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Impact of the time interval from completion of neoadjuvant chemotherapy to initiation of postoperative adjuvant chemotherapy on the survival of patients with advanced ovarian cancer

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HIGHLIGHTS

- We examined the relationship between the NAC-POAC interval and survival.
- Patients with intervals >42 days showed poorer progression-free and overall survival.
- Longer time intervals were thus associated with higher risks of recurrence and death.

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ABSTRACT

Objective. To investigate the relationship of the time interval from the completion of neoadjuvant chemotherapy (NAC) to the initiation of postoperative adjuvant chemotherapy (POAC) with the survival outcomes in patients with ovarian cancer.

Methods. We retrospectively investigated 220 patients with pathologically confirmed epithelial ovarian cancer who received NAC at Yonsei Cancer Hospital between 2006 and 2016. The time interval was defined as the period from the completion of NAC, spanning interval debulking surgery (IDS), to the initiation of POAC.

Results. The median time interval was 42 (range 16–178) days; 103 patients (53.1%) received POAC within 42 days after NAC while 91 patients (46.9%) received it after 42 days. There were no significant differences in patient characteristics between these 2 groups. Kaplan-Meier analysis showed that patients with longer time intervals (>42 days) had poorer progression-free survival and overall survival ($P = 0.039$ and 0.005, respectively). In the multivariate analysis, patients with longer time intervals had significantly poorer progression-free (hazard ratio, 1.41; 95% confidence interval, 0.98–2.03; not significant) and overall survivals (hazard ratio, 2.03; 95% confidence interval, 1.16–3.54). When the patients were categorized according to time interval quartiles (≤37, 38–42, 43–50, and >50 days), longer time intervals were associated with higher risks of recurrence and death (P for trend: 0.006 and <0.001, respectively).

Conclusion. The time interval from the completion of NAC to the initiation of POAC appears to influence survival. Efforts to reduce the time interval might improve the outcomes in ovarian cancer patients undergoing NAC.

1. Introduction

Ovarian cancer is a highly lethal gynecologic cancer, and its incidence and mortality rates in Korea are increasing [1,2]. Primary cytoreductive surgery (PDS) followed by platinum-based chemotherapy is the current standard of care for advanced ovarian cancer [3]. Recently, several phase 3 clinical trials have demonstrated that survival and the postoperative morbidity and mortality rates after receiving neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) are not inferior to those following PDS in women with stage III–IV ovarian cancer [4–7]. Therefore, NAC followed by IDS is an alternative approach for treating advanced-stage ovarian cancer [8]. Moreover, the tumor response to NAC predicts survival and can be considered a surrogate prognostic marker [9].

IDS and postoperative adjuvant chemotherapy (POAC) are mandatory following NAC. However, the appropriate time interval between the completion of NAC and the initiation of POAC has not been thoroughly addressed in large randomised clinical trials; in fact, most previous trials did not specify a recommended interval. Surgery after NAC is

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usually performed when the neutropenic window is overcome; however, a delay in surgery frequently occurs in clinical practice. For various solid tumors, some studies have suggested that surgery should be performed within 4–6 weeks after NAC [10,11], while another study showed that the time to surgery after NAC did not impact the survival of patients with breast cancer [12]. Regarding adjuvant chemotherapy after surgery, several retrospective studies tried to identify the ideal interval between surgery and NAC in patients with advanced-stage ovarian cancer. As several studies showed that delaying chemotherapy after PDS worsened prognosis [13–17], there is a general consensus that unnecessary delays should be avoided. However, the optimal time interval between IDS completion and POAC initiation has not been determined.

With this in mind, in the present study, we evaluated the relationship of the time interval between the end of NAC and the initiation of POAC with the survival outcomes among patients with advanced-stage ovarian cancer. We hypothesized that delayed IDS after NAC may jeopardize the clinical benefit of NAC, and that a delay in the initiation of POAC after IDS may impair the clinical benefit of the latter in ovarian cancer patients.

