Survival and biomarker analysis for cancer-associated thromboembolism in ovarian clear cell carcinoma

TSUBASA ITO, MORIKAZU MIYAMOTO, NAOHISA KISHIMOTO, JIN SUMINOKURA, TAIRA HADA, SOICHIRO KAKIMOTO, KENTO KATO and MASASHI TAKANO

Department of Obstetrics and Gynecology, National Defense Medical College Hospital, Tokorozawa, Saitama 359-8513, Japan

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Abstract. The present study aimed to investigate the impact of cancer-associated thromboembolism (CAT) on the survival and biomarkers of ovarian clear cell carcinoma (OCCC). Patients with OCCC who underwent surgery at the National Defense Medical College Hospital (Tokorozawa, Japan) between January 2000 and December 2019 were included in the current study. Associations among CAT, clinicopathological features and prognosis were retrospectively compared. Furthermore, immunohistochemical staining was conducted in all patients to compare differences between patients with and without CAT. Among 111 patients with OCCC, 20 patients (18.0%) had CAT complications. CAT was detected in 12 patients (10.8%) before primary treatment and in 8 patients (7.2%) after primary surgery. Patients with CAT experienced more tumor recurrence (P=0.048) and platinum resistance (P=0.025), had worse progression-free survival (PFS; P<0.01) and overall survival (OS; P<0.01), and multivariate analysis showed that CAT was a prognostic factor for worse PFS [hazard ratio (HR)=2.10, P=0.039] and OS (HR=4.26, P<0.01). Moreover, immunohistochemical analysis revealed that more OCCC cases with CAT were positive for tissue factor (TF; P=0.030) and phosphorylated-Janus kinase 2 (JAK2; P=0.034) expression than those without CAT. In conclusion, CAT may be associated with platinum resistance and poor prognosis in patients with OCCC. Furthermore, TF and JAK2 could be considered potential novel therapeutic targets for OCCC complicated by CAT.

Correspondence to: Dr Morikazu Miyamoto, Department of Obstetrics and Gynecology, National Defense Medical College Hospital, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan
E-mail: morikazu1118@hotmail.co.jp

Abbreviations: OCCC, ovarian clear cell carcinoma; CAT, cancer-associated thromboembolism; VTEs, venous thromboembolic events; ATEs, arterial thromboembolic events; FIGO, International Federation of Gynecology and Obstetrics; TF, tissue factor; IL-6, interleukin-6; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; PE, pulmonary embolism; DVT, deep vein thrombosis; AMI, acute myocardial infarction; CI, cerebral infarction; DIC, disseminated intravascular coagulopathy; IHC, immunohistochemistry; TMA, tissue microarrays; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; EMT, epithelial-mesenchymal transition; TV, tisotumab vedotin

Key words: OCCC, CAT, platinum resistance, VTEs, ATEs

Introduction

Despite recent improvements in treatment modalities, ovarian carcinoma is the seventh most common cancer in women and the eighth most common cause of carcinoma-related deaths worldwide (1). The best management strategy is aggressive treatment including maximal cytoreductive surgery and subsequent adjuvant chemotherapy (2). Despite aggressive treatment, ovarian carcinoma has a poor prognosis.

Management of complications associated with ovarian cancer is essential for optimal treatment of patients with ovarian carcinoma. Cancer-associated thromboembolism (CAT) is a prevalent complication of ovarian carcinoma and includes venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs). The incidence of VTEs in all histological subtypes ranges from 5.2 to 13.3%, and the incidence of ATEs is 1.1 to 3.2% (3-5). Previous reports have indicated that CAT developed more frequently in ovarian clear cell carcinoma (OCCC) among the different histologic subtypes of ovarian carcinoma (5). Therefore, the management of CAT, particularly in patients with OCCC, is crucial in clinical settings.

OCCC is a histological subtype of epithelial ovarian carcinoma that comprises clear, proliferating, solid, tubular, or papillary cells with hobnail features (6). The incidence of OCCC is higher in Asia, particularly Japan (26.9%), which is higher than that in the U.S. (7). Compared with other histological subtypes, OCCC develops at a younger age, is discovered at an earlier stage, is complicated by endometriosis, and has a lower response to chemotherapy and a shorter response period (8,9). However, few studies have examined the association between CAT and OCCC (5,10,11).

