Am J Cancer Res 2025;15(11):4753-4764
www.ajcr.us /ISSN:2156-6976/ajcr0168689

Original Article

Comparative effectiveness of paclitaxel versus cyclophosphamide in platinum-based adjuvant treatment of high-risk early-stage epithelial ovarian cancer: an Asian population study

Mei-Yi Lin[1], Hao Lin[1], Yu-Che Ou[1], Hung-Chun Fu[1], En-Ling Sung[1], Chien-Hsiang Kao[1], Chen-Hsuan Wu[1,2]

[1]Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan; [2]Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan

Received September 9, 2025; Accepted October 25, 2025; Epub November 15, 2025; Published November 30, 2025

Abstract: In Taiwan, approximately half of ovarian cancer cases are diagnosed at an early stage. Although platinum-based adjuvant chemotherapy is recommended for high-risk early-stage epithelial ovarian cancer (EOC), the optimal regimen remains uncertain. Paclitaxel (PTX) is widely used based on evidence from advanced-stage disease, yet data comparing PTX and cyclophosphamide (CTX) in early-stage settings are limited. We retrospectively reviewed medical records of FIGO stage I-II EOC patients with high-risk features who received post-operative platinum-based chemotherapy with either PTX or CTX at Kaohsiung Chang Gung Memorial Hospital from January 2011 to December 2018. We analyzed associations between clinical characteristics, chemotherapy regimen, and survival outcomes. Baseline characteristics were compared using Chi-square tests for categorical variables and independent two-sample t-tests for continuous variables. Survival analysis was conducted using Kaplan-Meier and Cox regression methods. A total of 125 patients were included (mean age: 50.0 years), of whom 27.2%, 48.8%, and 24.0% were diagnosed with FIGO stage IA/IB, IC, and II, respectively. Clear cell (37.6%) and endometrioid (27.2%) carcinomas were the most common histologies. Eighty-one patients (64.8%) received PTX, and 44 (35.2%) received CTX. Multivariate analysis identified FIGO stage as the only independent predictor of disease-free survival (DFS; HR, 3.39; $P = 0.046$), while the chemotherapy regimen was not significantly associated with DFS (HR 2.58; $P = 0.111$). Since stage I patients constituted the majority of the cohort, we performed a subgroup analysis restricted to stage I patients, which similarly demonstrated no significant DFS difference between the two chemotherapy regimens ($P = 0.377$). CTX demonstrated comparable DFS outcomes to PTX in high-risk early-stage EOC. These findings support the use of CTX as a viable adjuvant chemotherapy alternative to PTX, particularly in Asian populations where clear cell and endometrioid histologies are more prevalent.

Keywords: Ovarian neoplasms, adjuvant chemotherapy, cyclophosphamide, paclitaxel, survival

Introduction

Epithelial ovarian cancer (EOC), which accounts for 90-95% of all ovarian malignancies, remains the most lethal gynecologic malignancy - primarily due to delayed diagnosis and the absence of effective screening methods [1, 2]. Unlike global trends, Taiwan demonstrates a higher proportion of early-stage diagnoses, likely attributable to routine gynecologic evaluations and broad accessibility to pelvic imaging [3]. Supporting this observation, 2021 data from the Taiwan Cancer Registry indicated that approximately 47% of ovarian cancers were confined to the ovaries (stage I) or limited to the pelvis (stage II) at diagnosis [4]. Given this high proportion, optimizing treatment for early-stage cases remains a clinical priority.

Current guidelines recommend comprehensive staging surgery - including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washings, and retroperitoneal lymphadenectomy - as the standard of care for early-stage EOC [5]. In those with low-risk tumors, such as FIGO stage IA or IB with well- or moderately differentiated histology, omission of adjuvant chemotherapy is considered safe [6]. In

