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ORIGINAL ARTICLE

Lymphopenia after induction chemotherapy correlates with incomplete surgical resection in patients with advanced ovarian cancer

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Abstract

Background Lymphopenia is associated with poor outcomes in patients with various cancers, but little is known about the prognostic impact of lymphopenia in patients with epithelial ovarian cancer (EOC) after induction chemotherapy (IC). This study investigated the prognostic significance of pre- and post-IC lymphopenia in patients with advanced EOC.

Methods We reviewed medical records of 68 patients with stage III/IV ovarian, fallopian tube, or peritoneal cancer treated with IC at our institution between 2009 and 2017. We assessed the associations of pre- and post-IC inflammatory markers, including lymphocyte counts, with several oncological outcomes, such as the implementation of interval debulking surgery (IDS), complete resection, progression-free survival (PFS), and overall survival (OS).

Results Lymphocyte counts increased significantly post-IC compared with the pre-IC values ($P=0.009$). Pre-IC lymphopenia was observed in 27 patients (40%), whereas only 16 patients (24%) displayed lymphopenia post-IC ($P=0.020$). Among several inflammatory markers, only post-IC lymphopenia was significantly associated with incomplete resection outcome during IDS ($P=0.012$). Moreover, post-IC lymphopenia was significantly associated with poor PFS (log-rank test, $P=0.009$), whereas pre-IC lymphopenia was associated with neither PFS nor OS.

Conclusions Post-IC lymphopenia may predict incomplete resection during IDS and poor prognosis in patients with advanced EOC.

Keywords Epithelial ovarian cancer · Induction chemotherapy · Lymphopenia · Interval debulking surgery

Introduction

Epithelial ovarian cancer (EOC) is often diagnosed at an advanced stage (stage III/IV) and is the leading cause of death from among gynecological malignant tumors worldwide [1]. The standard treatment for advanced EOC has been cytoreductive surgery followed by systemic adjuvant chemotherapy. However, neoadjuvant chemotherapy (NAC) combined with interval debulking surgery (IDS) has also been established for patients with bulky disease that may require extensive resection. The prognosis of advanced EOC remains poor due to recurrences that result mainly from chemotherapeutic resistance [2, 3]. Meanwhile, the size of residual tumors after IDS is an important prognostic factor for advanced-stage EOC; hence, all attempts should be made to achieve complete cytoreduction [4]. Therefore, predicting individual surgical outcomes is essential for management of advanced-stage EOC.

The neutrophil-to-lymphocyte ratio (NLR) has been associated with prognosis in various cancers [5–8], and studies have shown its association to prognosis in EOC [9–11]. A high NLR is attributable to both neutrophilia and lymphopenia. Neutrophilia reflects systemic inflammation and is associated with tumor growth and invasion in patients with cancer [12]. Lymphocytes play an important role as immune effector cells during immunosurveillance in cancer patients [13]. Tumor infiltrating lymphocytes reflect an immune response against tumor and are associated with more favorable prognosis [14–17]. In contrast, lymphopenia

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(low absolute lymphocyte counts in peripheral blood) has been associated with poor outcomes in EOC [18] as well as in various other cancers [19–28].

In general, hematotoxicity causes a decrease in absolute leukocyte and neutrophil counts during chemotherapy, but the lymphocyte counts are less affected and remain stable [18, 19]. Therefore, we speculated that lymphopenia is more likely to reflect disease activity and treatment response during chemotherapy than neutrophilia. However, little is known about the prognostic impact of lymphopenia in patients with EOC after induction chemotherapy (IC). The purpose of this study was to evaluate whether lymphopenia can predict the clinical outcome in patients with advanced EOC after IC (NAC) and investigate dynamic lymphocyte count changes during IC (NAC) in these patients.

