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Prognostic Benefit of ≥6 Cycles of Neoadjuvant Chemotherapy for Advanced Ovarian, Tubal, and Peritoneal Cancers

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Abstract. *Background/Aim: A higher number of neoadjuvant chemotherapy (NACT) cycles translate to a lower risk of morbidity and mortality, but few studies have analyzed the prognostic impact of >4 cycles of NACT. Patients and Methods: Overall, 52 patients [31 patients, NACT plus interval debulking surgery (IDS); 21 patients, NACT alone owing to progressive disease] who underwent NACT between January 2008 and December 2014 were evaluated. Results: In total, 6, 7-10, and 11-18 cycles of NACT were performed in 52.3%, 27.3%, and 20.5% of the patients, respectively. The median overall survival was 76.0 months (range=36.0-94.0 months), and the median progression-free survival was 26.0 months (range=18.0-54.0 months) in the NACT plus IDS group. Conclusion: At least six cycles of NACT plus IDS are associated with a lower rate of multi-organ resection and a high rate of complete resection or optimal (<1 cm) following IDS.*

The incidence of ovarian, tubal, and peritoneal cancer is increasing, with current rates approximately 1.3 times higher than they were 10 years earlier. In 2020, 313,959 incident cases of ovarian cancer and 207,252 deaths were reported worldwide (1). Ovarian cancer has the worst prognosis among all gynaecologic malignancies (2). Primary debulking surgery (PDS) followed by platinum and taxane chemotherapy is the standard treatment modality for advanced ovarian cancer (3). However, neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) are selected for patients with advanced ovarian cancer in whom complete cytoreduction to R0 is less likely to be achieved or for patients who are poor surgical candidates and expected to have a residual tumour of ≥1 cm at the initial surgery. Machida *et al*. reported a significant increase in the utilization of NACT in Japan, with one in seven women with epithelial ovarian cancer (EOC) receiving NACT in 2015 (4). Four randomized trials (*i.e*. the European EORTC 55971, CHORUS study, SCORPION trial, and JCOG 0602) demonstrated that NACT yields non-inferior overall survival (OS) outcomes to PDS, but patients receiving NACT + interval debulking surgery (IDS) develop fewer complications than do patients receiving PDS because of its less invasive nature (5-8). Meanwhile, the use of NACT in ovarian cancer is suggested to increase platinum resistance, possibly due to the presence of residual cancer stem cells after NACT (9, 10). A higher number of NACT cycles lowers the risk of morbidity and mortality following IDS. NACT was performed in three cycles in the EORTC 55971 trial, CHORUS study, and SCORPION trial and in four cycles in JCOG 0602. In EOC, NACT is generally administered in three or four cycles due to the risk of platinum resistance. However, the safety and prognostic benefit of ≥4 cycles of NACT are yet to be clarified. Plett *et al*. reported that surgery in patients with persistent disease after 5+ cycles of NACT could be associated with favourable outcomes if complete resection is achieved (11). However, few studies have analyzed the prognostic benefit of ≥4 cycles of NACT with respect to OS and progression-free survival (PFS) in patients with advanced ovarian cancer.

Therefore, this study aimed to analyze the prognostic impact of over six cycles of NACT in advanced ovarian, tubal, and peritoneal cancers and investigate the factors affecting OS and PFS in these cancers.

Patients and Methods

Study design and patients. This single-centre retrospective study was approved by the Ethics Committee of Mie University Hospital. Informed consent was obtained in the form of opt-out on the website. The subjects were consecutive patients diagnosed with EOC, tubal cancer, or peritoneal cancer between January 2008 and December 2014 and treated with NACT. The inclusion criterion was histologically confirmed International Federation of Gynecology and Obstetrics stage III to IV EOC, tubal cancer, or

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Key Words: Neoadjuvant chemotherapy, ovarian cancer, tubal cancer, peritoneal cancer, prognosis.

