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ORIGINAL ARTICLE

Effect of increased number of neoadjuvant chemotherapy cycles on tumor resectability and pathologic response in advanced stage epithelial ovarian cancer

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Summary

Purpose: *To identify the significance of the number of neoadjuvant chemotherapy (NACT) cycles on pathologic response and to define relationship between multiple cycles of NACT and the timing of interval debulking surgery (IDS) in epithelial ovarian cancer (EOC) patients.*

Methods: *This retrospective case-control study was carried out at the Baskent University in Ankara between 2007 and 2017. We reviewed 62 patients with advanced stage (IIIC-IV) EOC who received NACT in other institutes and operated in our clinic. On the basis of the number of NACT cycles, patients were divided into 2 groups: group 1 received 3 cycles and group 2 received 4 to 6 cycles.The influence of the number of NACT cycles on complete pathologic response, lymph node involvement, overall survival (OS), progression free survival (PFS), platinum resistance and residual tumor were evaluated.*

Results: *The median OS was 44.4 ±4.8 months and 48.8±4.49 months for group 1 and group 2 respectively (p=0.122). PFS was 19.3±3.75 months in group 1 and 24.3±4.67 months in group 2 (p=0.84). Tumor morphology according to lymph node involvement, no visible tumor and complete pathologic response were similar for both groups (p=0.49, p=0.79 and p=0.6 respectively). Pathological absence of residual disease were 13.6% vs 7.5% for group 1 and group 2 respectively (p=0.6) and complete pathologic response rate was 6/62 (9.67%). Platinum resistance developed in 4 (18.2%) patients and 18(45%) patients in group1 and 2 respectively (p=0.031). Complete resection rates were similar for both groups (p=0.9). After multivariate survival analyses, complete resection remained significant (p=0.000, odds ratio/OR 2.28 [1.41-3.70]), and was independent of age, platinum resistance and number of NACT cycles. Complete resection rates were almost equal in each groups, (68.2% [15/22] and 67.5% [27/40] for group 1 and group 2 respectively (p=0.9)).*

Conclusions: *Our data suggests that giving more than 3 cycles of NACT is unnecessary because increased number of cycles did not change the resectability and complete pathologic response, while it increased platinum resistance. Moreover OS and PFS remained similar.*

Key words: *epithelial ovarian cancer, interval debulking surgery, neoadjuvant chemotherapy*

Introduction

Ovarian cancer is the most common cause of death among all gynecological cancers [1,2], and approximately 60% of all EOC patients are in advanced stage when first diagnosed [3]. Standard treatment in advanced stage ovarian cancer is cytoreductive surgery followed by platinum-based chemotherapy.

The aim of surgery is to leave no residual tumor because it is the single most important prognostic factor for survival in EOC patients [4,5].

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Nowadays IDS (interval debulking surgery) has become a second option of treatment in advanced stage EOC in selected cases in order to obtain better resection rates and lower morbidity rates with the same oncologic outcome as proposed in EOTC and CHORUS trials [6-9]. The most important issue is to determine the timing of IDS.

NACT is also believed to be a risk factor for platinum resistance and may give rise to less sensitive recurrent disease [10].

The aim of this study was to identify the significance of the number of NACT cycles on pathologic response, resectability, and to define relationship between multiple cycles of NACT and the timing of IDS.The secondary end points were OS,PFS and platinum resistance according to number of cycles.

Methods

The institutional review board approved this retrospective analysis at Baskent University Ankara Hospital. We reviewed all EOC patients operated in our clinic between 2007 and 2017 and identified 62 patients who received NACT in other institutions and operated in our clinic. All patients had advanced stage disease (IIIC-IV). Forty seven patients had biopsy and 15 had undergone incomplete surgery (cystectomy, unilaretal salpingooophorectomy, abdominal hysterectomy, ommentectomy). All patients received paclitaxel 75 mg/m^2 and carboplatin AUC 5 i.v. every 3 weeks as NACT as outpatients; 22 had 3 cycles and 40 had 4 to 6 cycles.

Eleven patients who received less than 3 cycles were excluded.

All patients were evaluated during surgery and no evidence of regression was defined as platinum-refractory cases. After surgery patients who received 3 cycles of adjuvant paclitaxel-carboplatin regimen and had disease progression within 6 months were also considered as platinum-resistant, while patients who recurred after 6 months were considered as platinum-sensitive. The date of progression was determined by CT scan and/or elevated CA 125 levels.