Patients and methods

Patient selection

This study was performed in accordance with the Declaration of Helsinki. Our internal institutional review board approved this study. We retrospectively reviewed data from 85 patients with advanced EOC, fallopian tube cancer, or primary peritoneal cancer treated with IC (NAC) between Jan 2009 and Dec 2017 at the Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital. We defined IC as initial chemotherapy for patients who intended to undergo IDS, excluding palliative chemotherapy for patients who had serious complications and could not tolerate surgery. For patients who underwent IDS, IC is practically synonymous with NAC. However, for patients who relinquished IDS due to chemotherapy resistance, it is not appropriate to refer to the chemotherapy they received as NAC because they did not undergo IDS. Therefore, we used the term IC instead of NAC. All cases were confirmed based on pathological or cytological evidence, and the tumor stages were determined according to the International Federation of Obstetrics and Gynecology (FIGO) staging system. In the cases without IDS, histological types were speculated using cytological evaluation including the cell block method. Cases for which histological classification was difficult due to IDS renunciation or degeneration after IC (NAC) are referred to as unspecified carcinomas. The eligibility criteria for this study included patients with advanced EOC who underwent IC (NAC) followed by IDS or patients with advanced EOC who were initially treated with IC (NAC) but did not undergo IDS because of chemotherapy resistance. We excluded patients with incomplete clinical data and those with serious complications that were not eligible for surgery before treatment.

The clinicopathological findings

We extracted data on patients' clinical characteristics, pathology and cytology results, pre-IC and post-IC laboratory results, and surgical and survival outcomes from the patients' records. The patients' clinical characteristics included age at diagnosis, FIGO stages, Eastern Cooperative Oncology Group performance status (ECOG PS). The laboratory results included complete blood cell counts, such as absolute leukocyte, neutrophil, lymphocyte, and monocyte counts ($\times 10^9$/L) and platelet counts ($\times 10^9$/L); serum cancer antigen (CA)-125 protein (U/mL); and C-reactive protein (CRP) (mg/L). We used median values as the cut-off values of NLR, platelet count, CRP, CA-125, pre- and post-IC ratio of CA-125, pre- and post-IC ratio of NLR, and pre- and post-IC ratio of lymphocyte count. We defined lymphopenia as a peripheral blood lymphocyte count $< 1.0 \times 10^9$/L, and neutrophilia as a peripheral blood neutrophil count $> 7.7 \times 10^9$/L as published [19, 20, 29].

Pre-IC laboratory results were obtained the day before first chemotherapy for all patients, and post-IC laboratory results were obtained the day before IDS in patients who underwent IDS or the day before the fifth chemotherapy administration in patients who relinquished IDS and received continued chemotherapy due to chemotherapy resistance. Moreover, to investigate dynamic changes in lymphocyte count during IC (NAC), we evaluated lymphocyte counts after one, two, three, and four cycles. The laboratory data for each period were obtained the day before the next chemotherapy or IDS treatment.

Treatment

Among patients with stage III/IV disease, primary debulking surgery (PDS) was performed only if complete or optimal resection could be expected when evaluating disease progression and PS or general condition was so good that the patient could tolerate PDS, whereas those with bulky disease or poor PS that made it difficult to achieve complete or optimal resection in PDS underwent IC (NAC) and IDS. We assessed chemotherapy responses according to the Response Evaluation Criteria in Solid Tumors (version 1.1). Tumors with complete response (CR) or partial response (PR) were considered chemotherapy sensitive, whereas those with stable disease (SD) or progressive disease (PD) were considered chemotherapy resistant. Computed tomography (CT) after three or four IC (NAC) cycles was used for image evaluation. If tumor markers were elevated before the third IC (NAC) cycle, an earlier image evaluation using CT was individually considered. IDS was performed for patients in the chemosensitive

group, whereas patients in the chemoresistant group received continued chemotherapy or palliative care without IDS. In principle, patients received four cycles of chemotherapy and underwent IDS followed by four cycles of additional chemotherapy; however, there was variation in the number of IC (NAC) cycles. Paclitaxel and carboplatin were the first choice agents for the IC (NAC) regimen.

