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Incidence of venous thromboembolism following the neoadjuvant chemotherapy regimen for epithelial type of ovarian cancer

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Abstract

This study aims to analyze the risk of venous thromboembolism (VTE) in patients receiving neoadjuvant chemotherapy (NACT) for epithelial ovarian cancer (EOC).

A retrospective audit was conducted examining 147 patients treated for EOC. Surgical treatment with curative intent, with or without NACT and adjuvant chemotherapy, is the treatment approach, which was modified according to the patient's condition. The incidence of VTE with the most commonly used chemotherapy regimen, carboplatin, cisplatin, paclitaxel, docetaxel, and others were evaluated.

This study found a 13.6% incidence of VTE in patients undergoing therapy with curative intent for EOC. No association was seen between NACT and VTE compared to VTE after standard treatment: 2/16 (12.5%) vs 5/131 (3.8%) ($P = .16$). Univariate and multivariate analyses also demonstrated that NACT has no risk for VTE with odds ratio (OR) = 0.89 (95% CI = 0.18–4.28) and $P = 1$. Results did not vary significantly with the type of chemotherapy used. Furthermore, increased incidence of VTE as an incidental finding supports the well-established role of malignancy in VTE occurrence. Univariate and multivariate analyses demonstrated that VTE occurred more frequently in menopausal women than nonmenopausal women (17.9% vs 5.8%) with OR = 3.55 (95% CI = 0.99–12.78) and $P = .04$ in patients aged ≥60 (19.3% vs 10%) with OR = 2.15 (95% CI = 0.83–5.57) and $P = .13$ but is not statistically significant.

We conclude that NACT has no association with VTE and the currently used common chemotherapeutic drug combinations for ovarian cancer carry the minimal risk of thromboembolic events.

Abbreviations: 95% CI = 95% confidence intervals, C = carboplatin, Ci = cisplatin, CT = commuted tomography, D = docetaxel, DVT = deep venous thrombosis, EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics, IP = intraperitoneal, IPC = intermittent pneumatic leg compression, IVD = intravenous drip, NACT = neoadjuvant chemotherapy, OR = odds ratios, P = paclitaxel, PE = pulmonary embolism, TEs = thromboembolic events, VTE = venous thromboembolism.

Keywords: adjuvant chemotherapy, gynecological malignancy, neoadjuvant chemotherapy, ovarian cancer, venous thromboembolism

1. Introduction

The earliest reference for the association between cancer and thromboembolism dates back to the age of ancient Indian surgeon Sushruta who lived between 1200 and 600 BCE and was the first to make this observation.[1] Trousseau in 1865 proved this association between VTE and malignant disease.[1,2] This relationship is now well-established with many documented studies.[2–6] In comparison to the general population, cancer patients have a higher incidence of VTE, including pulmonary embolism (PE) and deep venous thrombosis (DVT).[7] In some malignancy cases, thromboembolic complications could be the initial presenting feature leading to significant morbidity and mortality.[8]

Thromboembolic events (TEs) occur in 4% to 20% of patients with cancer[9] with reported evidence of thrombosis in 50% of cancer patients at autopsy.[10] TEs and infections comprise the second common cause of death in cancer patients, after the cancer itself.[11] As it is a leading cause of cancer deaths among women, ovarian cancer also carries the highest risk of VTE among all the gynecological malignancies.[12] Over 70% of patients present at an advanced stage with a poor long-term prognosis. Routine management includes cytoreductive surgery (complete resection of the tumor), followed by postoperative chemotherapy.[13] Median survival after the initial cytoreduction is inversely related to the residual tumor mass.[14] Although the role of surgery in thromboembolic events is well established, increasing numbers of studies have noted a positive correlation between chemotherapy (both neoadjuvant and adjuvant) and VTE.

