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Original Research

The effect of six scheduled cycles of neoadjuvant chemotherapy on prognosis in advanced ovarian cancer

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Summary

Purpose: This study evaluated the appropriate number of cycles of neoadjuvant chemotherapy (NAC) before interval debulking surgery (IDS) in advanced ovarian cancer. *Materials and Methods:* Cases with advanced ovarian cancer who received a combination of taxane and platinum as NAC and IDS at this institution between 2001 to 2016 were identified. The cases were divided into two groups; patients who received six or four scheduled cycles of NAC (groups A and B, respectively). *Results:* Thirty-six cases were in group A and 35 cases in group B. Progression-free survival (PFS) and overall survival (OS) in group A were better than those in group B ($p = 0.01, < 0.01$). In multivariate analysis, six scheduled cycles of NAC was an independent better prognostic factor for PFS (hazard ratio (HR), 0.56, $p = 0.04$) and OS (HR, 0.39; $p = 0.01$). *Conclusion:* In advanced ovarian cancer, six scheduled cycles of NAC demonstrated a better prognosis.

Key words: Ovarian carcinoma; Neoadjuvant chemotherapy; Primary debulking surgery; Interval debulking surgery.

Introduction

Recently, the incidence of ovarian cancer has been increasing [1]. The prognosis of ovarian cancer, particularly in advanced stages, has not improved despite the development of anti-cancer treatments [2]. The standard treatment for advanced ovarian cancer consists of the combination of maximum debulking surgery and taxane-platinum-based chemotherapy [3]. Although chemotherapy plays an important role in the treatment of ovarian cancer, complete resection has the most significant impact on improving prognosis [4-7]. However, many cases cannot undergo complete resection, including patients with a wide range of multiple metastasis, poor conditions, and complications. For this reason, neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) have been developed.

Two recent randomized clinical studies compared groups treated with the combination of primary debulking surgery (PDS) and adjuvant chemotherapy to groups treated with NAC followed by IDS and adjuvant chemotherapy in patients with advanced ovarian cancer [8, 9]. Progression-free survival (PFS) and overall survival (OS) of the cases treated with NAC and IDS were not inferior to those in the cases treated with PDS. Thus, the combination of NAC and IDS may be an alternative strategy for patients with advanced ovarian cancer. In these randomized trials, the NAC comprised three cycles of platinum-based chemotherapy [8, 9]. However, it was unclear how many cycles of NAC were appropriate because, to the present authors' knowledge, no randomized trials have investigated this issue [10, 11]. Therefore, their purpose was to retrospectively investigate the effect of differences in the number of cycles of NAC on PFS and OS in patients with advanced ovarian cancer.

Materials and Methods

Cases with advanced ovarian cancer who received taxane-platinum based chemotherapy as NAC and IDS at this institution between 2001 to 2016 were identified. In thus institution, NAC was performed for cases that could not undergo a complete resection due to extended diseases on initial diagnosis. Between 2000 and 2012, most cases were scheduled to receive six cycles every three or four weeks unless complication became severe or patients refused the treatment (group A). Cases that were administered fewer than six cycles due to adverse effects were included in group A. Due to the results of the clinical trials described above, the institution changed the treatment schedules as follows [8, 9]. Between 2013 and 2016, almost all cases were scheduled to receive four cycles every three or four weeks (group B). Cases that were administered fewer than four cycles due to adverse effects, etc. were included in group B.

The taxane-platinum based chemotherapy regimens included 175-180 mg/m^2 paclitaxel and carboplatin (area under the curve (AUC) 5 or 6) (TC) or the combination of 70 mg/m^2 docetaxel and 60 mg/m^2 cisplatin (DP) or carboplatin (AUC 5 or 6) (DC). The criteria for the administration of NAC were granulocyte count greater than 1,500/μL,

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Table 1. — *Clinicopathological factors of all cases of advanced ovarian cancer.*

