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Risk factors for septic adverse events and their impact on survival in advanced ovarian cancer patients treated with neoadjuvant chemotherapy and interval debulking surgery

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HIGHLIGHTS

- Patients treated with NACT followed by IDS may be vulnerable to hematologic complications.
- Risk factors for septic complications were analyzed in patients treated with NACT-IDS.
- Grade 3 anemia during NACT was a significant risk factor for septic adverse events during adjuvant chemotherapy.
- Patients experienced septic complications had significant shorter overall survival.

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ABSTRACT

Objectives. The aim of this study was to analyze risk factors for septic complications during adjuvant chemotherapy and their impact on survival in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS).

Methods. We retrospectively reviewed the medical records of 69 patients with advanced epithelial ovarian cancer from 2004 to 2017. All patients underwent three cycles of NACT followed by IDS and adjuvant chemotherapy. We identified grade 3 or 4 hematologic complications and severe adverse events accompanied by neutropenia, including sepsis or septic shock, that occurred during treatment. Clinicopathologic data including demographic factors, preoperative medical conditions, surgical procedures, and survival times were evaluated.

Results. Of 69 patients, 27 (39.1%), 6 (8.8%), and 2 (2.9%) patients experienced grade 3 or 4 neutropenia, anemia, and thrombocytopenia, respectively, during NACT. Thirteen patients (18.8%) had a neutropenic fever with sepsis and 2 patients (2.9%) died of septic shock during adjuvant chemotherapy. Concurrent medical disease, splenectomy during IDS, and anemia or thrombocytopenia during NACT were significant risk factors for septic adverse events. In multivariate analysis, anemia (hemoglobin < 8 g/dL, $p = 0.004$) during NACT was the only significant factor associated with septic adverse events during adjuvant chemotherapy. Although there was no significant difference in progression-free survival, overall survival was significantly shorter in patients with septic adverse events (median, 82.3 vs. 17.3 months, $p = 0.007$).

Conclusions. Grade 3 anemia during NACT may be an early indicator for septic adverse events during adjuvant chemotherapy. Considering the adverse impact on survival, scheme and dose of adjuvant chemotherapy should be tailored, and careful follow-up evaluation should be ensured in this patient group.

1. Introduction

Ovarian cancer is a lethal gynecologic malignancy, and reported as the fifth leading cause of death across all ages in developed countries [1]. Optimal cytoreductive surgery leading to no gross residual disease followed by platinum-based adjuvant chemotherapy is the most effective therapeutic strategy for the treatment of advanced ovarian cancer

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[2,3]. Unfortunately, the optimal surgical procedure and compliance with the chemotherapy schedule is not always possible, especially in patients with extensive disease or poor performance status. Although, as an alternative, the guidelines from the Society of Gynecologic Oncology (SGO) recommend neoadjuvant chemotherapy (NACT) for these patients [4] and substantial studies suggest that NACT is non-inferior to primary debulking surgery, the advantages of NACT are still controversial in terms of long-term survival and perioperative adverse events [5–8].

In previous studies, grade 3 or 4 neutropenic events were reported in 37% to 88% of ovarian cancer patients treated with a paclitaxel-carboplatin regimen, of whom 4% to 8% experienced febrile neutropenia [9–11]. Septic adverse events are reported as a potentially fatal complication with a high mortality rate (2–21%) [12]. In patients treated with NACT followed by interval debulking surgery (IDS), the risk of septic adverse events may be even higher, as the risk of myelosuppression is increased in patients receiving a full dose of chemotherapeutic agents during NACT, aggressive surgical procedures, and multiple (three to six) cycles of adjuvant chemotherapy. Consequently, delivering chemotherapy at the full dose and on schedule may be difficult in a subset of patients because of complications from the accumulation of chemocycles. Therefore, identifying the risk factors for septic adverse events can be clinically worthwhile, especially for patients at high risk.

A few studies have suggested risk factors for septic adverse events during chemotherapy and examined the prognosis of patients who experience these events [13–16]. There are also several guidelines that recommend risk assessment for chemotherapy-induced neutropenia [17–19]. However, the criteria for patients at high risk of chemotherapy-induced neutropenia vary. Moreover, these studies are primarily based on non-gynecologic patients who are not treated with cytoreductive surgery, focusing on initial patient baseline characteristics and short-term clinical outcomes. Considering most adverse events stem from the cumulative effect of cytotoxic chemotherapeutic agents after IDS, we hypothesized that there may be clues in the response to chemotherapeutic agents during NACT.

The aim of the present study was to analyze risk factors for septic complications during adjuvant chemotherapy and the impact of septic complications on survival in patients with advanced epithelial ovarian cancer treated with NACT followed by IDS.

