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The prognostic significance of preoperative leukocytosis in epithelial ovarian carcinoma: A retrospective cohort study

Kyeong A So [a], Jin Hwa Hong [a,*], Hye Mi Jin [a], Jae Won Kim [b], Jae Yun Song [c], Jae Kwan Lee [a], Nak Woo Lee [b]

[a] Department of Obstetrics and Gynecology, Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea
[b] Department of Obstetrics and Gynecology, Ansan Hospital, College of Medicine, Korea University, Seoul, Republic of Korea
[c] Department of Obstetrics and Gynecology, Anam Hospital, College of Medicine, Korea University, Seoul, Republic of Korea

HIGHLIGHTS

- The mortality rate in patients with preoperative leukocytosis is higher than those without leukocytosis.
- Preoperative leukocytosis is an independent prognostic factor for recurrence-free and overall survival.
- Preoperative leukocytosis could be a prognostic biomarker in patients with epithelial ovarian carcinoma.

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ABSTRACT

Objective. Preoperative leukocytosis is known to be a negative prognostic factor for several gynecologic malignancies, but its relationship with epithelial ovarian carcinoma (EOC) is unknown. We sought to evaluate the prognostic implications of preoperative leukocytosis for women with EOC.

Methods. We retrospectively reviewed the medical records of patients who underwent primary debulking surgery and adjuvant platinum-based chemotherapy for EOC between January 1993 and October 2011. Associations between leukocytosis and recurrence-free survival (RFS) and overall survival (OS) were determined by univariate analyses. Multivariate Cox proportional hazards regression was used to identify independent prognostic factors for RFS and OS.

Results. Of 155 women, 23 (14.8%) had leukocytosis and 132 (85.2%) did not have leukocytosis. RFS and OS were significantly shorter for women with leukocytosis than for women without leukocytosis ($P = 0.009$ and $P < 0.0001$, respectively). The mortality rate was also higher among women with leukocytosis ($P < 0.0001$). Multivariate analysis revealed that preoperative leukocytosis (hazard ratio [HR]: 2.15; 95% confidence interval [CI]: 1.55–4.41; $P = 0.009$), advanced stage (HR: 3.12; 95% CI: 1.44–6.75; $P = 0.004$), and optimal cytoreduction (HR: 0.38; 95% CI: 0.14-0.70; $P = 0.031$) were independent prognostic factors for RFS. Additionally, preoperative leukocytosis was independently associated with decreased OS (HR: 7.66; 95% CI: 2.78–21.16; $P < 0.0001$).

Conclusions. Among women with EOC, preoperative leukocytosis might be an independent prognostic factor for RFS and OS. A larger-scaled, prospective study is needed to verify these results.

Introduction

Leukocytosis, a paraneoplastic syndrome, occurs in approximately 30% of women with solid tumors [1]. Anemia, thrombocytosis, leukocytosis, and other hematologic paraneoplastic manifestations are frequently observed in various malignancies, especially in advanced disease [2]. The malignancies that are most commonly associated with hematologic paraneoplastic syndromes include gynecologic tumors, lung cancer, breast cancer, and hematologic malignancies [3]. Recent studies investigating the role of leukocytes and other hematologic markers in disease progression have suggested that preoperative leukocytosis is a negative prognostic factor in some gynecologic malignancies [2,4].

Epithelial ovarian cancer (EOC) remains one of the major causes of death from gynecologic malignancy worldwide [5]. The majority of women with EOC are diagnosed at an advanced stage because EOC has an asymptomatic nature and effective screening programs do not exist. Even when women with advanced EOC receive primary cytoreductive surgery followed by adjuvant chemotherapy, their overall prognoses remain poor, with a 5-year survival rate of only 40% [6]. The known risk factors for adverse outcomes are advanced age,

* Corresponding author at: Department of Obstetrics and Gynecology, Guro Hospital, Korea University Medical Center, College of Medicine, Korea University, Gurodong-ro 148, Guro-gu, Seoul 152–703, Republic of Korea. Fax: +82 2 838 1560.
E-mail address: jhhong93@korea.ac.kr (J.H. Hong).

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advanced stage, high grade, clear cell histology, large volume of ascites, and suboptimal debulking at primary diagnosis [7]. Recently, molecular biomarkers have been increasingly investigated for ovarian cancer diagnosis and prognosis. Single-nucleotide polymorphisms in several cancer-related genes have been investigated in association with survival and response to chemotherapy in ovarian cancer patients. The rs4320932, an intronic single-nucleotide polymorphism of insulin-like growth factor-II, showed elevated risks of relapse and cancer-related death [8], whereas multiple single-nucleotide polymorphisms in fibroblast growth factors were associated with reduced risk of ovarian cancer and improved survival [9]. Cancer stem cells have also been extensively studied using cell surface markers, side population assay, or ALDEFLOUR assay to verify their association with clinical outcome [10]. However, there is a contradictory report revealing that a cancer stem cell marker does not work in some types of cells [11,12]. Therefore, it is necessary to validate the cell population isolated by cancer stem cell markers by other types of analysis. The literatures investigating cancer stem cells in relation to ovarian cancer prognosis also yielded discrepant results [10,13]. Multiple recent studies indicated that microRNA expression is significantly changed in ovarian cancer [14–16]. However, these profiling studies were mostly performed with microarrays, which tend to give relatively high false positive results. In addition, results vary significantly among studies, which might be attributed to differences of either microarray platforms or experimental design [17–19]. In contrast to the molecular biomarkers mentioned above, checking leukocytosis using peripheral blood sample is easy and has little technical variations among laboratories. Most importantly, literatures investigating the association between leukocytosis and cancer prognosis have shown consistent results among different kinds of cancers [20–23]. With respect to hematologic parameters, women with thrombocytosis showed significantly higher levels of preoperative cancer antigen (CA)-125, larger ascite volume, and poorer survival than those without thrombocytosis [24]. Anemia is also associated with poor recurrence-free survival (RFS) and overall survival (OS) in women with EOC [25]. However, the prognostic significance of leukocytosis in EOC has not yet been determined. The purpose of this study was to evaluate the prognostic impact of preoperative leukocytosis in women with EOC.