The pathological mechanisms of CAT are complicated and multifactorial, and include the tumor, tumor microenvironment, and hemostatic system (12). Tissue factor (TF) initiate the extrinsic coagulation pathway and produce thrombin (13). Janus kinases (JAK) are a family of intracellular non-receptor

tyrosine kinases that mediate signaling through the pathway of signal transducer and activator of transcription (STAT) proteins (14). Some studies have shown that TF and IL-6 are risk factors for OCCC (3,15), and another in vitro study showed that JAK-STAT signaling causes hypercoagulation through platelet activation (14). However, studies on the relationship between CAT and the JAK/STAT pathway in patients with ovarian carcinoma are scarce.

This study aimed to investigate the risk factors, prognosis, and proteins associated with CAT in patients with OCCC using previous data with extended follow-up and target periods.

Materials and methods

Patients and tissue samples. Patients with OCCC who underwent surgery at the National Defense Medical College Hospital (Tokorozawa, Japan) between January 2000 and December 2019 were included in this study. The data of patients treated between January 2000 and December 2017 were identified in our previous reports (5). The observational period of these patients was extended to approximately 2 years, and an analysis using these data was performed. Patient data from January 2018 to December 2019 were obtained and included in the final analysis. Clinical data were obtained from the medical and surgical records. Patients who did not receive primary treatment, including surgery; refused chemotherapy; or had no clinical records were excluded.

To identify risk factors for CAT in OCCC, the following variables were evaluated: Age at diagnosis, body mass index, comorbid conditions (hypertension, diabetes, heart disease, hyperlipidemia, stroke, and allergic immune disorders), performance status score, International Federation of Gynecology and Obstetrics (FIGO), residual tumor, response rates, ascites, recurrence, and pattern of recurrence. Performance status was measured using the World Health Organization Performance Status Scale. The diseases were staged according to the 2014 FIGO staging system (16). Residual tumors were defined as the presence or absence of residual tumors after the primary debulking surgery. The response rates were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (17). Evaluation was performed only in patients with residual tumors. Platinum-sensitive recurrence was defined as a disease that recurred more than six months after the final cycle of first-line chemotherapy, whereas platinum-resistant recurrence was defined as a disease that recurred or progressed within less than six months from the final cycles of first-line chemotherapy. This study was approved by the Institutional Review Board of the National Defense Medical College (approval no. 4346; Tokorozawa, Japan).

CAT evaluation protocol. Peripheral blood samples were obtained from all patients at the initial visit and before several rounds of treatment, including primary surgery and several courses of chemotherapy; D-dimer levels were also measured. We used D-dimer tests to detect CAT because D-dimer is useful for screening thromboembolism in ovarian carcinoma according to several previous reports (18-21). Inherited predisposition for thromboembolism was additionally examined if the patient had a family history of thrombotic predisposition, such as hemophilia or protein C&S deficiency. After the CAT incidents, if the symptoms or blood tests were suspicious, we examined acquired predisposition for thromboembolism such as anti-phospholipid syndrome and disseminated intravascular coagulopathy (DIC). In addition, all patients underwent computed tomography and magnetic resonance imaging before the primary surgery. When symptoms of suspected CAT appeared, including chest pain, dyspnea, pain, and swelling in one leg or elevated D-dimer levels exceeding the normal limit (1.0 μg/l), we additionally performed ultrasonography, computed tomography, magnetic resonance imaging, and angiography. Furthermore, if the D-dimer levels suddenly increased or symptoms were present during the observation or treatment period, CAT screening was performed.

The timing of CAT development was classified as before or after primary treatment, such as surgery or chemotherapy. CAT was used to evaluate VTEs, including pulmonary embolism (PE) and deep vein thrombosis (DVT), and ATEs, including acute myocardial infarction (AMI) and cerebral infarction (CI), as described in our previous report (5).