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Epidemiological studies have also identified chemotherapy as an additional risk factor for a hypercoagulability state and thrombosis.[15] Diminished anticoagulant synthesis, activation of a coagulation cascade leading to platelet aggregation, and endothelial damage are hypothesized to be responsible for the chemotherapy-induced thromboembolic phenomenon.[16] In a population-based study, chemotherapy was associated with a 7-fold risk of venous TEs compared to the normal population.[17] Among all chemotherapeutic agents, platinum analogues,[18] anthracyclines, and fluoropyrimidines carried the highest risk of thrombosis. Even within platinum-based regimens, cisplatin has a stronger association than oxaliplatin.[19] Gemcitabine and 5-fluorouracil are other drugs with remarkable thrombotic and vascular side effects.[20–24]

The adverse effects of chemotherapy have been well documented in most of the solid tumors. However, very few studies have assessed the chemotherapeutic side effects in EOC. We, therefore, conducted a retrospective cohort study to analyze the risk of thromboembolism with NACT. The most commonly administered chemotherapeutic combinations such as carboplatin (C)+ paclitaxel (P) /docetaxel (D); cisplatin (Ci) + P/D and others (cyclophosphamide/etoposide/epirubicin/lobaplatin/nedaplatin) were included in our study.

2. Materials and methods

In total, 147 consecutive patients with EOC undergoing treatment with curative intent between January 2012 and May 2015 were identified from the patient database maintained by a data manager at Qilu Hospital at Shandong University, Jinan, China. We have got the ethical approval from our institution and thoroughly checked all the patient records to ensure that no VTEs were missed. Inclusion criteria included patients with EOC (International Federation of Gynecology and Obstetrics, FIGO stages II to IV) who underwent surgical treatment with curative intent, with or without neoadjuvant and adjuvant chemotherapy. Exclusion criteria included patients with history of VTE, other histological types of ovarian cancer, and the use of anticoagulation for a different indication. All patients subjected to chemotherapy were contacted and followed up.

Chest and abdominal commuted tomography (CT) scans were performed in all patients while staging. Upon completion of NACT, radiological examinations were repeated prior to surgery. We divided the thromboembolic events into asymptomatic and symptomatic findings based on the mode of detection. Duplex venous ultrasound was used as clinically indicated and was not performed routinely on asymptomatic patients. Thromboprophylaxis was not given during chemotherapy. Standard perioperative thromboprophylaxis consisted of intraoperative intermittent pneumatic leg compression (IPC) and graduated stockings throughout the inpatient stay. Patients with VTE received 1.5 mg/kg subcutaneous enoxaparin daily for 3 months except during the perioperative period when this was reduced to a standard prophylactic dose of 40 mg once daily.

2.1. Data collection

For each patient, data were collected regarding the age at diagnosis; menopause status; FIGO stage; smoking history; use of hormone replacement therapy; history of other cancers; hemoglobin level; white blood cell count; type of chemotherapy regimen used; and the presence of other comorbid conditions such as diabetes mellitus, hypertension, and coronary artery disease. We divided the chemotherapy regimen into 3 groups: group 1 included C + P/ D, group 2 included Ci +P/D, and group 3 included others (cyclophosphamide/etoposide/epirubicin lobaplatin/nedaplatin).

The incidence of VTE among drug combinations were recorded as finding of DVT or PE during/after NACT and finding of DVT or PE after standard treatment (surgery with/without adjuvant chemotherapy). Each patient's record was reviewed and data were collected from those who met the inclusion criteria. The information regarding chemotherapy included the type of combination regimen and the route of administration, by intravenous drip (IVD) or by intraperitoneal (IP). For patients with an identified VTE, we also recorded the type of VTE (DVT/PE) and the method of detection.

2.2. Statistical analysis

All the statistical analyses were performed using the Vassar Stats software. Fisher's exact test was used to evaluate VTE association with the treatment method. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. All statistical analyses performed were 2 sided and a significance level of $P = .05$ was used. Univariate and multivariate analyses were used to establish significant factors influencing the occurrence of any venous thromboembolic event. The total number of participating patients with EOC was n = 147.