Table I. *Background characteristics of NACT alone and NACT plus IDS in ≥6 cycles of the NACT group.*

Variable	Level	NACT alone	NACT plus IDS	*p*-Value
n		13	31	
Age (median [IQR])		62.0 [57.5, 77.5]	58.0 [51.5, 65.5]	0.049
ECOG PS (%)	0	1 (7.7)	13 (41.9)	0.097
	1	7 (53.8)	14 (45.1)	
	2	3 (23.1)	4 (12.9)	
	3	2 (15.3)	0	
Histology (%)	High-grade serous	9 (69.2)	27 (87)	0.209
	Endometrioid	2 (15.4)	2 (6.4)	
	Clear cell	3 (23.1)	0	
	Mucinous	1 (7.7)	2 (6.4)	
Stage (%)	3B	1 (9.5)	2 (6.5)	0.287
	3C	6 (46.1)	21 (67.7)	
	4	6 (46.1)	8 (9.1)	
NACT cycles	6	4	19	
	7-9	4	8	
	11-18	5	4	
Dose down (%)		-	15 (48)	
Date from end of the NACT day to date of IDS (days)	median	-	39 (20-60)	
Surgical characteristics (%)	TAH+			
SO+Omentectomy	-	31 (100)		
	+PLA, PALA	-	17 (54.8)	
	+Bowel resection	-	3 (9.7)	
	+Liver resection	-	1 (3.2)	
	+Cholecystectomy	-	1 (3.2)	
Postop CTX cycles (%)	0-5	-	6 (19.3%)	
	6	-	23 (74.1%)	
	7-10	-	2 (6.5%)	
	Median	-	6	

NACT: Neoadjuvant chemotherapy; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; IDS: interval debulking surgery; CTX: chemotherapy; SO: salpingo-oophorectomy; PLA: pelvic lymphadenectomy; PALA: para-aortic lymphadenectomy.

peritoneal cancer. Of the 79 patients identified, we excluded 27 patients who underwent PDS (n=19) and had missing data or were lost to follow-up (n=8), Finally, 52 patients with EOC (n=50), tubal cancer (n=1), or peritoneal cancer (n=1) were evaluated. Of them, 31 and 21 patients underwent NACT plus IDS and NACT alone for progressive disease (PD), respectively. Of the 21 patients in the NACT alone group, NACT was given for <4 cycles due to disease progression in 8 patients, while 13 patients received ≥6 cycles. Data including age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histological subtype, primary stage, number of NACT cycles, surgical characteristics, residual tumour following IDS, and number of postoperative chemotherapy cycles were collected from medical records at our hospital.

Treatment protocol and response assessment. For patients with advanced ovarian, tubal, and peritoneal cancer who are poor surgical candidates and in whom complete cytoreduction to R0 is considered unlikely, our institutional policy includes six cycles of NACT and IDS. NACT involved paclitaxel +carboplatin (TC) (with 6 to 18 cycles of paclitaxel at the physician's discretion of 175 mg/m^2 q3w or 80 mg/m^2 weekly) plus carboplatin AUC 5 to 6 q3w. Treatment response to NACT was evaluated using imaging and serological CA-125 values. The need for IDS was decided according to the gynaecologic oncologist's decision based on whether the patient achieves complete or partial response (CR or PR) to NACT at 6 cycles. IDS was performed for patients who achieved CR or PR assessed using imaging studies and with serum CA-125 levels <100 U/ml; if no patients achieved CR or PR, we continued NACT until our IDS performed criteria.

Variable definitions. We investigated the OS, PFS, adverse events, and date from the end of the NACT to the date of IDS. OS was compared using the following criteria: ECOG (PS), histological subtype, primary stage, number of NACT cycles, surgical characteristics, residual tumour following IDS, and number of postoperative chemotherapy cycles in the NACT plus IDS and NACT alone groups. Residual tumour following IDS was categorized as follows: complete, R0; optimal <1 cm, R1; and suboptimal >1 cm, R2. Postoperative adjuvant therapy with six cycles of TC was performed only if the pathological histology after IDS showed a residual tumour.