https://doi.org/10.62347/VNGO9832

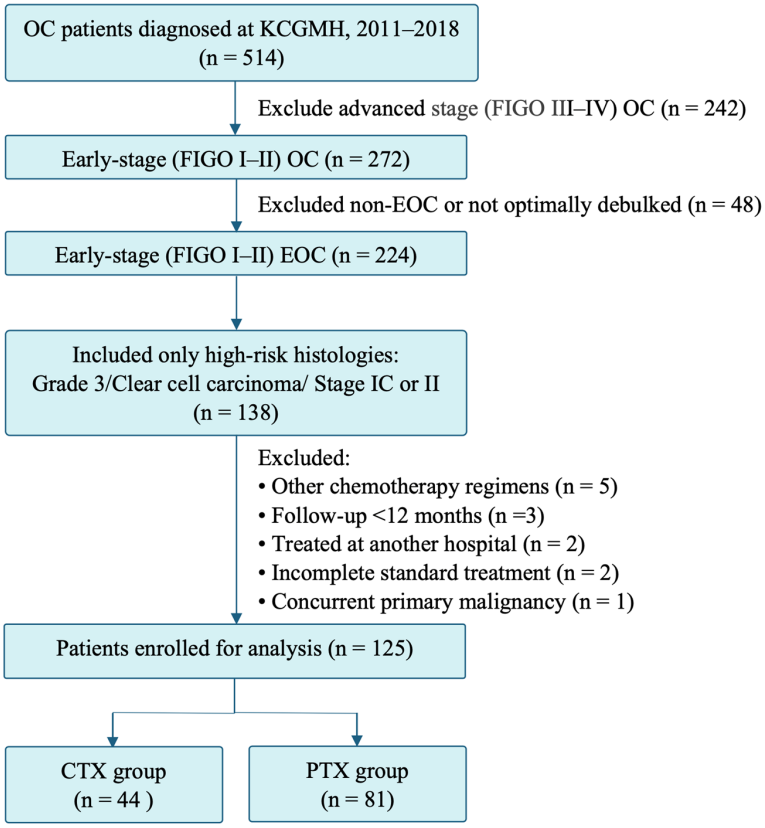

Figure 1. Flowchart of patient selection and inclusion process.

contrast, adjuvant chemotherapy is generally recommended for high-risk features (e.g., FIGO IC/II, high-grade histology, or clear cell type). Although trials like ICON1 and ACTION confirmed the survival benefit of platinum-based chemotherapy in early-stage disease, the optimal combination regimen remains uncertain [7, 8].

In practice, paclitaxel (PTX) is often chosen in platinum-based regimens due to its efficacy in advanced EOC [9, 10], but data comparing PTX with agents like cyclophosphamide (CTX) in early-stage disease are limited. Given the lack of consensus regarding the optimal platinum-based regimen, we conducted this retrospective study to compare the clinical outcomes of PTX and CTX in high-risk early-stage EOC.

Material and methods

Study population and treatment protocol

We retrospectively reviewed patients diagnosed with EOC at Kaohsiung Chang Gung Memorial Hospital between January 2011 and December 2018. Eligibility was limited to FIGO (Inter-national Federation of Gynecology and Obstetrics) stage I-II disease. Included patients had high-risk early-stage disease (stage IC or II, or grade 3/clear cell tumors) treated with platinum-based adjuvant chemotherapy (PTX or CTX) following optimal cytoreductive surgery. We excluded patients with non-epithelial histologies, suboptimal debulking, early-stage low-risk disease (e.g., FIGO stage IA/IB, grade 1-2 non-clear cell histologies), chemotherapy administered elsewhere, incomplete chemotherapy course due to toxicity, or concurrent major malignancies (e.g., synchronous FIGO stage II endometrial carcinoma). Patients with follow-up <12 months were also excluded to ensure sufficient event observation. The detailed inclusion and exclusion process is illustrated in **Figure 1**.

Surgical approaches were categorized as follows: (1) complete staging surgery (including restaging procedures), (2) fertility-sparing unilateral salpingo-oophorectomy with lymphadenectomy, (3) unilateral or bilateral salpingo-oophorectomy without lymphadenectomy, and (4) abdominal total hysterectomy with bilateral salpingo-oophorectomy without lymphadenectomy. All patients achieved optimal cytoreduction, defined as no gross residual disease which were confirmed through operative reports. For patients with pathologically confirmed ovarian cancer who did not undergo standard staging surgery, postoperative imaging was reviewed to confirm the absence of residual disease.

All patients received platinum-based adjuvant chemotherapy every three weeks, consisting of either PTX (175 mg/m^2) plus carboplatin (AUC 5) or CTX (750 mg/m^2) plus cisplatin (75 mg/m^2). FIGO stage I patients received three to six cycles based on histologic risk, while all stage II

patients received six cycles. Targeted therapies were not administered to any patient in this cohort.