3. Results

3.1. Patient characteristics

The majority of patients were postmenopausal women (95/147; 64.6%) with an average age of 54.6 years (26–75 years). Of 147 patients, 16 (10.9%) had NACT; 5 (31.2%) had group 1 drugs, 8 (50%) had group 2 drugs, and 3 (18.8%) had group 3 drugs. A total of 144 (98%) had adjuvant chemotherapy; 66 (45.8%) had group 1 drugs, 60 (41.7%) had group 2 drugs, and 18 (12.5%)

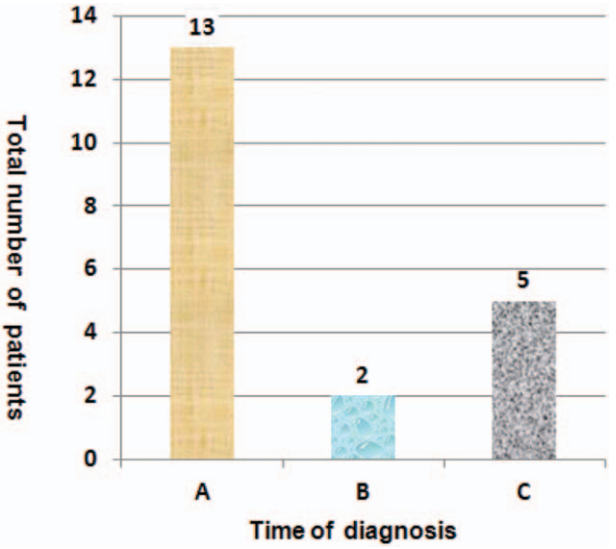

Figure 1. Incidence and time of diagnosis of VTE in patients with the epithelial type of ovarian cancer (N = 147). Note: (A) at diagnosis/incidental finding; (B) during/after NACT; (C) after surgery. There were 13 patients diagnosed at diagnosis/incidental finding; 2 patients diagnosed during/after NACT; 5 patients diagnosed after surgery. NACT = neo-adjuvant chemotherapy, VTE = venous thromboembolism.

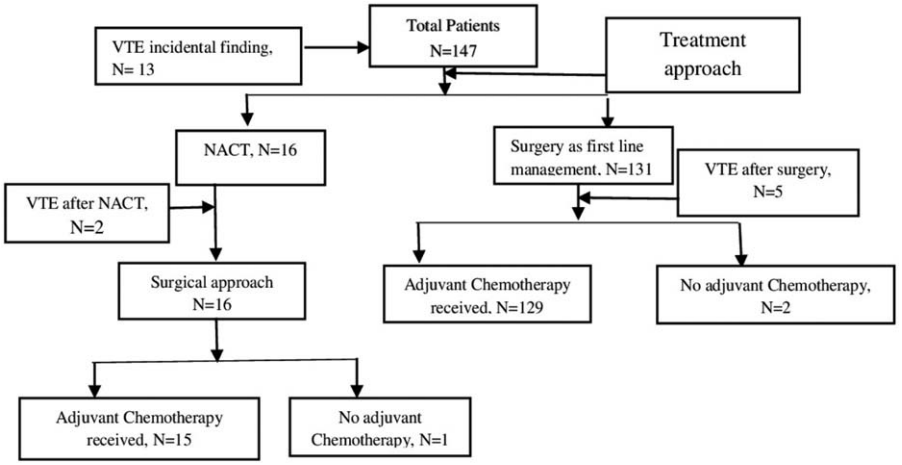

Figure 2. Diagrammatic presentation of patient management by neo-adjuvant chemotherapy (NACT), surgical, and adjuvant chemotherapy with point of incidences of VTE. Note: venous thromboembolism, VTE; neoadjuvant chemotherapy, NACT. There were 147 patients in total, 16 patients received NACT+ surgical approach, then 15 patients received adjuvant chemotherapy, one didn't; 131 Patients received surgery as first line management, then 129 patients received adjuvant chemotherapy, 2 patients didn't. The total patients of VTE were 20, 13 patients diagnosed at diagnosis/incidental finding; 2 patients diagnosed during/after NACT; 5 patients diagnosed after surgery. NACT = neo-adjuvant chemotherapy, VTE = venous thromboembolism.

had group 3 drugs. Two (1.4%) had no chemotherapy. For chemotherapy administration, we routinely use IVD and IP route in our hospital, and central venous access was used in less than 5% of the patients. Data concerning the incidence and time of VTE occurrence for the total cohort (n = 147) are represented as a bar graph (Fig. 1).