Immunohistochemistry (IHC). IHC was performed on 111 formalin-fixed, paraffin-embedded tissues in accordance with our previous study (22). Tissue microarrays (TMA) were constructed using a manual tissue array (KIN-2; AZUMAYA, Tokyo, Japan). TMA slides were deparaffinized and rehydrated using a stepwise ethanol series. Antigens were removed using citrate (pH 6.0) and Tris-EDTA (pH 9.0) buffers. TMA slides were autoclaved in citrate buffer at 121˚C for 5 min or boiled in Tris/EDTA buffer at 98˚C for 40 min. The primary antibodies are listed in Table I. All TMA slides were incubated with primary antibodies for 1 day at room temperature. After incubation, the slides were incubated with the DAKO EnVision+ System-HRP Labeled Polymer (DAKO Denmark A/S, Glostrup, Denmark, Code: K4000) as a secondary antibody for 30 min at room temperature. Finally, we visualized specific antigen-antibody reactions using 0.2% diaminobenzidine tetrahydrochloride (MUTO PURE CHEMICALS CO. LTD, Tokyo, Japan, Code: 40651) and hydrogen peroxide (FUJIFILM Wako Pure Chemical CO, Osaka Japan, Code: 08-0421), and counterstained with Mayer's hematoxylin (MUTO PURE CHEMICALS CO. LTD, Tokyo, Japan, Code: 30002). The proportion score was determined as the proportion of cells in the carcinoma tissue as follows: 0, no tumor cells stained; 1+, between 1 and 10% of cells stained throughout the carcinoma tissue; 2+, between 10 and 50%; 3+, 50% or more. The staining intensity score was determined as follows: 0, no tumor cells stained throughout the carcinoma tissue; 1+, incomplete staining and slight or mostly imperceptible staining; and 2+, total staining and/or more than moderate staining. The immunohistochemical interpretation is shown in Table I.

Statistical analysis. Using JMP 11.0 software (SAS Institute Inc., Tokyo, Japan), statistical analyses were performed using the χ^2 test and Fisher's exact test to compare the differences in characteristics between the two groups. Progression-free survival (PFS) was defined as the period from the date of primary treatment to the date of disease progression or death. Overall survival (OS) was defined as the period from the date of

Table I. Primary antibodies.

Molecule	Type	Manufacturer	Antibody cat. no.	Dilution	Localization	Control tissue	Antigen retrieval	Interpretation
TF	Monoclonal (Mouse)	Santa Crus	sc-374441	1:50	Membrane	Kidney	Citrate	Proportion score 3 and staining intensity score 2 to 3 were defined as positive
IL-6	Polyclonal (Rabbit)	Abcam	ab6672	1:400	Cytoplasm	Lung	EDTA	Proportion score 3 and staining intensity score 2 to 3 were defined as positive
Phosphorylated-JAK2	Monoclonal (Rabbit)	Abcam	ab32101	1:100	Nucleus	SCC	Citrate	Proportion score 3 and staining intensity score 2 to 3 were defined as positive
Phosphorylated-STAT3	Monoclonal (Rabbit)	Cell Signaling	9145	1:50	Nucleus	Heart	EDTA	Proportion score 1 to 3 and staining intensity score 1 to 3 were defined as positive

TF, tissue factor; IL-6, interleukin-6; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3.

Figure 1. Representative images of immunohistochemical staining of (A) TF, (B) IL-6, (C) JAK2, and (D) STAT3. Magnification, x200. TF, tissue factor; IL-6, interleukin-6; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3.

primary treatment to death. Survival curves for PFS and OS were generated using the Kaplan-Meier method. A log-rank test was conducted to compare the survival distributions. Univariate and multivariate analyses of PFS and OS were performed using Cox proportional hazards regression. The variables in the multivariate analysis were those with statistical significance as identified by univariate analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 111 patients were enrolled during the observation period. The median follow-up duration was 61 months (range, 1-195 months). Among these 111 patients, 20 (18.0%) with OCCC developed CAT complications. The prevalence of CAT is shown in Table II. None of these patients had acquired and inherited predisposition for thromboembolism including DIC or a history of thromboembolism. Twelve patients (10.8%) were diagnosed with CAT before primary treatment and eight patients (7.2%) were diagnosed with CAT after primary treatment.

Table III shows the incidence of relapse in 13 patients (26.5%) with CAT and 36 patients (73.5%) without CAT, which was significantly higher than that in patients with CAT ($P=0.048$). In addition, platinum-resistant recurrence was significantly more frequent in patients with CAT than in those without CAT ($P=0.025$). The differences in the other characteristics between the two groups were not statistically significant. Representative images of IHC staining are shown in Fig. 1. Table III shows the results of the immunohistochemical staining for OCCC.

Table II. The prevalence of cancer-associated thromboembolism in ovarian clear cell carcinoma.

