

RESEARCH ARTICLE

Role of Neoadjuvant Chemotherapy in the Management of Advanced Ovarian Cancer

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Abstract

Objective: To analyze efficacy of neoadjuvant chemotherapy for advanced ovarian cancer. **Materials and Methods:** A total of 107 patients with advanced ovarian cancer undergoing cytoreductive surgery were divided into a neoadjuvant chemotherapy group (n=61) and a primary debulking group (n=46) and retrospectively analyzed. Platinum-based adjuvant chemotherapy was applied to both groups after cytoreductive surgery and overall and progression-free survival times were calculated. **Results:** No significant difference was observed in duration of hospitalization (20.8 ± 6.1 vs. 20.2 ± 5.4 days, $p > 0.05$). The operation time of neoadjuvant chemotherapy group was shorter than the initial surgery group (3.1 ± 0.7 vs. 3.4 ± 0.8 h, $p < 0.05$). There were no significant differences in median overall survival time between neoadjuvant chemotherapy group and surgery group (42 vs. 55 months, $p > 0.05$). Similarly, there was no difference in median progression-free survival between neoadjuvant chemotherapy group and surgery group (16 vs. 17 months, $p > 0.05$). The surgical residual tumor size demonstrated no significant difference between initial surgery and neoadjuvant chemotherapy groups ($p > 0.05$). Multivariate analysis showed that more than 3 cycles of regimen with neoadjuvant chemotherapy was associated with more resistance to chemotherapy compared with patients without receiving neoadjuvant chemotherapy (OR: 5.962, 95% CI: 1.184-30.030, $p < 0.05$). **Conclusions:** Neoadjuvant chemotherapy can shorten the operation time. However, it does not improve survival rates of advanced ovarian cancer patients.

Keywords: Neoadjuvant chemotherapy - ovarian cancer - cytoreductive surgery - chemotherapy sensitivity

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Introduction

Ovarian cancer is a common form of cancer in women and the main cause of death among all gynecologic cancers. Due to the lack of effective means of early detection, patients with obvious symptoms have been in advanced stage of the disease. Primary cytoreductive surgery followed by chemotherapy represents the current standard treatment for patients with advanced ovarian cancer (McGuire et al., 1996; Monk et al., 2013). Primary cytoreductive surgery aims at removing as much primary and metastatic tumor as possible in order to facilitate response to subsequent chemotherapy and improve survival (Gadducci et al., 2013; Bian et al., 2014). For patients with poor general condition or not satisfied with tumor resection, several cycles of chemotherapy before surgery was used.

Neoadjuvant chemotherapy represents any cytotoxic therapy given prior to any cytoreductive surgery (Lawton et al., 1989; Schwartz et al., 1994; Schwartz et al., 1999). Frei (1982) in 1982 originally introduced the definition of neoadjuvant chemotherapy to describe chemotherapy treatment of primary solid tumors before surgical ablation. Neoadjuvant chemotherapy followed

by interval debulking surgery has been proposed as an alternative approach for the initial management of ovarian cancer, aiming at the improvement of surgical efficiency and patients' quality of life. In a retrospective study by Mazzeo et al. (2003), patients with primarily unresectable ovarian cancer received a median of four platinum-based neoadjuvant chemotherapy courses, followed by surgery and adjuvant chemotherapy in patients with an objective response or stable disease after induction of chemotherapy. In addition to improving the patient's general condition and control the pleural effusion, the main purpose of neoadjuvant chemotherapy is to improve the cytoreductive surgery satisfaction rate. Vergote et al. (2010) Of the 670 patients randomly assigned to a study treatment, The largest residual tumor was 1 cm or less in diameter in 41.6% of patients after primary debulking and in 80.6% of patients after interval debulking. Complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting overall survival.

The aim of this study was to determine the impact of the neoadjuvant chemotherapy on optimization of cytoreductive surgery, and analyze the impact of neoadjuvant chemotherapy on postoperative chemotherapy

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sensitivity and patient survival so as to evaluate the role of neoadjuvant chemotherapy in the management of advanced ovarian cancer compared to conventional therapy.