Clinicopathological factors	Cases with six scheduled cycles of neoadjuvant chemotherapy n = 36	Cases with four scheduled cycles of neoadjuvant chemotherapy n = 35	*p*-value
Neoadjuvant chemotherapy cycles, median (range)	6 (5-6)	4 (1-4)	< 0.01
Age at diagnosis (years), mean ± SD (range)	59.0 ± 10.8 (31-78)	61.5 ± 8.2 (44-75)	0.39
CA125 level at diagnosis, mean ± SD (range) (UI/ml)	421 ± 3152 (11-18820)	591 ± 2275 (31-15310)	0.19
FIGO Stage, number (%)			0.8
III	23 (63.9)	24 (68.6)	
IV	13 (36.1)	11 (31.4)	
Histological subtype, number (%)			0.26
High-grade serous carcinoma	33 (91.7)	29 (82.8)	
Non-high-grade serous carcinoma	3 (8.3)	6 (17.2	
Response to NAC at IDS, number (%)			0.99
Complete response	7 (19.4)	7 (20.0)	
Partial response	29 (80.6)	28 (80.0)	
Residual tumor diameters at IDS, number (%)			0.04
Optimal surgery	32 (88.9)	24 (68.6)	
Suboptimal surgery	4 (11.1)	11 (31.4)	
Operative time at IDS, mean ± SD (minutes) (range)	241.0 ± 85.1 (68-420)	207 ± 92.7 (84-566)	0.02
Blood loss at IDS, mean ± SD (ml) (range)	943 ± 704 (30-2572)	562 ± 308 (107-1420)	0.04
Allogenic blood transfusion at IDS (%)			< 0.01
Done	21 (58.3)	9 (25.7)	
Not done	15 (41.7)	26 (74.3)	
Adjuvant chemotherapy regimen, number (%)			0.71
Taxane-platinum based chemotherapy*	31 (86.1)	32 (91.4)	
Other**	5 (13.9)	3 (8.6)	

SD = standard deviation, NAC = neoadjuvant chemotherapy, IDS = interval debulking surgery. *Paclitaxel plus carboplatin, and docetaxel plus carboplatin or cisplatin. ** Single-agent carboplatin, the combination of irinotecan and nedaplatin, or no treatment due to patient's request.

platelet count greater than 100,000/μL, hemoglobin levels greater than 7 g/dL, and a non-hematologic toxicity below grade 1. If these criteria were not met on day 1 of the next cycle, the administration was delayed for one week. If these criteria were not met for two consecutive weeks, the dose of several agents was reduced to 80% and the regimen after IDS changed taxane-platinum based chemotherapy into single-agent carboplatin or the combination of irinotecan and nedaplatin or no treatment for side effects, such as peripheral neuropathy and the refusal of patients. These patients were also included in this study.

Toxicities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version in accordance with the medical charts. Staging was evaluated according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system. All surgical procedures were performed by gynecologic oncology surgeons at this institution. Optimal and suboptimal surgeries were defined as residual tumors $<$ 1 cm and residual nodules $\geq$ 1 cm in maximum diameter, respectively. The medical charts and database of the cases were retrospectively reviewed. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Serum levels of tumor markers including cancer antigen 125 (CA125) were not used for the assessment of response to chemotherapy.

JMP Pro 14 was used for statistical analysis. $\chi 2$ test, Fisher's exact test, and Mann–Whitney U test were used to evaluate the clinical significance of the clinicopathological factors. PFS was defined as the duration from the primary date of NAC to the date of death or disease recurrence or progression. OS was defined as the duration from the date of primary NAC to the date of death. PFS and OS curves were generated using the Kaplan–Meier method. The survival distributions were compared by log-rank tests. A Cox proportional hazards model was used for the multivariate analysis of PFS and OS. Statistical significance was defined as a p-value < 0.05.

This retrospective study was approved by the Institutional Board of National Defense Medical College, Toko-

Table 2. — *Adverse events during neoadjuvant chemotherapy in all cases of advanced ovarian cancer.*

	Cases with six scheduled cycles of neoadjuvant chemotherapy	Cases with four scheduled cycles of neoadjuvant chemotherapy	
	n = 36	n = 35	*p*-value
Grade 2-4 toxicity at NAC, number (%)	9 (25.0)	9 (25.7)	0.99
Thrombocytopenia	4 (11.1)	1 (2.9)	0.36
Anemia	0 (0.0)	1 (2.9)	0.49
Leukopenia	1 (2.8)	3 (8.6)	0.36
Drug allergy	3 (8.3)	0 (0.0)	0.24
Neuropathy	1 (2.8)	3 (8.6)	0.36
Hepatobiliary disorders	0 (0.0)	1 (2.9)	0.49
Not evaluable/missing data	2 (5.6)	3 (8.6)	0.67

NAC = neoadjuvant chemotherapy

Table 3. — *Multivariate analysis of progression-free and overall survival in all cases receiving neoadjuvant chemotherapy.*