Variable	VTEs, n (%)	ATEs, n (%)	VTEs + ATEs, n (%)
Total	14 (70.0)	3 (15.0)	3 (15.0)
DVT	8 (40.0)	-	-
PE	3 (15.0)	-	-
DVT + PE	3 (15.0)	-	-
CI	-	3 (15.0)	-
DVT + CI	-	-	1 (5.0)
PE + AMI	-	-	1 (5.0)
DVT + PE + CI	-	-	1 (5.0)

VTEs, venous thromboembolic events; ATEs, arterial thromboembolic events; PE, pulmonary embolism; DVT, deep vein thrombosis; AMI, acute myocardial infarction; CI, cerebral infarction.

Although the IL-6 and phosphorylated-STAT3 levels were not significantly different between the two groups, cases of OCCC with CAT were more positive for TF (P=0.030) and phosphorylated-JAK2 (P=0.034) than those with OCCC without CAT. Patients with CAT had worse PFS (Fig. 2A, P<0.01) and OS (Fig. 2B, P<0.01) than those without CAT. Multivariate analysis (Table IV) showed that CAT [hazard ratio (HR), 2.10; P=0.039] and advanced stage (HR=3.46; P<0.01) were independent predictors of worse PFS. In addition, CAT (HR=4.26; P<0.01) and residual tumor (HR=3.53; P=0.018) were identified as significant worse prognostic factors for OS.

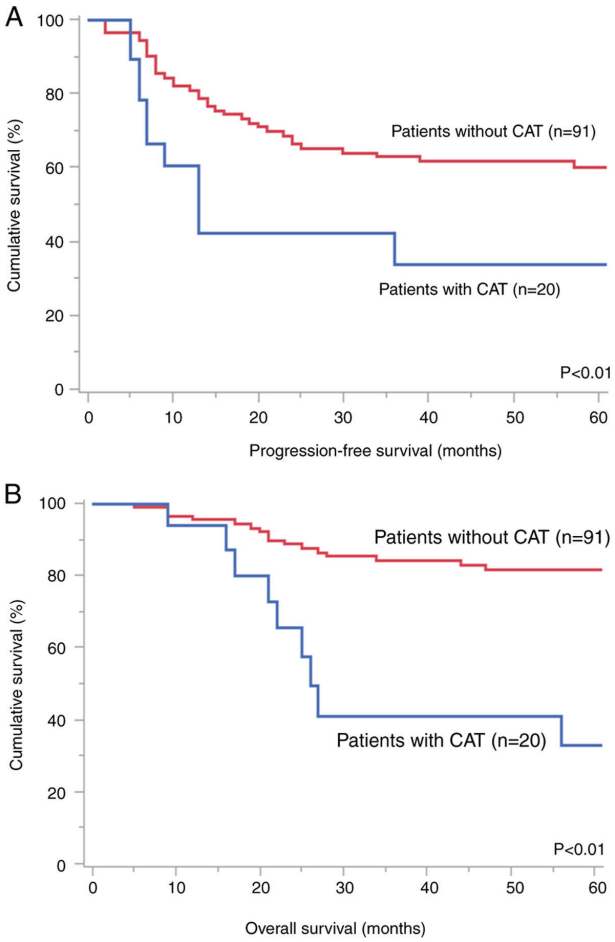

Figure 2. PFS and OS curves in patients with CAT and in those without CAT. (A) PFS and (B) OS curves of patients with CAT were shorter than those of patients without CAT. PFS, progression-free survival; OS, overall survival; CAT, cancer-associated thromboembolism.

Discussion

In our study, the rate of CAT-related complications in patients with OCCC was 18.0%. Patients with CAT were more likely to experience relapse (P=0.048) and platinum-resistant recurrence (P=0.02). CAT is a poor prognostic factor in patients with OCCC. In addition, we showed for the first time that JAK2 signaling is associated with CAT in OCCC.

Our results indicated that the incidence of OCCC patients with CAT (18.0%) was within the range of previous studies (14.5-27.3%) (10,23). Similarly, the incidence of patients with OCCC complicated with CAT before primary treatment in our study (10.8%) was within the range of previous studies (5.3-14.9%) (11,23). Conversely, the incidence of CAT after primary treatment (7.2%) was lower than that of previous studies (9.3-19.7%) (11,23). Thus, the incidence at several time points in our study did not differ significantly from that in previous reports.