Statistical analysis. Continuous variables were compared using the Mann–Whitney test, while categorical variables were compared using Fisher's exact test. OS and PFS were estimated using the Kaplan–Meier method, and compared statistically using the log rank test. The Cox proportional hazards model was used to identify independent predictors of OS in advanced ovarian cancer. Factors

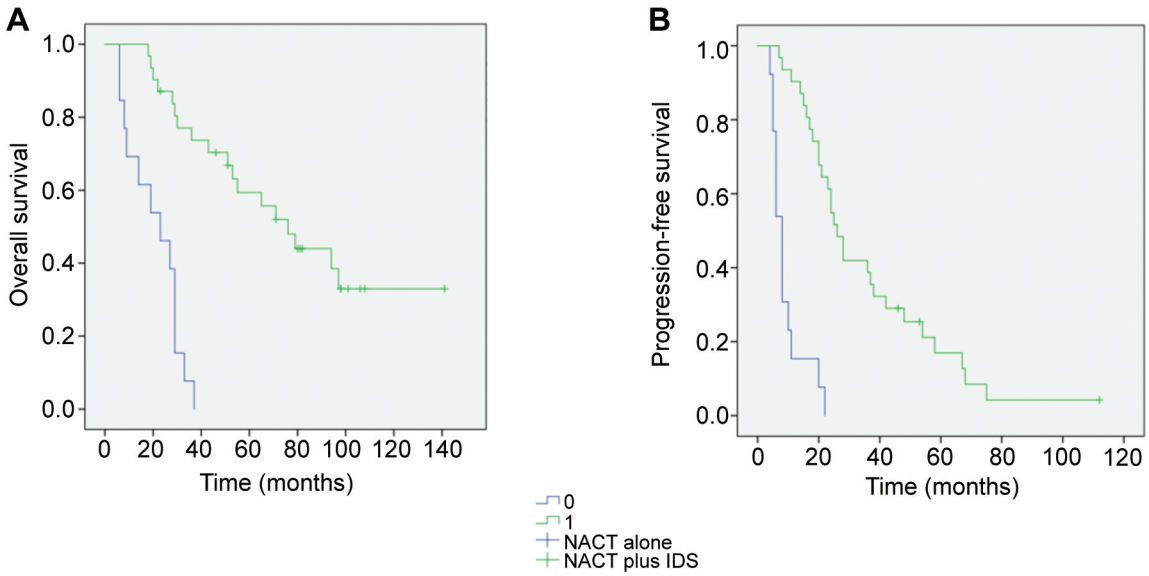

Figure 1. *Survival curves for sensitivity analysis. Overall survival (A) and progression-free survival (B) Kaplan–Meier plots for NACT alone vs. NACT plus IDS groups.*

entered in the univariate and multivariate analyses included age, primary stage, histology, and residual tumour following IDS and PS. All statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, version 24.0, Armonk, NY, USA). A *p*-value of <0.05 was considered statistically significant.

Results

Patient characteristics. All patients were aged 18 years or older [median, 58 (range=51.5-67.5) years]. Most patients had stage IIIC disease (61.5%) and had high-grade serous carcinoma (HGSC) (79%). The clinicodemographic background characteristics of the patients in the ≥6 cycles of NACT group that received NACT plus IDS or NACT alone are shown in Table I. None of the three patients with clear cell carcinoma (CCC) underwent IDS owing to PD. The median follow-up time was 29.5 months (range=2-141 months). All patients were discontinued treatment owing to PD in the <4 cycles of NACT group. NACT was performed in 6, 7-10, and 11-18 cycles for 52.3%, 27.3%, and 20.5% of the patients in the ≥6 cycles of NACT group. Dose reduction owing to neutropenia occurred in 48% of the patients. The median interval between the end of NACT to IDS was 39 days (range=20-60 days).