Materials and Methods

Patients

The study included 107 patients with advanced ovarian cancer (FIGO stages III - IV) treated at the department of Gynecologic Oncology, Tumor hospital, Chinese Academy of Medical Sciences during 2004-2010 (Table 1). 61 cases of the patients were treated with 1-5 cycles of neoadjuvant chemotherapy, 46 cases received cytoreductive surgery. For the neoadjuvant chemotherapy regimen among these 61 cases, 38 cases were treated with TC scheme, 8 cases treated with CP regimen, 5 cases treated with CAP regimen, 10 cases treated with TP regimen. 9 patient's received 1 course of neoadjuvant chemotherapy treatment, 41 cases with 2 courses, 11 cases with more than three courses. All the studied patients underwent combined treatment of primary cytoreductive surgery followed by adjuvant chemotherapy (treated with TC, TP, CP or CAP regimen). Optimal cytoreduction was considered to be achieved when the largest residual tumor diameter was ≤ 1 cm. Follow up of patients were observed for more than 6 months after adjuvant chemotherapy, the median follow-up time was 48 months.

Chemotherapy sensitivity

The clinical criteria of chemosensitivity: Imaging methods and the concentraion of serum CA125 was

assessed to evaluate the clinical efficacy. Clinical platinum-sensitive group had no recurrence within 6 months after the end of chemotherapy; clinical platinum-resistant group had recurrence within 6 months in the progression or chemotherapy. Progression or completion of chemotherapy in cancer chemotherapy within 6 months after the recurrence. Progression in cancer chemotherapy or tumor recurrence within 6 months after chemotherapy.

Statistical analysis

All data in the study were evaluated with SPSS version 13.0 software (SPSS Inc.). The χ^2 test was performed to determine the differences of the postoperative residual tumor cases. The t-test analysis was used to analyze the differences of the surgical bleeding, operative time and hospital stay. Overall and progression-free survival rates were assessed by the Kaplan-Meier method and Logistic regression analysis of the significance of prognostic factors (Grading, staging, pathology, surgical approach, residual tumor size and the effect of neoadjuvant chemotherapy on clinical chemosensitivity). Differences were considered significant at value of $p \leq 0.05$.

Results

The comparison of operation time, blood loss, hospital stay and the residual tumor

To evaluate the effect of neoadjuvant chemotherapy on cytoreductive operation, we compared the optimal cytoreductive operation (the largest residual tumor diameter was ≤ 1 cm) rates between patients who received

Table 1. The General Information of the Patients

Clinical parameters	primary debulking (n=46)	neoadjuvant (n=61)	<i>p</i>
Age(years)	57.4 \pm 9.4	56.0 \pm 10.1	0.465
Stage(%)			0.079
IIIA	1(2.17%)	0	
IIIB	4(8.69%)	1(1.64%)	
IIIC	37(80.43%)	47(77.05%)	
IV	4(8.69%)	13 (21.31%)	
Classification			0.114
Poorly differentiated	32	48	
Moderately differentiated	11	13	
Well differentiated	3	0	
Pathological type			0.465
Serous adenocarcinoma	29	33	
Endometrioid adenocarcinoma	5	25	
Clear cell carcinoma	4	3	
Transitional cell carcinoma	4	0	
Mixed epithelial carcinoma	2	0	
Mucinous adenocarcinoma	2	0	
Mucinous adenocarcinoma	2	0	
Surgical approach			0.356
Total abdominal hysterectomy +bilateral salpingo-oophorectomy +mentectomy+appendectomy + cytoreductive surgery	31	33	
Total abdominal hysterectomy +bilateral salpingo-oophorectomy +mentectomy+appendectomy + cytoreductive surgery + excisional biopsy of lymph node enlargement	4	6	
Total abdominal hysterectomy +bilateral salpingo-oophorectomy +mentectomy+appendectomy + cytoreductive surgery + pelvic and paraaortic lymphadenectomy	11	22	