Statistical analysis

We performed statistical analysis using the JMP software version 12.0.1. We compared the pre- and post-IC continuous variable values using the *t* test or the Mann–Whitney *U* test. We used the McNemar test to compare the number of patients with lymphopenia and neutrophilia between pre-IC and post-IC conditions. The associations of pre-IC and post-IC biomarkers with the successful complete resection during the IDS were evaluated using the Chi square test. We calculated the overall survival (OS) and the progression-free survival (PFS) using the Kaplan–Meier method. PFS was calculated from the date of diagnosis to the date of disease recurrence or progression. OS was calculated from the date of diagnosis to the date of death from any cause. We evaluated associations between pre- and post-IC lymphopenia and OS or PFS using the log-rank test for univariate analyses and the Cox hazard model for multivariate analyses. We then correlated the lymphocyte counts during IC after one, two, three, and four cycles with pre-IC lymphocyte counts using the paired *t* test. We also evaluated whether lymphopenia after each IC cycle can predict the outcome of IDS renunciation or incomplete resection using the Chi square test. We defined a two-tailed $P < 0.05$ as statistically significant.

Results

Clinicopathological characteristics

A total of 85 patients with stage III/IV EOC, fallopian tube cancer, or primary peritoneal cancer were identified during the study period. We excluded cases with incomplete data or if they were ineligible for surgery due to serious complications, such as thrombosis, liver cirrhosis, infections, intestinal obstruction, or cerebral infarction, resulting in a total of 68 cases in the study (Fig. 1). The clinicopathological characteristics of the study population are listed in Table 1. The median patient age was 64 years (range 43–81). The clinical diagnoses included EOC in 64 patients (94%), fallopian tube cancer in 3 patients (4.4%), primary peritoneal cancer in 1 patient (1.5%). In terms of histological types, 59 patients (87%) had serous carcinoma, 1 (1.5%) had clear cell carcinoma, 1 (1.5%) had endometrioid carcinoma, and 7 (10%) had unspecified adenocarcinomas in which the

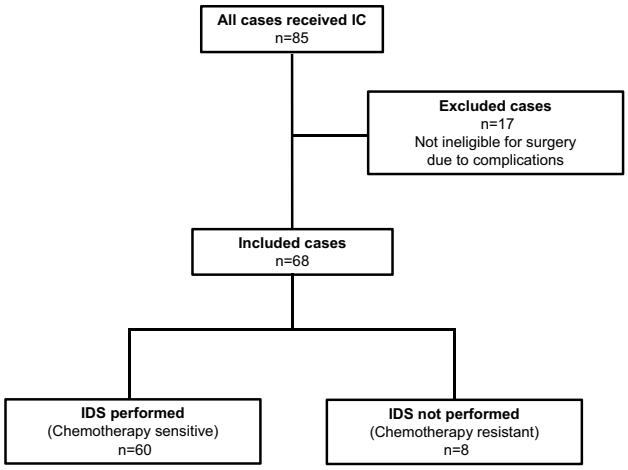

Fig. 1 Flow chart of patient enrollment. *IC* induction chemotherapy, *IDS* interval debulking surgery

histological classification was difficult due to IDS renunciation or IC (NAC) degeneration. The median number of IC cycles completed was 4 (range 2–6). The IC (NAC) cycles in patients who underwent IDS were as follows: three cycles in 6 patients (10%), four cycles in 41 patients (68%), five cycles in 8 patients (13%), and six cycles in 5 patients (8.3%). All patients received platinum-based chemotherapy [paclitaxel and carboplatin, 64 (94%); docetaxel and carboplatin, 3 (4.4%); and irinotecan and carboplatin, 1 (1.5%)]. After IC (NAC), 60 patients underwent IDS, whereas 8 relinquished IDS due to chemotherapy resistance. Overall, 2 out of 8 patients had worsening PS and general condition during IC (NAC) and did not undergo IDS due to disease progression. Among the 60 patients who received IDS, 39 patients (65%) achieved complete cytoreduction, whereas 21 patients (35%) did not undergo complete resections, and 17 patients were left with a residual disease ≤ 1 cm (optimal) and 4 patients with a residual disease > 1 cm (suboptimal).