2. Materials and methods

A total of 76 ovarian cancer patients treated with NACT followed by IDS from September 2004 to May 2017 at Ajou University Hospital were identified. The institutional review board approved this retrospective study. NACT was performed mainly for the following conditions (Ajou University Medical Center criteria): i) Age > 70, ii) poor performance status (ECOG 3-4) or medical co-morbidities, iii) surgically proactive criteria for 'unresectable' disease on computed tomography scan, laparoscopy or laparotomy: stage IV disease-multiple parenchymal liver metastases that would require more than a major hepatic resection to achieve optimal residual disease or multiple (≥2) extra-abdominal metastases, extensive diaphragm lesions, extensive lesions at the epigastrium, extensive small bowl or small bowel mesenteric lesions, extensive peritoneal thickening (surface "caking" spread pattern), extensive retroperitoneal or supradiaphragmatic nodal disease, requirement for resection leading to limited or no gastrointestinal functionality. Among the 76 patients, patients who received only NACT without receiving proper debulking procedures (only biopsy) owing to comorbidity or old age were excluded (n = 5), as were patients who did not receive adjuvant chemotherapy after IDS (n = 2). All the enrolled patients (n = 69) had histologically confirmed epithelial ovarian cancer before NACT by transvaginal sonography-guided core biopsy or diagnostic laparoscopy [20]. The patients were treated with three cycles of systemic chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (area under the curve 5) as NACT. After the completion of NACT, patients underwent IDS with the attempt of maximal cytoreduction. For those patients who underwent splenectomy because of tumor invasion, vaccinations were given on the 7th postoperative day (Polyvalent pneumococcal vaccine, Haemophilus influenzae b vaccine, Meningococcal polysaccharide vaccine). Adjuvant chemotherapy was administered when the patient's wound healing was complete without any sign of infection, and generally corresponded with completion of diet build-up. Hematologic complications during chemotherapy, including neutropenia, anemia, and thrombocytopenia, were evaluated with the CTCAE Version 4.0 [21]. Patients' blood cell counts were evaluated for early signs of hematologic complications after each cycle of chemotherapy. Neutropenic fever was defined as a febrile episode (single temperature > 38.3 °C or a sustained temperature ≥ 38.0 °C for more 1 h) during chemotherapy-induced neutropenia (absolute neutrophil count [ANC] < 1000/μL). Septic adverse events were defined as events of neutropenic fever with sepsis or septic shock. Sepsis was defined as any pathogenic organism in the blood culture of a neutropenic patient. Septic shock was defined as the need for vasopressor therapy to elevate mean arterial pressure ≥ 65 mm Hg, despite adequate fluid resuscitation in patients with sepsis [22]. If a patient was confirmed with grade 4 neutropenia or neutropenic fever, GCSF (filgrastim) was administered with prophylactic antimicrobial agents until the absolute neutrophil count was recovered. If a patient experienced febrile neutropenia or grade 4 neutropenia in a prior cycle, prophylactic GCSF was initiated from the ANC < 1500/μL. Red blood cell (RBC) transfusion was indicated if a hemoglobin value fell below 8 g/dL or a patient had anemic symptoms with any grade of anemia.

We retrieved patient characteristics, including medical disease, International Federation of Gynecology and Obstetrics (FIGO) stage, number of chemotherapy cycles, possible procedures related to septic conditions, and interval from IDS to start of adjuvant chemotherapy, from the medical records. To evaluate the risk factors for septic adverse events, clinicopathologic factors, including patient age, FIGO stage, medical disease status, procedures, time from IDS to initiation of adjuvant chemotherapy, number of chemotherapy cycles, and hematologic events during NACT, were evaluated. Furthermore, to assess the impact of septic adverse events during chemotherapy, survival analysis was performed in patients with and without septic adverse events.

Descriptive statistics were used to characterize the patient population. Risk factors for septic adverse events were analyzed with univariate and multivariate logistic regression analyses. Survival analysis was performed using the Kaplan-Meier method. Statistical analysis was performed with IBM SPSS Statistics for Windows (version 20.0, IBM Corp., Armonk, NY, USA). A p value of <0.05 was defined as statistically significant.

3. Results

A total of 69 patients fulfilled the study criteria during the period of this study. The median patient age was 57 years, and 25% (17/69) of the patients had a concurrent medical disease, most commonly cardiovascular disease. Twenty-one patients (30%) had FIGO stage IV disease. After IDS, 52 patients (75.4%) had no gross residual disease, and 17 patients (24.6%) had gross residual disease (<1 cm). The median interval between IDS and adjuvant chemotherapy was 19 days (Table 1).

During NACT, 27 (39.1%), 6 (8.7%), and 2 (2.9%) patients experienced grade 3 or 4 neutropenia, anemia, and thrombocytopenia, respectively. Nine patients experienced two or more discrete neutropenic events during NACT. The number of hematologic complications increased during adjuvant chemotherapy. During adjuvant chemotherapy, neutropenia, anemia, and thrombocytopenia were confirmed in 44 (63.8%), 27 (39.1%), and 17 (24.6%) patients, respectively. Among them, 13 patients experienced three or more discrete neutropenic events (Table 2). During adjuvant chemotherapy, 22 patients experienced neutropenic fever; sepsis was confirmed in 11 (15.9%) patients and septic shock in 2 (2.9%) patients, which was lethal in both patients (Table 3).

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