neoadjuvant chemotherapy and those patients who did not receive it. In neoadjuvant chemotherapy group, optimal cytoreduction was subsequently achieved in 37 of 61 patients (60.66%), whereas achieved in 21 of 46 patients (45.65%) in no received neoadjuvant chemotherapy group (Table 2), with no statistical difference. However, the cytoreductive operation rates in neoadjuvant chemotherapy group was higher than the initial surgery group. The amount of bleeding and duration of hospitalization had no significant difference between initial surgery and

neoadjuvant chemotherapy group (431.5±259.3 ml vs. 382.0±231.1 ml, $p>0.05$; 20.8±6.1 days vs. 20.2±5.4 days, $p>0.05$). Neoadjuvant chemotherapy group operative time was statistically shorter than the initial surgery group (3.1±0.7h vs. 3.4±0.8h, $p<0.05$).

Comparison of the sensitivity of chemotherapy

Logistic regression multivariate analysis was used and found the residual tumor size was correlated with clinical chemosensitivity (Table 3). Patients with tumors larger

Table 2. The Comparison of Operation Time, Blood Loss, Hospital Stay and the Residual Tumor

Clinical parameters	primary debulking (n=46)	neoadjuvant (n=61)	p
Residual tumor size			0.297
≤1cm	21(45.65%)	37(60.66%)	
1-2cm	8	7	
>2cm	17	17	
Blood loss(ml)	431.5±259.3	382.0±231.1	0.3
operation time (hours)	3.4±0.8	3.1±0.7	0.041
hospital stay (days)	20.8±6.1	20.2±5.4	0.561

Table 3. Multivariate Logistic Regression Analysis Of clinically Relevant Factors Affecting the Chemosensitivity

Risk factors	wald value	OR	95% CI	P value
Classification(poor vs moderate/well)	0.018	1.071	0.393-2.920	0.893
Staging(stage 3 vs stage 4)	2.655	2.86	0.808-10.127	0.103
Pathology	2.855			0.24
Endometrioid adenocarcinoma vs serous adenocarcinoma	0.539	0.674	0.235-1.933	0.463
Others * vs serous adenocarcinoma	1.876	2.489	0.675-9.181	0.171
Surgical approach	3.745			0.154
2 vs 1	0.33	0.62	0.121-3.169	0.565
3 vs 1	2.812	2.413	0.862-6.755	0.094
Residual tumor size	7.507			0.023
1-2cm vs ≤1cm	0.001	0.982	0.246-3.915	0.979
>2cm vs ≤1cm	6.59	3.913	1.381-11.088	0.01
Neoadjuvant chemotherapy	4.702			0.095
1-2courses vs 0	1.035	1.688	0.616-4.631	0.309
≥3courses vs 0	4.685	5.962	1.184-30.030	0.03

* Includes ovarian clear cell carcinoma, transitional cell carcinoma, mixed epithelial carcinoma and mucinous adenocarcinoma

1: Total abdominal hysterectomy +bilateral salpingo-oophorectomy+omentectomy+appendectomy + cytoreductive surgery, 2: Total abdominal hysterectomy +bilateral salpingo-oophorectomy+omentectomy+appendectomy + cytoreductive surgery + excisional biopsy of lymph node enlargement, 3: Total abdominal hysterectomy +bilateral salpingo-oophorectomy+omentectomy+appendectomy + cytoreductive surgery + pelvic and paraaortic lymphadenectomy