On the basis of the number of NACT cycles, patients were divided into 2 groups: group 1 received 3 cycles and group 2 received 4 to 6 cycles.

The influence of the number of NACT cycles on complete pathologic response, lymph node involvement, OS, PFS, platinum resistance and residual tumor were evaluated.

Statistics

Statistical analyses were performed using SPSS v.22 for MAC. Univariate analysis was performed using x^2 or Fisher's exact test. Factors significant in univariate analysis were included in the Cox proportional hazard regression model to determine the independent factors of the survival. Survival was evaluated using the Kaplan-Meier method and differences were assessed by the log-rank test. P values less than 0.05 were considered significant.

Results

The median age was 56.5 years (range 36-80) and the median follow-up time was 33 months (range 5-84 months).Twenty two patients received 3 cycles of NACT and 40 had 4 to 6 cycles. Group 1 and 2 patients characteristics are shown in Table 1.

The mean OS was 44.4 ± 4.8 months and 48.8 ± 4.49 months for group 1 and group 2 respectively (p=0.122) (Figure 1). PFS was 19.3 ± 3.75 months in group 1 and 24.3 ± 4.67 months in group 2 (p=0.84).

Tumor morphology according to lymph node involvement, no visible tumor and complete pathologic response were similar for both groups (p=0.49,

Table 1. Characteristics of patients according to the number of NACT cycles

Characteristics	*Group 1 n (%)*	*Group 2 n (%)*	*p value*
Patients	22	40	
Age, years	5 (22.7)	10(25)	0.8
<65			
≥65			
Histology			
High grade serous	22	40	0.95
Diagnosis			
Biopsy	18 (81.8)	29 (72.5)	0.5
Incomplete surgery	4 (18.2)	11 (27.5)	
Surgery			0.54
Standard	16 (72.7)	31 (79.5)	0.76
Extensive	6 (27.3)	8 (20.5)	
Ca 125 before NACT,U/ml, mean ± SD	875 ± 224	957 ± 310	

p=0.79 and p=0.6 respectively) (Table 2). Pathological absence of residual disease were 13.6% vs 7.5% for group 1 and group 2, respectively (p=0.6) and complete pathological response was 6/62 (9.67%).

Platinum resistance developed in 4 (18.2 %) patients and 18(45 %) patients in group 1 and 2 respectively (p=0.031). Complete resection rates were similar for both groups (p=0.9) (Table 3).

After multivariate survival analyses complete resection remained significant [p=0.000, OR 2.28 (1.41-3.70)], and was independent of age, platinum resistance and number of NACT cycles. Complete resection rates were almost equal in each groups; they were 68.2% (15/22) and 67.5% (27/40) for group 1 and group 2 respectively (p=0.9).

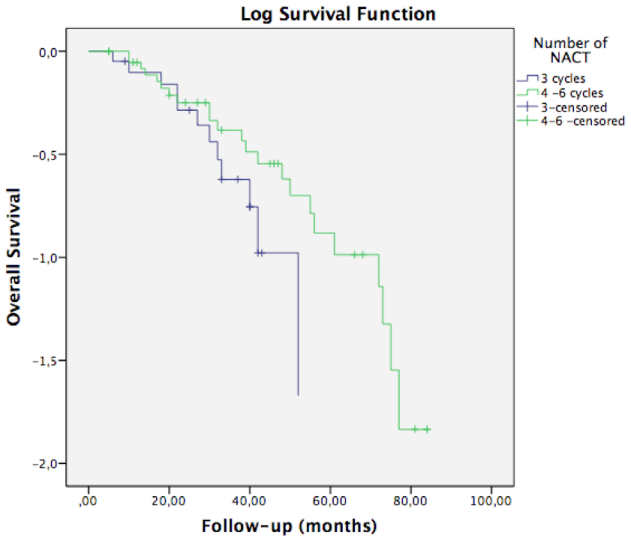

Figure 1. Kaplan-Meier 5 year overal survival rates of epithelial ovarian cancer patients with 3 cycles or 4-6 cycles neoadjuvant chemotherapy (NACT) (p=0.122).