Pre- and post-IC inflammatory markers

When compared with the pre-IC values, the following variables decreased significantly post-IC: leukocyte counts (7.40 vs 3.55×10^9/L, $P < 0.001$); neutrophil counts (5.74 vs 1.97×10^9/L, $P < 0.001$); monocyte counts (0.44 vs 0.28×10^9/L, $P < 0.001$); NLRs (5.20 vs 1.60×10^9/L, $P < 0.001$); platelet counts (370 vs 171×10^9/L, $P < 0.001$); CRP levels (23.7 vs 0.80 mg/L, $P < 0.001$); and serum CA-125 levels (1220 vs 25 U/mL, $P < 0.001$). In contrast, the lymphocyte counts increased significantly post-IC (1.17 vs 1.28×10^9/L, $P = 0.009$) (Table 2). The median of the pre-IC lymphocyte counts was 1.17×10^9/L, which is lower than the mean for healthy women at $1.9–1.95 \times 10^9$/L [30].

Table 1 Patients' clinicopathological characteristics

	Median/number (%)
Median age (range)	64 (43–81)
ECOG PS	
0	1 (1.5)
1	31 (46)
2	20 (29)
3	16 (24)
FIGO stage	
III	42 (62)
IIIA	1 (1.5)
IIIB	2 (2.9)
IIIC	39 (57)
IV	26 (38)
IVA	9 (13)
IVB	17 (25)
Histological type	
Serous	59 (87)
Clear cell carcinoma	1 (1.5)
Endometrioid carcinoma	1 (1.5)
Unspecified carcinoma	7 (10)
Median IC cycles (range)	4 (2–6)
IC regimen	
Paclitaxel + carboplatin	64 (94)
Docetaxel + carboplatin	3 (4.4)
Irinotecan + carboplatin	1 (1.5)
IDS	
Complete	39 (57)
Optimal	17 (25)
Suboptimal	4 (5.9)
Not performed	8 (11.8)
Chemosensitivity	
CR/PR	60 (88.2)
SD/PD	8 (11.7)

ECOG PS Eastern Cooperative Oncology Group performance status, *NOS* not otherwise specified, *IC* induction chemotherapy, *IDS* interval debulking surgery, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

We found that the number of patients with neutrophilia and lymphopenia decreased significantly post-IC ($P=0.002$ and 0.008, respectively). Additionally, 11 patients exhibited pre-IC neutrophilia, but only 1 patient exhibited post-IC neutrophilia. Meanwhile, we evidenced pre-IC lymphopenia in 27 patients (40%). However, only 16 patients (24%) had it post-IC (Table 2).

Association of inflammatory markers with successful complete resection during IDS

Complete resection during IDS is important for favorable prognosis in patients with advanced EOC treated with IC (NAC) [4, 31]. In this study, the median PFS was 16.4 months [95% confidence interval (CI) 13.5–22.6 months], and the median OS was 69.8 months (95% CI 43.7–91.2 months). The patients with complete resection had better OS and PFS than those who relinquished IDS or who did not undergo complete resection during the procedure (log-rank test, $P=0.025$ and $P=0.043$, respectively, Fig. 2). We compared the clinical characteristics and inflammatory marker values between the patients with complete resection and those without it, to assess predictive significance of the markers for successful complete resection. As shown in Table 3, we found no significant differences between pre- and post-IC values in terms of age, staging, IC-cycle number, CA-125 values, or pre- and post-IC CA-125 ratio between the two groups. Also, the pre-IC/post-IC NLR, pre- and post-IC NLR ratio, pre-IC lymphopenia, pre- and post-IC lymphocyte count ratio, or the pre-IC/post-IC CRP levels were not associated with the surgery outcome. Only post-IC lymphopenia was significantly associated with incomplete resection during IDS (Chi square test, $P=0.012$).

Changes in lymphocyte count during induction chemotherapy and correlation with complete resection

To investigate dynamic changes in lymphocyte count during IC (NAC), we correlated the lymphocyte counts during IC after one, two, three, and four cycles with pre-IC lymphocyte counts. The lymphocyte count significantly increased after one IC (NAC) cycle (paired *t* test, $P<0.001$) and tended to decrease gradually; however, a higher level than pre-IC was maintained (Table 4). With regard to the correlation between lymphopenia and complete resection, lymphopenia after one, two, three, and four IC cycles was significantly associated with the outcome of IDS renunciation or incomplete resection (Chi square test, $P=0.005$, 0.021, <0.001, and 0.006, respectively) (Table 5). Thus, lymphopenia at an early stage after initiating IC (NAC) may predict the possibility of complete resection during IDS.