Our previous report demonstrated that CAT was associated with worse prognosis and OCCC (5). We did not perform a sub-analysis to determine the significance of CAT in patients with OCCC. Our findings are consistent with those of previous studies that found that patients with OCCC and CAT had a poor prognosis (10,11,23). In this study, comorbid conditions were not risk factors to develop CAT, and did not influence PFS or OS between patients with and without CAT. A potential confounding factor that CAT might affect patient outcomes is the delay or discontinuation of OCCC treatment because CAT could induce a poor general condition. This study showed that the development of severe CAT, such as massive PE, AMI, and CI, could reduce performance status and require immediate treatment, resulting in the delay and discontinuation of OCCC treatment. From another perspective, bevacizumab, a humanized anti-vascular endothelial growth factor monoclonal antibody, may improve OCCC prognosis (24). However, this is associated with severe thromboembolism as a side effect. Thus, treatments with promising drugs are limited.

Our results also demonstrated that OCCC with CAT recurred more frequently and was platinum resistant. CAT in OCCC may indicate not only the formation of a tumor microenvironment, such as hypoxia, but also immunosuppression due to TF and IL-6/JAK2/STAT3. TF activates various signaling pathways that promote cancer cell proliferation, metastasis, angiogenesis, and cancer stem cell-like cell maintenance (25). In addition, TF is overexpressed during inflammation, leading to the activation of JAK2, which promotes platelet activation and epithelial-mesenchymal transition (EMT) via STAT3 (14.26.27). Furthermore, JAK2/STAT3 signaling suppresses tumor-infiltrating lymphocytes induced by hypoxia (28). Therefore, the inhibition of TF and JAK2 prevents EMT in cancer cells and improves the

Table III. Characteristics and results of immunohistochemistry staining of all ovarian clear cell carcinoma patients with or without cancer-associated thromboembolism.

Variable	Patients with CAT, n (%)	Patients without CAT, n (%)	P-value
Total	20 (18.6)	91 (81.4)	
Age at diagnosis			0.560
≥65 years	6 (30.0)	20 (22.0)	
<65 years	14 (70.0)	71 (78.0)	
Body mass index			0.760
≥25 kg/m^2	3 (15.0)	18 (19.8)	
<25 kg/m^2	17 (85.0)	73 (80.2)	
Comorbid conditions			0.206
Yes	6 (30.0)	15 (16.5)	
No	14 (70.0)	76 (83.5)	
Performance status score			0.150
0	18 (90.0)	89 (97.8)	
1	2 (10.0)	2 (2.2)	
FIGO stage			0.455
I	12 (60.0)	64 (70.3)	
II	4 (20.0)	8 (8.8)	
III	4 (20.0)	17 (18.7)	
IV	0 (0.0)	2 (2.2)	
Residual tumor			0.715
Yes	3 (15.0)	11 (12.1)	
No	17 (85.0)	80 (87.9)	
Best response			0.923
CR/PR	1 (33.3)	4 (36.3)	
SD/PD	2 (66.7)	7 (63.7)	
Ascites			0.228
Yes	13 (65.0)	45 (49.5)	
No	7 (35.0)	46 (50.5)	
Recurrence			0.048
Yes	13 (65.0)	36 (39.6)	
No	7 (35.0)	55 (60.4)	
Pattern of recurrence			0.025
Platinum-sensitive recurrence	2 (15.4)	19 (52.8)	
Platinum-resistant recurrence	11 (84.6)	17 (47.2)	
Immunohistochemistry staining			
TF (%)			0.030
Positive	18 (90.0)	51 (63.0)	
Negative	2 (10.0)	30 (37.0)	
IL-6 (%)			0.625
Positive	11 (55.0)	39 (48.2)	
Negative	9 (45.0)	42 (51.8)	
JAK2 (%)			0.034
Positive	11 (55.0)	23 (28.4)	
Negative	9 (45.0)	58 (71.6)	
STAT3 (%)			0.203
Positive	11 (55.0)	30 (37.0)	
Negative	9 (45.0)	51 (63.0)	

Comorbid conditions include hypertension, diabetes, heart disease, hyperlipidemia, stroke, allergic immune disorders. Among all patients, the incidence of recurrence is 13 with TEEs and 21 without CAT. Platinum-sensitive recurrence is defined as a disease that recurs more than six months after the final cycle of first-line chemotherapy, while platinum-resistant recurrence is defined as a disease that recurs less than six months from the final cycles of first-line chemotherapy to recurrence or progression within less than six months. The best response variable included only OCCC patients with residual tumor. CAT, cancer-associated thromboembolism; FIGO, International Federation of Gynecology and Obstetrics; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; TF, tissue factor; IL-6, interleukin-6; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3.