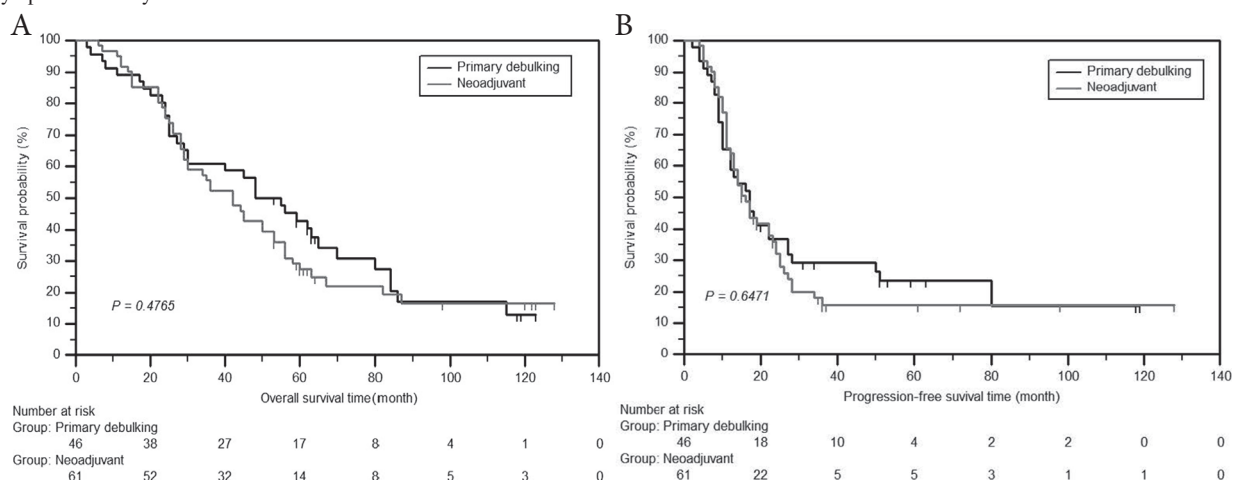


Figure 1. Overall Survival Time and Progression-Free Survival Time for Patients with Ovarian Cancer in the Primary Debulking and Neoadjuvant Chemotherapy Groups. No statistically significant difference was observed in the overall survival between the group treated with neoadjuvant chemotherapy and the no neoadjuvant chemotherapy treated group ($p=0.4765$) (A). There was also no statistical difference was founded in the progression-free survival between these two groups ($p=0.6471$) (B).

than 2cm are more prone to resistance to chemotherapy than residual tumor smaller than 1cm instance (OR: 3.913 95%CI: 1.381-11.088 $p=0.010$).

Multivariate analysis showed that more than 3 cycles of regimen with neoadjuvant chemotherapy was prone to resistance to chemotherapy compared with patients without receiving neoadjuvant chemotherapy (OR: 5.962, 95%CI: 1.184-30.030, $p<0.05$). However, there are no statistical between the patients with 1-2 courses of neoadjuvant chemotherapy compared to patients without receiving neoadjuvant chemotherapy.

Survival analysis

In the neoadjuvant chemotherapy group of patients, the median overall survival was 42 months, and the median progression-free survival 16months. In the no neoadjuvant chemotherapy group, the median overall survival was 55 months, and the median progression-free survival was 17 months. No statistically significant difference was observed in the overall survival between the group treated with neoadjuvant chemotherapy and the no neoadjuvant chemotherapy treated group ($p=0.4765$) (Figure 1A). There was also no statistical difference was founded in the progression-free survival between these two groups ($p=0.6471$) (Figure 1B).

Discussion

Neoadjuvant chemotherapy represents a few cycles of chemotherapy given prior to tumor cytoreductive surgery which especially suitable for patients with advanced ovarian cancer. Ovarian cancer is chemotherapy sensitive epithelial tumor, total efficiency can achieve 70% ~ 80% and 40% ~ 50% can achieve clinical complete remission after application of platinum based chemotherapy (Dewdney et al., 2010). McClug et al. (2002) confirmed the chemotherapy affection of advanced ovarian cancer through the pathological changes.