Prognosis of patients with post-IC lymphopenia

Post-IC lymphopenia was predictive for IDS renunciation or incomplete resection during the procedure. Therefore, we evaluated the association between the post-IC lymphopenia and the prognosis of patients with advanced EOC. As shown in Fig. 3c, d, although the post-IC lymphopenia was not associated with OS ($P=0.13$), it was significantly associated with poor PFS ($P=0.009$). After adjusting for confounding variables, including age (≥ 64 years) and FIGO stage (III vs IV), only post-IC lymphopenia remained an independent predictor of PFS (hazard ratio 2.40; 95% CI 1.21–4.56; $P=0.013$). We also assessed the association between pre-IC

Table 2 Correlation of clinical data before and after induction chemotherapy

Variables	Pre-IC Median (range)/*n* (%)	Post-IC Median (range)/*n* (%)	*P* value
Leukocyte count (10^9/L)	7.40 (3.90–23.1)	3.55 (1.70–10.5)	< 0.001
Neutrocyte count (10^9/L)	5.74 (2.02–21.0)	1.97 (0.37–9.80)	< 0.001
Neutrophilia (> 7.7×10^9/L)	*n* = 11 (16%)	*n* = 1 (1.5%)	0.002
Lymphocyte count (10^9/L)	1.17 (0.41–3.26)	1.28 (0.53–2.72)	0.009
Lymphopenia (< 1.0×10^9/L)	*n* = 27 (40%)	*n* = 16 (24%)	0.008
Monocyte count (10^9/L)	0.44 (0.22–0.99)	0.28 (0.08–0.80)	< 0.001
NLR	5.20 (0.90–23.1)	1.60 (0.20–18.5)	< 0.001
Platelet count (10^9/L)	370 (181–570)	171 (56–423)	< 0.001
CRP value (mg/L)	23.7 (0.40–228)	0.8 (0.40–213)	< 0.001
CA-125 value (U/mL)	1220 (34–52,950)	25 (4–1345)	< 0.001

The paired *t* test was used for normally distributed variables and the Mann–Whitney *U* test was used for non-normally distributed variables. The McNemar test was used for the percentages of neutrophilia and lymphopenia

IC induction chemotherapy, *NLR* neutrocyte-to-lymphocyte ratio, *CRP* C-reactive protein, *CA-125* cancer antigen-125

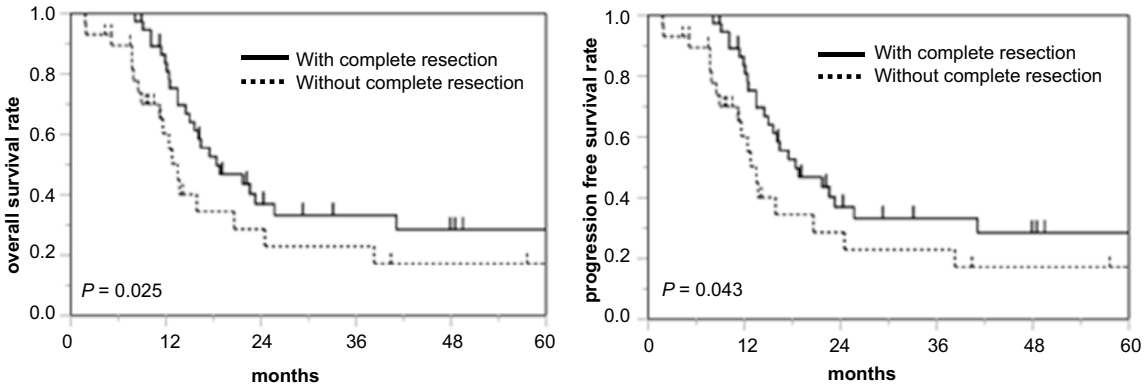

Fig. 2 Kaplan–Meier survival analysis of patients with and without complete resection during IDS. **a** Overall survival rate according to complete resection during IDS. **b** Progression-free survival rate according to complete resection during IDS. Log-rank test for *P* values

lymphopenia and survival outcomes but found no significant differences in either PFS or OS between patients with pre-IC lymphopenia and those without it (log-rank test, $P = 0.78$, $P = 0.82$, respectively, Fig. 3a, b).