3.2. Incidence of VTE

VTEs were observed in 20 of 147 (13.6%) patients. Of these, 13/20 (65%) were detected at the time of diagnosis/incidental finding, 2/20 (10%) after NACT, and 5/20 (25%) after standard treatment (surgery with/without adjuvant chemotherapy). Figure 2 details the point of incidence of VTE in relation to NACT and standard treatment. Among them, 16/20 (80%) were asymptomatic and 4/20 (20%) had symptomatic events.

PE accounted for 1/20 (5%) of VTE and DVT for 19/20 (95%). All the events were diagnosed by CT or duplex ultrasound. No deaths were observed in cases diagnosed with VTE during the treatment phase. Of the VTE (N = 20), all symptomatic events (N = 3) were diagnosed using a duplex ultrasound scan and 1 with PE was diagnosed with a CT scan. The remaining 16 events were diagnosed by a routine duplex ultrasound scan and CT chest, abdomen, and pelvis imaging.

3.3. Risk factors for VTE with patient characteristics

Table 1 shows OR for VTE in patients with EOC. The following variables to determine the risk of VTE were used in the univariate and multivariate analyses: use of NACT regimen; age at diagnosis; menopause status; FIGO stage; smoking history; use of hormone replacement therapy; history of other cancer; hemoglobin level; white blood cell count; other comorbid conditions such as a history of diabetes mellitus; hypertension; and coronary artery disease. Of these, postmenopausal women showing significant results in univariate analyses were chosen for multivariate analysis. The multivariate analysis confirmed these variables as independently and significantly associated with the risk of VTE before treatment in the epithelial type of ovarian cancer (Table 2).

Table 1

Evaluation of potential risk factors of VTE according to patient characteristics.

Variables	VTE incidence n, %	OR, 95% CI	*P*
NACT			
Yes	2/16 (12.5%)	0.89 (0.18–4.28)	1.00
No	18/131 (13.7%)		
Age			
≥60	11/57 (19.3%)	2.15 (0.83–5.57)	.13
<60	9/90 (10%)		
Menopausal status			
Yes	17/95 (17.9%)	3.55 (0.99–12.78)	.04
No	3/52 (5.8%)		
FIGO stage			
II	9/44 (20.5%)	2.15 (0.82–5.63)	.12
III–IV	11/103 (10.7%)		
Smoking			
Yes	1/3 (33.3%)	3.28 (0.28–38.06)	.35
No	19/144 (13.2%)		
History of other cancer			
Yes	0/4 (0%)	–	1.00
No	20/143 (14%)		
Hormonal therapy			
Yes	0/1 (0%)	–	1.00
No	20/146 (13.7%)		
History of diabetes			
Yes	3/16 (18.8%)	1.54 (0.39–5.99)	.69
No	17/131 (13%)		
History of hypertension			
Yes	3/31 (9.7%)	0.62 (0.17–2.28)	.56
No	17/116 (14.7%)		
History of CAD			
Yes	1/10 (10%)	0.69 (0.08–5.76)	1.00
No	19/137 (13.9%)		
Hemoglobin, g/L			
≥115	9/85 (10.6%)	0.54 (0.21–1.41)	.23
<115	11/62 (17.7%)		
WBC, $\times 10^9$/L			
≥5.9	8/88 (9.1%)	0.39 (0.14–1.02)	.08
<5.9	12/59 (20.3%)		

95% CI = 95% confidence interval, CAD = coronary artery disease, FIGO = International Federation of Genecology and Obstetrics, OR = odds ratio, VTE = venous thromboembolism, WBC = white blood cell.