Treatment allocation

The choice between CTX-platinum and PTX-platinum was determined through shared decision-making (SDM) between the attending gynecologic oncologist and the patient, in accordance with standard clinical practice in Taiwan for early-stage ovarian cancer. Patients were informed of the common adverse effects of each regimen - alopecia and peripheral neuropathy with PTX versus bone marrow suppression, nausea, and vomiting with CTX to facilitate an informed discussion. In Taiwan, CTX regimens are fully reimbursed for stage I-II ovarian cancer, whereas PTX are reimbursed only for advanced-stage disease and therefore require out-of-pocket payment for early-stage cases; therefore, financial considerations were also discussed. Patient age and anticipated drug tolerance were also evaluated to support individualized selection. No formal treatment protocol or randomization was applied, as this reflects real-world, equitable allocation without exclusionary criteria beyond standard clinical eligibility.

Data collection and follow-up assessment

Clinical data were extracted from electronic records and independently reviewed by two investigators; discrepancies were resolved by consensus. Laboratory and pathology data were verified according to standardized hospital formats. Data collection followed a predefined protocol and included patient demographics, FIGO stage, histologic subtype, surgical procedures, chemotherapy regimen, and pretreatment laboratory values (platelet count, CA125), defined as those obtained prior to surgery. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (No. 202400936B0) and conducted in accordance with the Declaration of Helsinki.

Post-treatment follow-up monitored disease recurrence and survival. Patients were followed every 2-4 months for the first 2 years, every 3-6 months during years 3-5, and at individualized intervals thereafter. Treatment outcomes were assessed retrospectively according to RECIST guidelines and CA125 response criteria established by the Gynecological Cancer Intergroup [11].

Statistical analysis

Statistical analyses were conducted using SPSS software (version 25.0; IBM Corporation). Baseline characteristics were compared using the Chi-square test for categorical variables and the independent two-sample t-test for continuous variables. Disease-free survival (DFS) and disease-specific survival (DSS) were used to evaluate treatment efficacy. DFS was defined as the interval from the completion of chemotherapy to either disease recurrence or the last follow-up without recurrence. DSS was defined as the interval between the date of primary surgery and the date of cancer-related death or the last follow-up.

Survival curves were estimated using the Kaplan-Meier method, with between-group comparisons performed using the log-rank test. Multivariate analyses were conducted using Cox proportional hazards regression models. For variables with unstable estimates, Firth's penalized maximum likelihood method was applied to improve reliability. A two-sided *p*-value <0.05 was considered statistically significant.

Results

Patient characteristics and comparable clinical variables between PTX and CTX groups

A total of 125 patients were enrolled (mean age, 50.0 years; median follow-up, 75.6 months). Baseline characteristics are shown in **Table 1**. FIGO stages IA/IB, IC, and II were observed in 34 (27.2%), 61 (48.8%), and 30 (24.0%) patients, respectively. Clear cell carcinoma (CCC) was the most common histologic subtype (37.6%), followed by endometrioid carcinoma (EMC, 27.2%), high-grade serous carcinoma (HGSC, 15.2%), and mucinous carcinoma (8.8%). At diagnosis, 85 patients (68.0%) had CA125 levels >35 U/mL, and 101 patients (80.8%) had platelet counts $<400\times10^9$/L. Of all patients, 81 (64.8%) received PTX and 44 (35.2%) received CTX. **Table 2** compares clinical variables between the two groups. No significant differences were observed in age, histologic type, platelet count, or CA125 levels.

Table 1. Clinicopathological characteristics of all patients (n = 125)

Age, mean (SD, range)	50.0 (11.3, 24-80)
Follow-up, months, median (range)	75.6 (21.0-141)
FIGO stage, n (%)	
IA/IB	34 (27.2)
IC	61 (48.8)
II	30 (24.0)
Histology, n (%)	
HGSC	19 (15.2)
Non-HGSC	106 (84.8)
CCC	47 (37.6)
EMC	34 (27.2)
Low grade	31 (24.8)
High grade	3 (2.4)
Mucinous	11 (8.8)
LGSC	6 (4.8)
Mixed	6 (4.8)
Adenocarcinoma	2 (1.6)
Pretreatment platelet, n (%)	
$<40\times10^4$/uL	101 (80.8)
$\geq40\times10^4$/uL	21 (16.8)
Missing	3 (2.4)
Pretreatment CA-125, n (%)	
<35 U/mL	20 (16.0)
≥35 U/mL	85 (68.0)
Missing	20 (16.0)
C/T regimen, n (%)	
Paclitaxel	81 (64.8)
Cyclophosphamide	44 (35.2)

CCC = clear cell carcinoma; C/T = chemotherapy; EMC = endometrioid carcinoma; HGSC = high grade serous carcinoma; LGSC = low grade serous carcinoma; n = number; SD = standard deviation.