Discussion

In this study, we analyzed peripheral blood inflammatory markers, including the presence of neutrophilia and/or lymphopenia in 68 patients with advanced EOC, fallopian tube cancer, or primary peritoneal cancer who underwent IC (NAC). Our univariate analysis showed that post-IC lymphopenia was a poor prognostic factor for PFS. Additionally, the patients in the post-IC lymphopenia group showed lower rates of complete cytoreduction during IDS compared to those in the non-lymphopenia group.

An association of lymphopenia to poor prognosis has been reported in different malignancies [19–28]. However, the evidence linking lymphopenia to the prognosis for advanced-stage EOC is still insufficient. In a related report, pretreatment lymphopenia was associated with PFS in patients treated with primary cytoreductive surgery followed by platinum-based chemotherapy, and patients with suboptimally debulked disease (visible residual lesions) after the primary surgery had lower pretreatment lymphocyte counts than those with optimally debulked disease [18]. Similarly, our results suggest an association between the likelihood of complete cytoreduction in IDS and post-IC lymphocyte counts. Our data indicates that post-IC lymphocyte counts may assist in identifying patients who may benefit from IDS treatment. Thus, post-IC lymphocyte counts may predict surgical prognosis and contribute to the choice of management of patients undergoing IC (NAC).

Table 3 Clinical features and laboratory data of patients with complete resection

	Complete resection $n=39$ (%)	Non complete resection $n=21$ (%)	*P* values
Age < 64 years	21 (53.8)	8 (38.1)	0.24
Age ≥ 64 years	18 (46.2)	13 (61.9)	
Stage III	23 (59.0)	14 (66.7)	0.56
Stage IV	16 (41.0)	7 (33.3)	
3–4 IC cycles	31 (79.5)	16 (76.2)	0.77
5–6 IC cycles	8 (20.5)	5 (23.8)	
High pre-IC CA-125 value (≥ 1220)	21 (53.8)	12 (57.1)	0.80
High post-IC CA-125 value (≥ 25)	16 (41.0)	12 (57.1)	0.23
Pre- and post-IC CA-125 ratio (≥ 0.026)	16 (41.0)	11 (52.4)	0.40
High pre-IC NLR (≥ 5.20)	18 (46.2)	11 (52.4)	0.42
High post-IC NLR (≥ 1.60)	18 (46.2)	11 (52.4)	0.65
Pre- and post-IC NLR ratio (≥ 0.29)	19 (48.7)	10 (47.6)	0.94
Pre-IC lymphopenia	13 (33.3)	9 (42.9)	0.47
Post-IC lymphopenia	4 (10.3)	8 (38.1)	0.012
Pre- and post-IC lymphocyte count ratio (< 1.13)	21 (53.8)	6 (28.6)	0.057
Pre-IC neutrophilia	7 (17.9)	3 (14.3)	0.71
Post-IC neutrophilia	0 (0.0)	0 (0.0)	——
High pre-IC CRP value (≥ 23.7)	21 (53.8)	13 (61.9)	0.46
High post-IC CRP value (≥ 0.80)	18 (46.2)	19 (90.5)	0.19

IC induction chemotherapy, *NLR* neutrophil-to-lymphocyte ratio, *CRP* C-reactive protein, *CA-125* cancer antigen-125

Table 4 Changes in lymphocyte count during induction chemotherapy

	Median lymphocyte count (10^9/L) (range)	*P* value Correlation with pre-IC lymphocyte count
Pre-IC ($n=68$)	1.17 (0.41–3.26)	–
After 1 cycle ($n=68$)	1.43 (0.44–3.62)	< 0.001
After 2 cycles ($n=66$)	1.42 (0.66–3.01)	< 0.001
After 3 cycles ($n=64$)	1.35 (0.57–3.04)	< 0.001
After 4 cycles ($n=59$)	1.30 (0.66–2.72)	0.006