Table 2

Multivariate analysis for the risk factors of VTE in patients with epithelial type of ovarian cancer.

Variables	VTE incidence n, %	RRs, 95% CI	*P*
NACT			
Yes	2/16 (12.5%)	0.90 (0.23–3.56)	1.00
No	18/131 (13.7%)		
Menopausal status			
Yes	17/95 (17.9%)	3.10 (0.95–10.09)	.04
No	3/52 (5.8%)		

95% CI = 95% confidence interval, NACT = neoadjuvant chemotherapy, RR = relative risk, VTE = venous thromboembolism.

A history of metabolic disorders such as hypertension, diabetes, coronary artery disease, and smoking did not have any statistically significant effect upon the incidence of VTE (Table 1). Univariate and multivariate analyses demonstrated that VTE occurred more frequently in menopausal women than in non-menopausal women OR = 3.55 (95% CI = 0.99–12.78) and $P = .04$, ages ≥60 with OR = 2.15 (95% CI = 0.83–5.57) but was not statistically significant ($P = .13$) and in FIGO stages II and III-IV OR = 2.15 (95% CI = 0.82–5.63) but was not statistically significant ($P = .12$). It should however be noted that ovarian cancer is more common among elderly women who are mostly menopausal.

3.4. Association of VTE with treatment modality

There were 15/20 events diagnosed in the pre-operative period, 13 at diagnosis of malignancy and 2 associated with NACT administration. The 2 pre-operative VTEs associated with NACT were asymptomatic and all events were DVT. Of these events, 1 patient had received Ci +P/D and 1 received another drug regimen. No association was found between NACT and VTE in comparison with VTE after standard treatment 2/16 (12.5%) vs 5/131 (3.8%) ($P = .16$). Univariate and multivariate analyses also demonstrated that NACT had no risk of VTE with OR = 0.89 (95% CI = 0.18–4.28) and $P = 1$. Nonsignificant determinate of VTE comparing different drug combinations occurring both preoperatively (during or after neoadjuvant therapy) versus after standard treatment is shown in Table 3.

There were 13/20 events diagnosed in the pretreatment period, that is, at the time of diagnosis of malignancy with all 7 remaining events associated with treatment modalities (NACT and/or surgery with/without adjuvant chemotherapy administration). Of the 7 post-treatment events, 4 (3 DVT and 1 PE) were symptomatic and the remaining 3 asymptomatic events were DVT.

Table 3

Comparing DVT/PE during or after NACT with DVT/PE after standard treatment in each group of drugs.

Drug regimen	VTE	DVT/PE during or after NACT	DVT/PE after standard treatment	*P*
Group 1	3	DVT, 0	3	.42
Group 2	2	DVT, 1	PE,1	1.00
Group 3	2	DVT, 1	DVT,1	1.00

Group 1 carboplatin C + paclitaxel P/docetaxel D; Group 2 cisplatin Ci +P/D; Group 3 others (cyclophosphamide/etoposide/epirubicin/lobaplatin/nedaplatin).

DVT = deep venous thrombosis, NACT = neoadjuvant chemotherapy, PE = pulmonary embolism, VTE = venous thromboembolic events.

VTE incidence did not vary by the treatment approach or by the use/no use of NACT. There was no significant difference in the incidence of VTE by individual NACT regimens. However, we noted that ovarian cancer itself acted as an independent risk factor for VTE occurrence in 13/20 (65%).