Materials and methods

Our study population comprised 155 women who underwent primary debulking surgery and adjuvant platinum-based chemotherapy for EOC at Guro Hospital, College of Medicine, Korea University between January 1993 and October 2011. Surgical procedures consisted of total hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or paraaortic lymphadenectomy, infracolic omentectomy, washing cytology, appendectomy, and multiple peritoneal biopsies. Chemotherapy was initiated no more than two weeks after surgery. The chemotherapy regimen comprised 6–8 cycles of paclitaxel (175 mg/m^2) and carboplatin (area under the curve = 5) every three weeks. After obtaining institutional review board approval, we retrospectively retrieved clinical and pathologic data from the medical records of women with EOC who were treated at Guro Hospital. We excluded all women whose medical records included any of the following: acute or chronic infection, neoadjuvant chemotherapy, coexisting malignancies, preoperative corticosteroid use, or administration of recombinant granulocyte colony stimulating factor.

Preoperative leukocytosis was defined as a white blood cell (WBC) >10,000/μL within two weeks prior to the operation [26]. Women were divided into two groups based on the presence or absence of preoperative leukocytosis. The two groups were compared with respect to age, parity, body mass index (BMI), International Federation of Gynecology and Obstetrics (FIGO) stage, histologic cell type, grade, residual tumor size, and serum CA-125 level. Survival data were also collected and analyzed. RFS was defined as the interval between the date of primary surgery and the date of either recurrence or, for women who had no disease progression, the date of latest contact. OS was defined as the interval between the date of primary surgery and the date of death from any cause or the date of latest contact. Separately, given that the duration of enrollment (between January 1993 and October 2011) is quite long in this study and treatment strategy has been changed during this time period, survival data were analyzed based on the year of diagnosis. For this, women were divided into 2 groups (those who were diagnosed before 2000 versus those after 2000) and survival data were compared between 2 groups. To evaluate disease status, gynecological oncologists conducted examinations using computed tomography, positron emission tomography - computed tomography, and serum CA-125 level assessment.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as median (range). We used Mann–Whitney tests for analyses of continuous variables and chi-squared tests or Fisher's exact tests for analyses of categorical variables. Univariate analyses were performed to determine the association between leukocytosis and RFS or OS. For each group, survival curves were estimated according to the Kaplan–Meier method. Survival estimates were compared using the log-rank test. Cox proportional hazards regression models were used to identify independent prognostic factors for RFS and OS. Associations are shown as hazard ratios (HR) with 95% confidence intervals (CI) and values of $P < 0.05$ were considered statistically significant. All analyses were performed using the SAS statistical package (SAS Institute, Cary, NC).

Results

A total of 155 women with EOC were included in this study. Their clinicopathologic characteristics are summarized in Table 1. Their mean age was 47.9 years, mean parity was 1.9, and mean BMI was 23.3 kg/m^2. Of the 155 women, 76 (49.0%) had advanced stage cancer (FIGO stages III–IV). Pathologically, 67 (43.2%) women had high-grade disease. Serous adenocarcinoma was the most common form of EOC.

Preoperative leukocytosis was observed in 23 (14.8%) women, whereas 132 (85.2%) women did not have leukocytosis. The preoperative WBC count of women with leukocytosis ranged from 10,100 to 19,500/μL, whereas that of women without leukocytosis ranged from 2900 to 10,000/μL. Age, parity, BMI, histologic type, residual tumor size, and CA-125 levels were similar between the leukocytosis and non-leukocytosis groups. As shown in Table 1, women with leukocytosis presented with more advanced stages of cancer (III and IV) than women without leukocytosis (91.3% vs. 41.7%; $P = 0.001$). Women with leukocytosis were also more likely to present with pathologic grade 3 cancer (86.9% vs. 35.6%, $P = 0.002$). Together, these results suggest that leukocytosis could be an indicator for more aggressive EOC. In addition, women who were diagnosed before 2000 had leukocytosis significantly more than those after 2000 (78.3% vs. 21.7%, $P = 0.005$).

Univariate analyses were conducted to investigate the prognostic significance of preoperative WBC count in women with EOC. As presented in Table 2, older age, lower parity, advanced stage, serous and clear cell histology, WBC count >10,000/μL, year of diagnosis (2001–2011), and suboptimal cytoreduction were associated with poor prognosis, as measured by RFS. During the follow-up period, recurrence was observed more frequently in women with leukocytosis than in women without leukocytosis (91.3% vs. 46.2%; $P < 0.0001$). The mean time to recurrence was 27.2 months (range: 3–124 months) in women with leukocytosis, compared with 40.4 months (range: 5–99 months) in women without leukocytosis. Women with leukocytosis had a significantly shorter RFS than those without leukocytosis (log-rank test: $P < 0.001$; Fig. 1). Table 2 presents the results of multivariate analysis,