		Progression-free survival		Overall survival	
3-6 Clinicopathological factors	This section was collected	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age at diagnosis	$\geq$ 60 years *vs.* < 60 years	1.07 (0.63-1.87)	0.8	0.85 (0.42-1.75)	0.66
NAC cycles	Six scheduled cycles *vs.* four scheduled cycles	0.56 (0.32-0.96)	0.04	0.39 (0.18-0.82)	0.01
FIGO stage	III *vs.* IV	1.14 (0.66-2.01)	0.65	1.31 (0.63-2.93)	0.48
Residual tumor diameters at IDS	Optimal *vs.* suboptimal	0.65 (0.66-2.01)	0.18	1.06 (0.48-2.60)	0.9
Histology	High grade serous carcinoma *vs.* non-high-grade serous carcinoma	0.66 (0.33-1.52)	0.3	0.89 (0.34-3.06)	0.83

NAC = neoadjuvant chemotherapy, IDS = interval debulking surgery

rozawa, Japan. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent was not required as it is a retrospective analysis.

Results

This study enrolled a total of 71 cases. The median age at diagnosis was 61 (range, 31-78) years and the median follow-up time was 56 (range, 6-189) months. Groups A and B included 36 (50.7%) and 35 (49.3%) cases, respectively. The clinicopathological factors of both groups are shown in Table 1. Three cases in group A and five cases in group B could not undergo the scheduled NAC cycles due to adverse events. Clinicopathological factors such as age, CA125 level at diagnosis, FIGO Stage, histological subtype, response to NAC, and adjuvant chemotherapy regimen after IDS did not differ significantly between groups. The adverse events at NAC in groups A and B are shown in Table 2. There were no statistically significant differences between groups. Group A received more optimal surgery at IDS compared to that in group B ($p = 0.04$). Group A had a longer operative time ($p = 0.02$), more blood loss during IDS ($p = 0.04$), and received more allogenic blood transfusions during IDS ($p < 0.01$) compared to those in Group B.

The PFS and OS of Group A were significantly better than those in group B ($p = 0.01$ and $p < 0.01$, respectively; Figures 1A and 1B). In multivariate analysis of PFS and OS, the number of NAC cycles was an independent prognostic factor for PFS (HR, 0.56; $p = 0.04$) and OS (HR, 0.39; $p = 0.01$; Table 3).

Discussion

In the present study, cases administered six scheduled cycles of NAC more frequently underwent optimal IDS. Moreover, six scheduled cycles of NAC were a better prognostic factor in cases with advanced ovarian cancer.

Maximum debulking resection plays the most important role in the management of advanced ovarian cancer [7]. Two randomized studies reported rates of optimal surgery in cases that received PDS ranging from 41.0 % to 41.6%.