4. Discussion

This study reveals an incidence of 13.6% for VTE in patients receiving multimodal treatment with curative intent for the epithelial type of ovarian cancer. As a routine follow-up scan following surgery with/without adjuvant chemotherapy was not conducted in our patients, this figure is most likely an underestimation. However, as all the patients receiving NACT were scanned prior to surgery, it is likely a very good estimate of VTE incidence at present. This observed level of VTE is lower than previous studies have reported.[25] There was no statistically significant increased risk of VTE occurring with NACT administration compared to surgery with/without adjuvant chemotherapy, that is, standard treatment ($P = .16$). This lack of significance may be due to the lower sample ratio receiving NACT versus receiving surgery with/without adjuvant chemotherapy: 16/147 (10.9%) vs 131/147 (89.1%). We observed an increased incidence of VTE at the time of diagnosis of malignancy, 13/20 (65%), without any association with the treatment modality. In the present study, univariate and multivariate analyses revealed the risk factors for VTE in patients with EOC in postmenopausal women. Another limitation is the smaller sample size.

VTE is a well-established complication that is being increasingly reported in cancer patients. In 1865, Trousseau first observed an epiphenomenon of "hypercoagulability" and thrombosis in cancer. However, several studies confirmed the strong causative role of malignancy in thromboembolic complications.[8] Interestingly, this risk was particularly high among certain type of malignancies[26] such as ovarian cancer.[22] Thrombin activation, a tumor-induced procoagulant state, and underlying comorbidities[27–30] are thought to be responsible for the hypercoagulable states in malignancy with the clinical VTE incidence ranging from 1% to 11%[3–6,31–33] in patients with cancer. The relationship between VTE and chemotherapy has been widely reported in the literature.[11,34–36] Mereu et al[37] published a retrospective review in 2009 of 203 ovarian cancer patients receiving chemotherapy as primary modality from 1990 to 2004. The risk for symptomatic VTE was 7.8% at 6 months. On multivariate analysis, BMI, histology, single-agent chemotherapy, and FIGO stages were predictive of VTE.

In recent years, advanced stage ovarian cancer (FIGO stages IIIc and IV) is being approached by "sandwich therapy" that aims to reduce the tumor volume, optimize cytoreduction, and improve the chances of complete remission. As this treatment protocol showed better outcomes than standard treatment (surgery followed by chemotherapy), it is currently under evaluation for the primary management of advanced ovarian cancer. "Sandwich therapy" is NACT followed by interval debulking surgery and post-surgical chemotherapy.[13,38] Despite clinical and laboratory indicators to predict treatment response and prognosis, patients presented with varied therapeutic outcomes after "sandwich therapy."[13,14,39]

The alterations following chemotherapy have been well described in other tumors such as nonsmall cell lung carcinoma,[40] breast carcinoma,[41,42] carcinoma of the stomach,[43] and malignant bone tumors.[44] As NACT is expected to become a

standard treatment for unselected patients with advanced ovarian cancer when favorable results are confirmed by phase III trials, more studies are warranted to scrutinize the chemotherapy-induced changes to confirm the efficacy and safety of NACT before surgery.[45] The primary objective of our study was to determine whether a neoadjuvant chemotherapy regimen carries a risk of incidence of VTE in comparison to treatment with surgery with/without adjuvant chemotherapy for the epithelial type of ovarian cancer, and we found no such association.

5. Conclusion

In conclusion, this study reports an overall incidence of VTE of 13.6% in patients treated for the epithelial type of ovarian cancer. No association was found between NACT and VTE in comparison with VTE after standard treatment 2/16 (12.5%) vs 5/131 (3.8%), $P = .16$. Univariate analysis also demonstrated that NACT has no risk for VTE with OR = 0.89 (95% CI = 0.18–4.28) and $P = 1$. Our study implies that NACT carries minimal risk of VTE and therefore should be considered more often as a pre-operative treatment modality to improve the therapeutic outcome in patients with ovarian cancer; this can be beneficial to both the patient and to the surgeon. We also noted that cancer itself played a causative role in the occurrence of VTE, which is in concordance with previous studies. However, larger studies are warranted to understand the association of NACT with VTE and to evaluate the role of prophylactic anticoagulation in patients receiving chemotherapy for ovarian cancer.

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