Neoadjuvant chemotherapy has the following advantages: *i*) neoadjuvant chemotherapy drug administration through thoracic and abdominal cavity can control the ascites, improve the general condition so as to improve the operation tolerance; *ii*) Destroy the liver, lung metastasis, reduce tumor staging, increase the operation feasibility; *iii*) Reduce tumor volume, loose tumor and normal tissue adhesions, reduce operation risk; reduction of abdominal tumor metastasis, shorten operation time, reduce intraoperative bleeding, effectively improve the cytoreductive surgery success rate; *iv*) obtain the operation resection specimens to evaluated the chemotherapy sensitivity; *v*) The neoadjuvant chemotherapy is especially suitable for advanced cancer patients with generally poor quality, large metastasis tumor, high serum CA125 level or tumor difficult to clean (Le et al., 2007; Akita et al., 2009).

Researchers showed that the neoadjuvant chemotherapy is helpful to improve the prognosis and the quality of life of patients (Sternberg et al., 1995; Chan et al., 2003; Tatematsu et al., 2013). Here, we compared the 61 cases patients received new adjuvant chemotherapy and 46 cases of patients without preoperative chemotherapy, found no

significant differences in patients age, tumor stage, grade, histological type and surgical approach. Patients in the chemotherapy group, after neoadjuvant chemotherapy, the general condition was improved, created conditions for the operation, optimal cytoreductive surgery rate was 60.66%, which was higher than the no received preoperative chemotherapy group, optimal cytoreductive surgery rate was 45.65%, there was no significant difference between these two groups. Neoadjuvant chemotherapy can shorten the operation time, reduces operation bleeding. Barry (Rosen et al., 2014) retrospectively analyzed 326 patients with advanced ovarian cancer and the satisfaction rate of the patients received neoadjuvant chemotherapy was significantly higher than the direct surgery group (50.1% vs. 41.5% $p=0.03$). However the 7-year survival rate was significantly lower than the direct surgery group (8.6% vs. 41% $p<0.0001$). This study compares the satisfaction of cytoreductive rate with neoadjuvant chemotherapy group of tumor size less than 1cm was higher than direct surgical group, but did not reach statistical significance. Thus, the sample size in the study should be expanded.

Effect of neoadjuvant chemotherapy on survival: generally, neoadjuvant chemotherapy can reduce the pleural effusion and ascites volume, reduce tumor volume, so that to improve optimal cytoreduction opportunities of patients with advanced ovarian cancer. But studies found that neoadjuvant chemotherapy cannot improve the prognosis of patients with ovarian cancer. Inciura et al. (2006) retrospective analysis of 213 cases ovarian cancer patients received neoadjuvant chemotherapy and 361 patients treated by standard mode therapy, results showed that there was not significant differences between the two groups in OS and PFS ($p>0.05$). Loizzi et al. (2005) founded that the median survival time, median progression free survival time and 3-years survival rate of neoadjuvant chemotherapy patients compared with the standard treatment for patients had no significant difference.

Meta-analysis (Bristow and Chi, 2006) indicated the cycle numbers of preoperative chemotherapy was negatively correlated with survival rate in ovarian cancer patients; patients with each additional 1 cycle of chemotherapy, the OS will be reduced 4.1 months. In this study, there was no statistical difference between the overall survival time and no time to disease progression, neoadjuvant chemotherapy can not improve the prognosis, consistent with previous findings.

Effect of neoadjuvant chemotherapy on drug sensitivity: Logistic regression analysis was used to analyze the multiple clinical indicators on the impact of chemotherapysensitivity. In multivariate analysis, we found patients received more than three courses of neoadjuvant chemotherapy treatment are prone to resistance to chemotherapy (OR: 5.962, 95%CI: 1.184-30.030, $p<0.05$). The clinical chemosensitivity had no statistical difference of patients with 1-2 courses of neoadjuvant chemotherapy compared with patients without receiving neoadjuvant chemotherapy. Increase the courses of neoadjuvant chemotherapy medications can increase the incidence of clinical drug resistance, which may be associated with tumor acquired drug resistance,

which may be combined with no obvious CA125 decline. The mechanism of drug resistance is influenced by many factors, therefore a larger randomized clinical study need to further investigate.

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