Survival outcomes and adverse events. The median OS was 33.0 months [interquartile range (IQR)=18.0-94.0], and the median PFS was 17.0 months (IQR=6.0-28.0) in the whole cohort of patients. A total of 52 patients with NACT in both the ≥6 cycles of NACT and <4 cycles of NACT groups were examined. The median OS was 43.0 months (IQR=23.0-97.0), and the median PFS was 20.0 months (IQR=8.0-37.0) in the ≥6 cycles of NACT group. The median OS was 6.0 months (IQR=2.0-6.0), and the median PFS was 2.0 months (IQR=0.0-3.0) in the <4 cycles of NACT group.

In the NACT plus IDS group, the median OS and PFS were 76.0 months (IQR=36.0-97.0) and 26.0 months (IQR=18.0-54.0), respectively. In the ≥6 cycles of NACT alone group, the median OS and PFS were 23.0 months (IQR=9.0-29.0) and 8.0 months (IQR=6.0-10.0), respectively. The Kaplan–Meier OS and PFS curves are shown in Figure 1A and B, respectively. The median OS and PFS were significantly different between the two groups [hazard ratio (HR)=8.385; 95% confidence interval (CI)=3.33-21.09; log-rank $p<0.01$, HR=8.271; 95%CI=3.54-19.32; log-rank $p<0.01$].

In the NACT plus IDS group, the outcomes of IDS were R0, R1, and R2 in 20, 9, and 2 patients, respectively. The median OS was 76 months for the R0 patients, 97 months for R1 patients, and 29 months for R2 patients, with no significant difference between them (R0 *vs*. R1 and 2, HR=1.108; 95%CI=0.429-2.863; log-rank $p=0.832$). Meanwhile, the median PFS was 28 months for R0 patients and 23 months for R1 and R2 patients.

The most common grade >3 haematological adverse events were neutropenia (45%) and anaemia (23%), while the most common non-haematological adverse event was peripheral neuropathy (32%). No treatment-related death occurred.

Influencing factors of survival. Univariate and multivariate analyses showed that ECOG PS (PS 2, 3 *vs*. PS 0, 1 HR=2.96; 95%CI=1.16-7.53; log-rank $p=0.023$) and the histological subtype (others *vs*. HGSC; log-rank $p=0.011$), and CCC *vs*.

HGSC (HR=79.7; 95%CI=4.63-1372; p=0.003) were independent predictors of OS. The histological subtype, particularly CCC, could influence the effectiveness of NACT.

Discussion

The prognostic benefit of ≥4 cycles of NACT in patients with advanced ovarian cancer remains unknown. In this study, we focused on the prognostic benefit of ≥6 cycles of NACT for advanced ovarian, tubal, and peritoneal cancer. Among 52 patients, 44 patients received ≥6 cycles of NACT; 52.3%, 27.3%, and 20.5% of the patients received 6, 7-10, and 11-18 cycles , respectively. Of them, 31 patients were able to undergo IDS. There was no serious adverse event, no delay interval between the end of NACT to IDS, and fewer complications. Furthermore, in our study, abdominal organ resection was performed in 19.3% of the patients (bowel resection, 3 patients; partial liver resection, 1; and cholecystectomy, 1). We found that ≥6 cycles of NACT for advanced ovarian, tubal, and peritoneal cancers in patients may be effective treatment except in patients with ECOG PS 2/3 or the histological subtype, CCC.

NACT plus IDS has been shown to achieve non-inferior OS to PDS, but with fewer complications (5-8). Onda *et al*. reported that the median OS of patients with NACT plus IDS for advanced EOC was 67 months; R0, 34 months; R1 and R2, 32 months (8).