IC induction chemotherapy

The paired *t* test was used for *P* values

In this study, we focused especially on patients with post-IC lymphopenia. Although it has been well established that pretreatment lymphopenia is associated with poor outcomes in various cancers [20, 21, 23], post-treatment lymphopenia has been associated with inferior survival outcomes only recently [19, 22, 24–28]. For evaluating leukocyte proportions in patients undergoing chemotherapy, it is necessary to consider the influence of hematotoxicity. Majority of anticancer drugs cause bone marrow suppression as an adverse reaction and reduce neutrophil numbers in peripheral blood. Therefore, chemotherapy is expected to decrease neutrophil counts and NLR via its bone marrow suppression, and it is hard to distinguish between this effect and the effect

Table 5 Correlation between lymphopenia during induction chemotherapy and complete resection during IDS

	Lymphopenia *n* (%)	Complete resection in lymphopenia group *n* (%)	Complete resection in non-lymphopenia group *n* (%)	Correlation between lymphopenia and complete resection *P* value
Pre-IC ($n=68$)	27 (39.7)	13 (48.1)	26 (63.4)	0.21
After 1 cycle ($n=68$)	13 (19.1)	3 (23.1)	36 (65.5)	0.005
After 2 cycles ($n=66$)	13 (19.7)	4 (30.8)	35 (66.0)	0.021
After 3 cycles ($n=64$)	11 (17.2)	1 (9.1)	36 (67.9)	< 0.001
After 4 cycles ($n=59$)	13 (22.0)	3 (23.1)	30 (65.2)	0.006