However, a significant imbalance was noted in FIGO stage distribution: 29 of 30 (96.7%) stage II patients received PTX, while only one received CTX ($P<0.001$). This reflects the retrospective and non-randomized nature of treatment allocation.

FIGO stage drives prognosis while chemotherapy regimens show equivalent outcomes

Univariate analysis revealed that FIGO stage was the only factor significantly associated with DFS (stage II vs. stage I: HR, 2.45; 95% CI, 1.04-5.74; $P = 0.039$), and showed a borderline association with DSS (HR, 2.89; 95% CI, 0.98-8.47; $P = 0.054$). In contrast, the chemotherapy regimen was not significantly associated with DFS or DSS (**Table 3**). The 5-year DFS rates were 61.7% in the PTX group and 68.2% in the CTX group ($P = 0.687$), while the 5-year DSS rates were 69.1% and 77.3%, respectively ($P = 0.472$) (**Figure 2**). Subgroup analysis for histologic subtype also showed no significant association with either survival endpoint in univariate analysis (**Figure 3**). Multivariate analysis (**Table 4**) confirmed FIGO stage as the only independent predictor of DFS (stage II vs. stage I: HR, 3.39; 95% CI, 1.02-11.20; $P = 0.046$), while the association with DSS approached significance (HR, 3.89; 95% CI, 0.94-17.99; $P = 0.082$). Chemotherapy regimen remained non-significant for DFS (HR, 2.58; 95% CI, 0.81-8.24; $P = 0.111$) and DSS (HR, 2.06; 95% CI, 0.47-9.19; $P = 0.347$).

Stage I subgroup: clear cell histology marginally affects prognosis while regimen choice does not

To further evaluate prognostic factors in stage I patients, a multivariate Cox regression analysis was performed (**Table 5**). Compared to non-clear cell carcinoma (non-CCC), CCC showed a marginal association with poorer DFS (HR, 5.27; 95% CI, 1.16-49.97; $P = 0.082$), although this trend was not observed for DSS (HR, 5.73; 95% CI, 0.54-783.69; $P = 0.321$). In contrast, patients with EMC did not differ significantly from those with non-endometrioid histology in terms of DFS (HR, 0.98; $P = 0.983$) or DSS (HR, 1.21; $P = 0.921$). Notably, the chemotherapy regimen (PTX vs. CTX) was not significantly associated with DFS (HR, 1.72; 95% CI, 0.54-5.64; $P = 0.377$) or DSS (HR, 1.91; 95% CI, 0.40-9.06; $P = 0.443$). In stage II, only one patient received CTX. Due to the extremely limited sample size, statistical comparison between chemotherapy regimens in this subgroup was not feasible.

Discussion

Our study demonstrates that CTX plus platinum is not inferior to PTX plus platinum as adjuvant chemotherapy for high-risk early-stage EOC. In our cohort of 125 patients, FIGO stage was the strongest predictor of PFS, while chemotherapy regimen showed no significant association with either DFS or DSS. Among stage I patients, survival did not differ between regimens. These findings suggest that CTX offers comparable

Table 2. Factors associated with chemotherapy regimen in patients of stage I-II epithelial ovarian cancer (n = 125)

Chemotherapy regimen	Paclitaxel n = 81	Cyclophosphamide n = 44	*p* value
Age, years			0.652
mean (SD)	50.4 (12.2)	49.4 (9.6)	
Stage, n (%)			<0.001
IA/IB	18 (22.2)	16 (36.4)	
IC	34 (42.0)	27 (61.4)	
II	29 (35.8)	1 (2.3)	
Histology, n (%)			
CCC	32 (39.5)	15 (34.1)	0.551
Non-CCC	49 (60.5)	29 (65.9)	
EMC	19 (23.5)	15 (34.1)	0.202
Non-EMC	62 (76.5)	29 (65.9)	
HGSC	15 (18.5)	4 (9.1)	0.199
Non-HGSC	66 (81.5)	40 (90.9)	
Platelet[a], 10^4/uL			0.532
mean (SD)	31.8 (9.9)	30.6 (10.7)	
CA-125[b], U/mL			0.205
medium (IQR)	269.3 (707.3)	67.1 (468.6)	

[a]total n = 122, [b]total n = 105. CCC = clear cell carcinoma; EMC = endometrioid carcinoma; HGSC = high grade serous carcinoma; IQR = interquartile range; n = number; SD = standard deviation.

efficacy across common histologic subtypes in Asia patients, focus on CCC and EMC, providing clinicians greater flexibility in treatment selection.