In EOC, NACT is usually limited to only three to four cycles because it is suggested to increase platinum resistance, possibly owing to the presence of residual cancer stem cells after treatment (9, 10). In this study, ≥6 cycles of NACT plus IDS for advanced EOC, tubal cancer, and peritoneal cancers helped patients achieve a median OS of 76 months, consistent with that in other studies (8). However, the 13 patients who received 6 cycles NACT were platinum resistant. Meanwhile, they would have had better prognosis if they had received IDS after four cycles of NACT. The median OS was 23 months (range=9-29 months), and the median PFS was 8 months (range=6-10 months) for the 13 patients. In the AURELIA trial, the median OS was 13.3 months with chemotherapy and 16.6 months with chemotherapy+bevacizumab (12). The PFS and OS in this study were similar to those reported in other studies, supporting that there are no particular disadvantages in performing six cycles of NACT. There were 25% of the patients with PS 2 or 3, and this group had a clearly poor prognosis. All cases of PS3, which were excluded from the other studies, were included. Matsuo *et al*. reported that considering the time interval between chemotherapy and cytoreductive surgery, increased platinum resistance after neoadjuvant chemotherapy may be associated with the sustenance of drug-resistant tumours. While paclitaxel resistance is common after postoperative chemotherapy (9).

In the JCOG 0602 and SCORPION trials, abdominal organ resection was performed for 27.7% and 42.3% of the patients. Reportedly, among patients with NACT plus IDS, diaphragmatic peritonectomy was performed in 30% of them, while other upper abdominal procedures were performed in 14% (7, 8, 13). Glover *et al*. reported that the median surgical complexity scores of IDS were similar to those of PDS (14). Meanwhile, in our study, abdominal organ resection was performed in 19.3% of the patients (bowel resection, 3 patients; partial liver resection, 1; and cholecystectomy, 1).

The rate of residual disease (<1 cm) cases in this study differed significantly from that of a previous study (93.5% *vs*. 82%) (8). Our results showed that the rate of multi-organ resection may be lower when ≥6 cycles of NACT plus IDS than 3-4 cycles are administered, furthermore, the rate of complete resection, R0 or residual disease <1 cm, R1 following IDS may also be high. With respect to survival, the median OS of the NACT alone group was significantly lower than that of the NACT plus IDS group. Multivariate analysis showed that an ECOG PS of 2-3 and the CCC histology were independent predictors of OS. CCC is generally resistant to first-line chemotherapy, and thus, it remains to have poor prognosis (15). The most common adverse event was haematological grade >3 adverse events, but no treatment-related deaths occurred. Compared with other studies, our study of the median NACT plus postoperative chemotherapy cycles was 12 to 18 cycles, higher than 6 to 8 cycles. Therefore, a hypersensitivity reaction (HSR) was developed for nine patients in this study. Approximately 12-19% of patients treated with carboplatin develop carboplatin HSR, with the first episode usually occurring within a median of 8 (range=6-21) courses (16, 17). The rate of HSR (29%) in this study was higher than those in previous studies (16, 17).

The patients treated with NACT plus IDS had good prognosis. In addition, R1 and R2 at IDS were associated with better prognoses than those in the previous study. However, it should be noted that only few patients had R2. Our study is limited by its small sample size and retrospective nature.

In conclusion, ≥6 cycles of NACT plus IDS may help patients achieve not only a lower rate of multi-organ resection, but also a high rate of complete resection or optimal following IDS compared to 3-4 cycles. As such, ≥6 cycles of NACT may be a more optimal choice of treatment in patients with advanced ovarian, tubal, and peritoneal cancers.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare in relation to this study.

Authors' Contributions

Conception and design: Eiji Kondo; Acquisition of data: Kenta Yoshida, Ryo Nimura, Shintaro Maki; Analysis and interpretation of data: Kenta Yoshida, Michiko Kaneda; Drafting of the

manuscript: Tsutomu Tabata, Eiji Kondo; Critical revision of the manuscript for important intellectual content: Tomoaki Ikeda, Masafumi Nii; Final approval of the article: Eiji Kondo.

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