IC induction chemotherapy, *IDS* interval debulking surgery

The Chi square test was used for *P* values

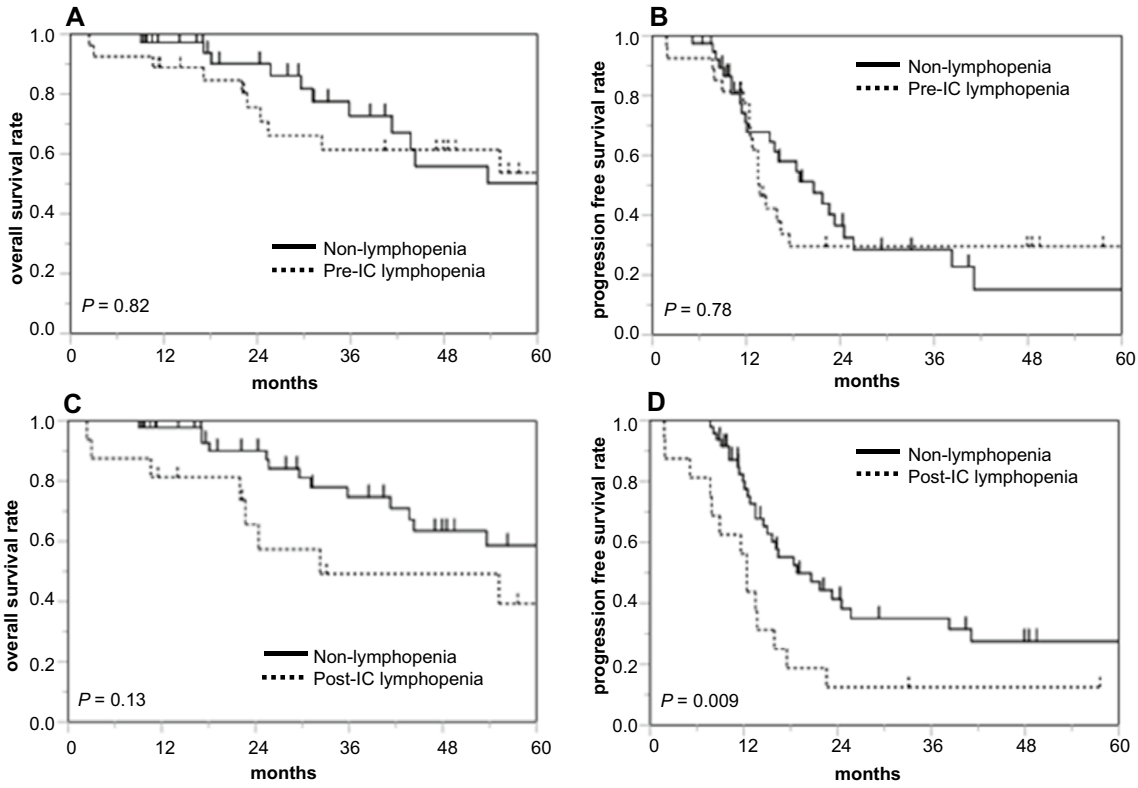

Fig. 3 Kaplan–Meier survival analysis of lymphopenia before (pre-) and after (post-) induction chemotherapy. **a** Overall survival rate according to pre-IC lymphopenia, **b** progression-free survival rate according to pre-IC lymphopenia, **c** overall survival rate according to post-IC lymphopenia, **d** progression-free survival rate according to post-IC lymphopenia. Log-rank test for *P* values. *IC* induction chemotherapy

resulting from improvement in systemic inflammation due to chemotherapeutic efficacy against the tumor. In contrast, although less data are available, the lymphocyte counts appear to be less affected by chemotherapy-induced bone marrow suppression and seem more suitable for post-treatment evaluation than other variables, including neutrophil count, particularly with respect to patients with EOC [18]. In this study, we found that 11 out of 27 patients with pre-IC lymphopenia recovered their lymphocyte counts in the course of chemotherapy regardless of chemotherapy-induced hematotoxicity and they had a more favorable prognosis than those with post-IC lymphopenia. As shown in Table 4, this recovery of lymphocyte counts occurred at an early stage after initiating IC (NAC) and was maintained at a higher level than pre-IC until after the fourth cycle, even under the influence of hematotoxicity. This result may indicate that improvement in tumor activity, systemic inflammatory, and immunological status as a result of therapeutic response is greater than the influence of hematotoxicity. Therefore, changes in lymphocyte counts can be used as biomarkers in patients undergoing chemotherapy.

In a study by Kim et al. on patients with advanced EOC who underwent neoadjuvant chemotherapy, a high pretreatment NLR (cut-off value 3.81) was identified as a risk factor for poor OS through a univariate analysis, and patients with increased NLR during chemotherapy showed significantly poorer PFSs than those without it [9]. However, our analysis did not identify pre- and post-IC NLR as a significant prognostic factor for PFS or OS. Additionally, the pretreatment NLR in our study (median level, 5.20) was relatively higher than that reported by Kim et al. Similarly, previously reported predictive factors of complete resection, such as pre-IC CA-125 value, post-IC CA-125 value, and pre- and post-IC CA-125 ratio were not of significant predictive value in this study [32–34]. Such inter-study discrepancies may be explained by differences in patient backgrounds or inflammation severity in the targeted populations. Therefore, the significance of these predictive factors requires further verification.

Reports have demonstrated a strong association between systemic inflammation and cancer progression; the number of peripheral inflammatory cells, including neutrophils and lymphocytes represents cancer progression and reflects patients' prognosis [9–11, 18, 20]. Lymphocytes play important roles in antitumor immunity, inducing apoptosis, suppressing tumor proliferation, inhibiting the growth and

metastasis of tumors [13, 35]; lymphopenia may weaken the antitumor immunity of patients. In this study, we observed that post-IC lymphopenia was associated with poor prognosis for patients with advanced EOC. Although the pathophysiological significance of post-IC lymphopenia is not clear from our results, this condition could also have been caused by the progression of cancer and by chemotherapeutic resistance; however, our results suggest that lymphopenia could be the cause of the deterioration of the immune system in patients with EOC, making it difficult to inhibit tumor progression.

The limitations of our study are as follows. The retrospective nature may lead to selection bias. In addition, we only included patients from a single institution, and our study population was small. These limitations need to be addressed in future studies to corroborate our findings.

Despite its limitations, our study revealed a significant increase in lymphocyte counts when comparing values pre- and post-IC. Moreover, we also showed the prognostic significance of post-treatment lymphopenia in patients with advanced EOC undergoing IC. These data may be useful for determining individual treatment strategies in the future.

In conclusion, post-IC lymphopenia may be a predictor of IDS renunciation or incomplete resection and poor prognosis in patients with advanced EOC.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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