgery tries to make the diameter of residual lesion <1 cm, and it is best to remove all residual lesions [8]. An EORTC-NCIC study showed that regardless of NACT-ICD group or PCS group, complete removal of all visible lesions is the most important independent prognostic factor of advanced EOC [6]. However, due to extensive metastases, fixed lesions and serious infiltration of surrounding tissues of advanced EOC surgery, only 30-40% of the patients can achieve a satisfactory cytoreductive surgery. In this study, the resection rate was 60.6% in NACT-ICD group and 38.7% in PCS group, significantly favoring the NACT-ICS group. This may be because NACT reduces the adhesion between tumor lesions and surrounding tissues, and decrease the tumor load, thereby reducing the difficulty of surgery. In recent years, some authors have defined the satisfactory cytoreductive surgery from the postoperative residual lesions <1 cm to no visible lesions, because the median survival of patients with no visible lesions is up to 70 months or even longer [9-11]. In a recent Cochrane study on the effects of postoperative residual lesions on the survival rate of advanced ovarian cancer [12], it was also found that the death ratio of patients with residual lesions <1 cm and no visible lesions was 2.2 (95%CI, 1.9-2.54), indicating that removing all the visible lesions as much as possible can improve the survival rate.

A previous study has shown that NACT can not only increase the cytoreductive rate, but also improve the patient's intraoperative conditions, such as reducing the bleeding losses, shortening the duration of operation, and improving the total effective rate of treatment [13]. In this study, it was also found that NACT combined with ICS could improve the intraoperative conditions, significantly reduce the duration of operation and reduce the intraoperative blood loss. The total efficiency rate was 72.7% in the NACT-ICS group and 53.2%

in the PCS group ($p<0.05$), suggesting that NACT significantly increases the total effective rate of treatment.

Can NACT improve the survival of patients? Kang and Nam [13] and other authors found no statistically significant differences in PFS and OS between NACT-ICS and PCS groups through meta-analyses. The European Organization for Research and Treatment of Cancer (EORTC) 55971 study was an international, multi-center, randomized controlled phase III clinical trial that compared the effects of NACT and conventional postoperative chemotherapy on ovarian cancer [14]. The data showed no significant differences in OS and PFS between NACT-ICD and PCS groups, and no significant differences according to age and postoperative residual lesion size, but the incidence rates of adverse reactions (such as hemorrhage, venous thromboembolism and infection) in the NACT group were significantly lower compared with the conventional postoperative chemotherapy group. However, there are still a few authors who express different views. A study of School of Medicine, Yale University [15], showed that the OS and PFS of NACT patients with extraperitoneal metastatic lesions were 31 and 15 months respectively, which were significantly higher than those of ovarian cancer patients treated with the traditional surgery. In our study it was found that the survival of patients in the NACT-ICD and PDS groups were similar, suggesting that NACT does not improve survival. In addition, the PFS and OS were not significantly different between NACT-ICS and PCS groups.

Conclusions

Compared with PCS, NACT-ICS can improve the intraoperative conditions, increase the cytoreductive rate, reduce the bleeding of operation, reduce the operation time and increase the clinical remission rate, but it has no impact on PFS and OS.

Conflict of interests

The authors declare no conflict of interests.

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