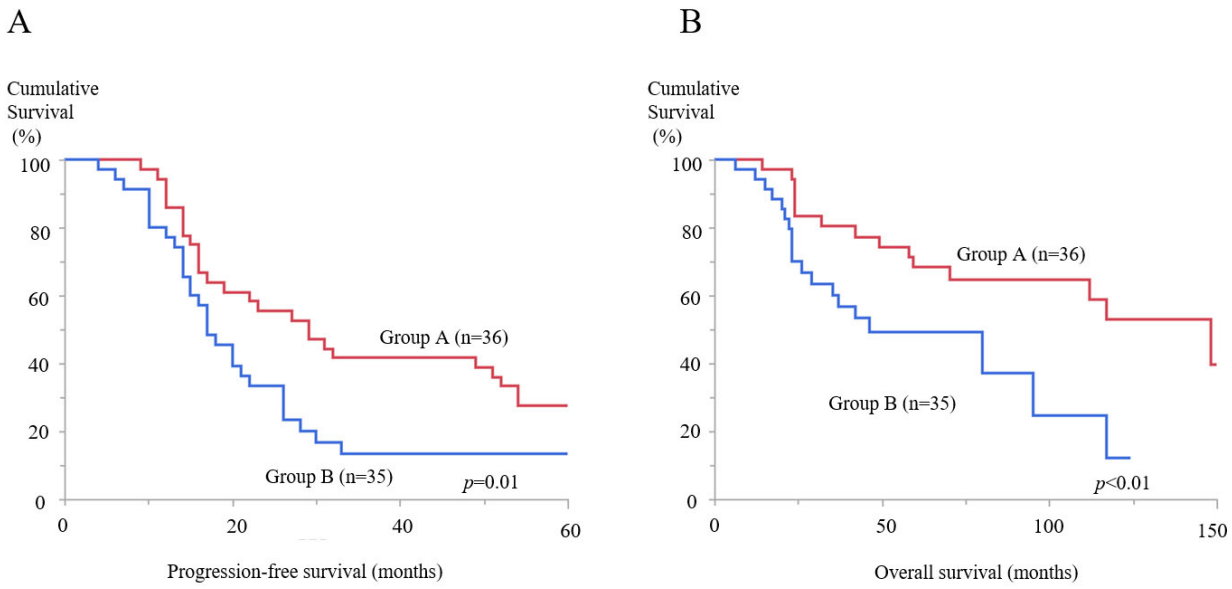

Figure 1. — Progression-free survival (PFS) curves and overall survival (OS) curves of all cases that received neoadjuvant chemotherapy (NAC). A) PFS curves of cases administered six (group A) or four (group B) scheduled cycles of NAC. There was a significant difference in PFS ($p = 0.01$) between the two groups. Red line, group A; blue line, group B. B) OS curves of cases administered six (group A) or four (group B) scheduled cycles of NAC. There was a significant difference in OS ($p < 0.01$) between two groups. Red line, group A; blue line, group B.

The rate for cases with NAC and IDS ranged from 71.0% to 80.6% [8, 9]. A current meta-analysis also reported that NAC was associated with an increase in achieving an optimal surgery [12]. In the present study, more cases with six scheduled cycles of NAC achieved optimal surgery. Thus, NAC might increase the rate of optimal surgery.

The appropriate number of NAC cycles remains controversial. In a meta-analysis, the number of cycles did not influence the prognosis [12]. After then, one report demonstrated that patients with advanced ovarian cancer undergoing a complete IDS after > 5 cycles of NAC had a poor prognosis, while another showed that patients administered six cycles of NAC had a good prognosis [13]. However, in these reports, the decision criteria for the number of cycles of NAC were unclear. In the present study, the selective criteria were periods. Thus, although this study was retrospective and included a limited number of cases, selection bias was minimized. Therefore, the present finding that six scheduled cycles of NAC could improve the prognosis of patients with advanced ovarian carcinoma is important. Randomized trials to validate this result are needed.

There were also no statistically significant differences in the development of side effects associated with NAC in this study. This result supports those of a previous report [14]. Thus, six scheduled cycles of NAC were tolerable. However, the IDS operative time was longer compared to that in a previous report on cases that also received six scheduled cycles of NAC [9], and blood loss during IDS might also be higher. Therefore, patients administered six scheduled cycles of NAC followed by IDS may require preparation such as allogenic blood transfusion.

Recently, vascular endothelial growth factor (VEGF) has been shown to be a key mediator of angiogenesis that is frequency expressed in ovarian cancer [15]. The Gynecologic Oncology Group (GOG) 218 trial reported that the maintenance use of bevacizumab, a humanized anti-VEGF antibody, after carboplatin and paclitaxel prolonged PFS in cases with advanced epithelial ovarian cancer [16]. Taxane also has an antiangiogenic activity [17]. A phase III randomized trial reported prolonged PFS with maintenance paclitaxel in cases with advanced ovarian cancer [18]. In this study, the administration of additional taxane in cases with six scheduled cycles of NAC may have positively influenced the prognosis.

The limitations of this study included its retrospective design and the small number of cases included in the single-institution analysis. In addition, this study excluded cases with progressive disease during NAC that could not receive IDS; thus, future studies should consider including these cases. Further prospective studies are needed to confirm the impact of the number of NAC cycles in advanced ovarian cancer.

In conclusion, six scheduled cycles of taxane-platinum-based NAC was an independent prognostic factor for better OS in advanced ovarian cancer. Six scheduled cycles of NAC could achieve higher cytoreductive surgery in IDS

and lead to a better prognosis in cases of advanced ovarian cancer.

Authors' contributions

HI, MM, MT, and KF designed the research study. HI, TA, HS, HM, and HI collected resouce. HI and MM performed the research. HI analyzed the data. HI, MM and KF wrote the manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Board of the National Defense Medical College, Tokorozawa, Japan (ethical approval number: #2514). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of interest

All authors declare no conflict of interest.

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