2. Materials and methods

2.1. Study population

We performed a retrospective review of the medical records of 220 patients with pathologically confirmed epithelial ovarian cancer who received at least 1 cycle of NAC at Yonsei Cancer Hospital between 2006 and 2016. All patients were histologically or cytologically confirmed to have International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer before starting chemotherapy. The diagnosis was performed either via laparoscopic or image-biopsy samples, or by using fine-needle aspiration of a tumor site or ascites/effusion. All surgical procedures were performed by 1 of 5 gynecologic oncology surgeons at our institute. The histological diagnoses were based on World Health Organization criteria, and all microscopic slides were reviewed by 2 experienced gynecologic pathologists. NAC was performed if at least 1 of the following 3 criteria was met: 1) pulmonary and/or hepatic parenchymal metastases were observed on imaging studies before surgery, 2) the patient was medically inoperable, and/or 3) optimal cytoreduction was not achievable due to a high tumor burden (Fagotti score ≧8) observed by diagnostic laparoscopy [18,19]. According to our institutional policy, IDS was performed after 3 cycles of NAC. The timing of IDS was delayed when optimal cytoreduction was not achievable, determined at the clinician's discretion. We excluded women who were still receiving POAC at the time of data collection (n = 9); those who did not undergo IDS after NAC (n = 6); those who underwent NAC, IDS, and POAC elsewhere and for whom medical records were not available (n = 2); and those who were lost to follow-up (n = 9). Ultimately, the final study population comprised 194 women (Fig. 1). All patients received taxane and platinum combination chemotherapy. Conventional surgical procedures included the sampling of free fluid or peritoneal washings for cytology; a thorough inspection of the abdomen and pelvis, including the upper abdominal viscera, diaphragm, and retroperitoneal spaces; and hysterectomy, bilateral oophorectomy and omentectomy, pelvic/para-aortic lymph node dissection, and appendectomy. Radical surgery included bowel resection; diaphragm or other peritoneal surface stripping; splenectomy; partial hepatectomy; partial gastrectomy; or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy [20–22]. Perioperative complications were graded according to the Memorial Sloan-Kettering Cancer Center surgical secondary events grading system [23,24]; a score ≥3 points indicated a major complication. Operative mortality was defined as death occurring within 30 days after surgery (grade 5).

The following data were extracted from the patients' medical records: age, body mass index, American Society of Anesthesiologists (ASA) score, pretreatment serum cancer antigen-125 (CA-125) levels, FIGO stage, histology, performance of radical surgery, residual disease after IDS, chemotherapy regimens, total chemotherapy cycles, date of surgery, date of NAC and POAC initiation, date of progression or recurrence, and date of last follow-up.

The time interval was defined as the period between the completion of NAC and the initiation of POAC. The time to surgery was defined as the time (in days) from the end of NAC to IDS, while the time to chemotherapy was defined as the time from IDS to the initiation of POAC (Fig. 2). The present study was reviewed and approved by our Institutional Review Board (Registration number: 4-2015-1158).

2.2. Statistical analysis

SPSS statistical software (version 21.0; IBM Corp., Armonk, NY) was used for the statistical analyses. Descriptive statistics were used for demographic data and are summarized as the median (range) or frequency (percentage). Differences in the patient characteristics were compared in relation to the time intervals using the chi-square or Mann-Whitney *U* test. The endpoints included the progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval between the date of diagnosis and the date of first recurrence. OS was defined as the interval between the date of diagnosis and the date of death. We routinely performed CA-125 and imaging studies for surveillance. Our institutional follow-up strategy was to follow-up with the patients every 3 months for the first 2 years after treatment and every 6 months thereafter. Recurrence was defined as the date of appearance of radiologically-detected disease during a follow-up examination. A rise of CA-125 without clinical signs of relapse was not counted as progression but generally triggered further radiological examinations. PFS and OS were analyzed with the Kaplan-Meier method and log-rank test. Factors identified as significant in the univariate analyses were

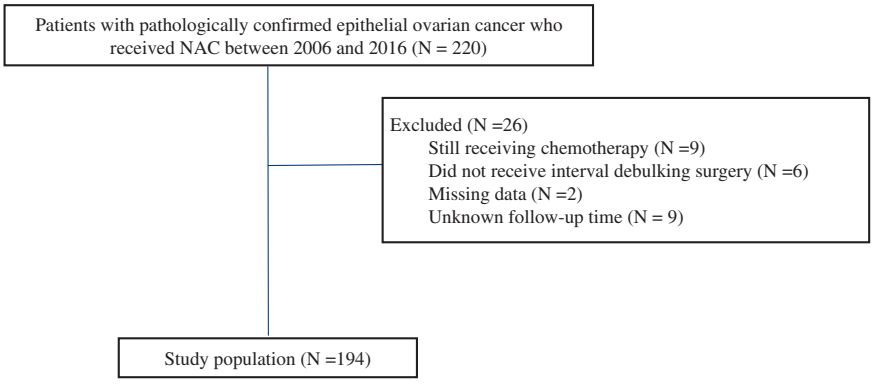

Fig. 1. Flow diagram of the study population. NAC, neoadjuvant chemotherapy.

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