Table IV. Univariate and multivariate analysis for progression-free survival and overall survival in all patients.

	Progression-free survival						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variable	HR	95% confidence interval	P-value	HR	95% confidence interval	P-value	HR	95% confidence interval	P-value	HR	95% confidence interval	P-value
Age at diagnosis												
≥65 years vs. <65 years	1.43	0.74-2.60	0.277				1.46	0.61-3.19	0.374			
Body mass index												
≥25 vs. <25 kg/m^2	1.17	0.55-2.26	0.648				1.22	0.48-2.71	0.656			
Complications												
Yes vs. no	1.21	0.56-2.38	0.599				1.12	0.41-2.62	0.801			
Performance status score												
≥1 vs. 0	2.43	0.59-6.73	0.166				3.55	0.57-12.1	0.147			
FIGO stage												
II-IV vs. I	4.31	2.42-7.73	<0.01	3.46	1.77-6.70	<0.01	3.10	1.49-6.48	<0.01	1.87	0.76-4.38	0.170
Residual tumor												
Yes vs. no	3.07	1.44-6.00	<0.01	1.35	0.58-2.99	0.471	4.18	1.72-9.22	<0.01	3.53	1.25-9.77	0.018
Ascites												
Yes vs. no	1.94	1.09-3.56	0.022	1.13	0.59-2.22	0.699	1.71	0.83-3.67	0.146			
CAT												
Yes vs. no	2.52	1.25-4.74	0.011	2.10	1.03-3.97	0.039	3.68	1.59-7.87	<0.01	4.26	1.77-9.57	<0.01

CAT, cancer-associated thromboembolism; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ration.

tumor microenvironment. Thus, TF and JAK2 are potential therapeutic candidates for OCCC.

From this perspective, several potential therapeutic targets for OCCC with CAT are candidates for new treatments that target the TF and JAK pathways compared with other histologic subtypes. The Phase 1-2 trial demonstrated that the objective response rate of tisotumab vedotin (TV), an antibody-drug conjugate against TF expressed on the cell surface of tumor cells, was five out of 36 (13.9%) (29). However, the expression varied among the histological subtypes and was most frequently found in OCCC. However, it was unclear whether OCCC was included in this clinical trial. Therefore, TV treatment was feasible. A clinical trial of TV for platinum-resistant ovarian cancer is ongoing (NCT03657043) (30). In IL-6/JAK2/STAT3 pathway, two studies have demonstrated that siltuximab, a humanized anti-IL-6 antibody, and tocilizumab, a humanized anti-human IL-6 receptor antibody, inhibit the proliferation of ovarian cancer cells (31,32). Recently, clinical trials have explored the role of ruxolitinib, a JAK/STAT inhibitor, in solid tumors (33). A phase I/II randomized clinical trial (NCT02713386) investigated the combination chemotherapy of ruxolitinib with paclitaxel and carboplatin for epithelial ovarian, fallopian tube, and primary peritoneal cancers. The study demonstrated that ruxolitinib was well tolerated and prolonged the PFS (34). As another potential therapy for OCCC, aspirin use might reduce the mortality of ovarian cancer, and aspirin and other nonsteroidal anti-inflammatory drugs might improve the prognosis owing to their anti-platelet activity (35,36).

The limitations of this study are its retrospective design, single-center analysis, and small sample size. In this study, only immunohistochemistry was used to validate the activity of the signaling pathways. And, we could not suggest any further analysis of the molecular mechanisms which CAT may affect outcomes in OCCC. Further studies using other experimental techniques and methods are required for a comprehensive validation. Moreover, studies with larger sample sizes are warranted to identify the clinical significance of the association between OCCC and CAT, and to evaluate other coagulation factors in OCCC.

In conclusion, our study found that the development of CAT was a poor prognostic factor related to platinum resistance and that TF and JAK2/STAT3 were associated with the occurrence of CAT in OCCC. Further studies are required to prevent and treat CAT in patients with OCCC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TI, MM, TH, SK and MT contributed to the study conception and design. Material preparation, data collection and analysis were carried out by TI, NK, JS and KK. All authors contributed to the data interpretation. MM and TH confirm the authenticity of all the raw data. The first draft of the manuscript was written by TI, and all authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Defense Medical College (Tokorozawa, Japan) on January 20, 2021, approval no. 4346. Records and information of all patients in this study were fully anonymized before the analysis to prevent the disclosure of their identities. Before the treatment, written informed consent for participation was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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