Table 2. Tumor morphology according to lymph node involvement

Groups	*No VT* *n (%)*	*No LN* *n (%)*	*CPR* *n (%)*
G1	9/22 (40.9)	8/22 (36.4)	3/22 (13.6)
G2	15/40(37.9)	16/40 (40)	3/40(7.5)
p value	0.79	0.49	0.6

VT: visible tumor, LN: lymph node metastasis, CPR: complete pathologic response

Table 3. The impact of NACT cycles on overall survival, progression free survival, platinum resistance and complete resection

	Group 1	*Group 2*	*p value*
OS	44.4 months	44.8 months	0.122
PFS	19.3 months	24.3 months	0.834
PR (%)	4/22 (18.2)	18/40 (45.0)	0.031
CR (%)	15/22 (68.2)	27/40 (67.5)	0.9

OS: overall survival, PFS: progression free survival, PR: platinum resistance, CR: complete resection

Discussion

In this study we aimed to determine the impact of the number NACT cycles in OS, PFS and platinum resistance. There were two important findings. Firstly, the number of NACT cycles did not alter lymph node involvement, visible tumor and complete pathologic response rates of patients and there were no survival differences between patients receiving 3 or 4 to 6 NACT cycles. Secondly, our data pointed out that giving more than 3 cycles of NACT increases the risk of platinum resistance (p=0.034) and does not change the complete respectability of the tumor (p=0.9). Moreover complete resection was the only independent factor affecting OS and PFS (p=0.000).

Surgical staging and resection of all visible tumor followed by platinum-based chemotherapy is the standard of care in the management of EOC and it is associated with better survival rates [11]. Since NACT is not a standard of care for EOC, the numbers of NACT cycles have shown differences among different health centers. Altough Vergotte et al. showed similar survival rates for NACT -IDS and PDS, other authors have shown inferior survival rates for NACT compared to IDS [12]. Ren and his colleagues from China demonstrated that with the increase of chemotherapy cycles, there was a decreasing trend in median survival time (p=0.029) [13]. Colombo et al. compared advanced-stage EOC patients receiving less than 4 cycles of NACT and more than 4 cycles before IDS to primary debulking surgery. Despite the higher rates of complete resection in the late IDS group (more than 4 cycles) they had worse survival compared to patients treated by primary surgery or early IDS (less than 4 cycles) (p=0.001) [14]. In our clinic, we prefer primary debulking surgery as standard of care of advanced-stage EOC patients who can tolerate surgery.

There is a variety of factors for platinum resistance such as increased drug usage, damaged DNA repair and altered apoptotic process, however the basic and main mechanism for platinum resistance is not yet fully understood [15]. In the literature, a few studies can be found that have investigated the association between the NACT or PDS and resistance to chemotherapy in ovarian cancer [16,17]. Da Costa et al. from Brazil suggested that patients who are treated with IDS have shorter time platinum-resistant recurrence than those who undergo

PDS(39.3 vs. 80.8 months; p=0.012) [16]. Raugh-Hain et al. analyzed 425 patients with stage IIIC and IV EOC patients who underwent PDS or IDS. When they compared platinum-resistant disease rate at first relapse this was higher in IDS group (44.2% vs 34.2%). However in multivariate analysis the difference was insignificant but the risk of platinum resistance at second relapse was higher for IDS group (HR:4.06, p=0.001) and the author suggested that the timing of IDS should be based on chemotherapy response and not in fixed number of NACT cycles [17]. Lim et al. revealed that NACT might induce chemotherapy resistance in colonies of cancer stem cells which are difficult to detect and be removed in IDS [18]. In another study, Petrillo et al. showed only 6.5% of pathological residual disease observed after surgery in advanced-stage EOC receiving NACT [19]. In our research this was 9.67%.

The present study has some limitations, among them its retrospective nature, the limited patient population and patients received NACT at other institutes, therefore additional well-designed prospective large-scale studies are required to enlighten this important topic.

In conclusion, our data showed that patients should be evaluated after 3 cycles of NACT because the increased number of cycles did not change resectability and complete pathologic response but bare the hazard of platinum resistance. Moreover, OS and PFS remained similar. In our opinion giving more than 3 cycles of NACT is unnecessary but larger prospective randomized studies are needed to clarify this approach.

Conflict of interests

The authors declare no conflict of interests.

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