Adjuvant chemotherapy strategies in early-stage EOC

Patients with stage IA or IB EOC and favorable histology who undergo comprehensive staging have >90% 5-year disease-free survival [12]. Adjuvant therapy is generally not required in this group. In contrast, approximately 25-45% of early-stage patients with high-risk features (stage IC/II, clear cell histology, or grade 3 tumors) develop recurrence despite surgery [10]. Although early-stage EOC has a favorable prognosis, post-recurrence survival is poor and similar to advanced disease [3]. Adjuvant chemotherapy is therefore warranted in high-risk patients. Randomized trials have established platinum-based regimens (cisplatin or carboplatin) as the standard adjuvant therapy for early-stage EOC [6, 7, 10]. For patients with early-stage ovarian cancer, there is still no consensus on the optimal regimen in platinum-based doublets.

The role of cyclophosphamide in platinum-based chemotherapy for ovarian cancer

In the 1960s, alkylating agents such as melphalan and CTX were the mainstay of treatment for advanced ovarian cancer. Since the mid-1970s, a series of trials have established cisplatin as one of the most active agents for ovarian cancer. Combination therapy with cisplatin and an alkylating agent became the standard of care for about a decade, based on trials demonstrating improved outcomes over monotherapy [13, 14], and no added benefit from three-drug regimens [15, 16]. The Gynecologic Oncology Group (GOG) 95 trial investigated adjuvant strategies for early-stage EOC, enrolling 205 patients with stage IA/IB (grade 3), and stage IC or IIA disease. Following surgery, patients were assigned to receive either intravenous cisplatin plus CTX or intraperitoneal phosphorus-32. Although overall survival was similar, the cisplatin-CTX group showed a lower cumulative recurrence rate, supporting its use as preferred adjuvant chemotherapy for this patient population [17].

The introduction of paclitaxel in ovarian cancer chemotherapy

Paclitaxel, a diterpenoid extracted from the Pacific yew tree (*Taxus brevifolia*), was discovered in the early 1960s. It exerts cytotoxic effects by promoting tubulin polymerization, stabilizing microtubules, and inhibiting chromosome separation during mitosis. In the 1980s, taxol was introduced as an effective treatment for ovarian cancer. Two pivotal trials - GOG No. 111 [9] and the EORTC/National Cancer Institute of Canada (NCIC) OV10 [8] - demonstrated that cisplatin-PTX significantly improved response rates, progression-free survival, and overall survival compared to cisplatin-CTX in advanced ovarian cancer. The success of PTX-platinum combinations in advanced disease prompted their adoption in high-risk early-stage ovarian cancer. Platinum-CTX regimens remain

Table 3. Univariate analysis of factors associated disease-free survival (DFS) and disease-specific survival (DSS) (n = 125)

Factors	DFS			DSS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, years						
(≥50 vs. <50)	1.77	0.74-4.23	0.197	1.38	0.47-4.00	0.556
FIGO stage						
(IC vs. IA/IB)	1.31	0.40-4.25	0.655	0.60	0.15-2.39	0.466
(II vs. I)	2.45	1.04-5.74	0.039	2.89	0.98-8.47	0.054
Histology						
(CCC vs. non-CCC)	2.14	0.92-4.95	0.076	2.26	0.79-6.54	0.132
(EMC vs. non-EMC)	0.38	0.11-1.29	0.120	0.20	0.03-1.50	0.116
(HGSC vs. non-HGSC)	1.25	0.42-3.70	0.684	1.62	0.45-5.84	0.464
Platelet, 10^4/uL						
(≥40 vs. <40)	0.84	0.25-2.85	0.777	1.36	0.37-4.94	0.641
CA-125, U/mL						
(≥35 vs. <35)	4.26	0.57-32.02	0.159	28.63	0.05-1.610[4]	0.301
C/T regimen						
(Paclitaxel vs. Cyclophosphamide)	0.83	0.34-2.04	0.688	0.65	0.20-2.11	0.471

CCC = clear cell carcinoma; C/T = chemotherapy; DFS = disease-free survival; DSS = disease-specific survival; EMC = endometrioid carcinoma; HGSC = high grade serous carcinoma; HR = hazard ratio; n = number.

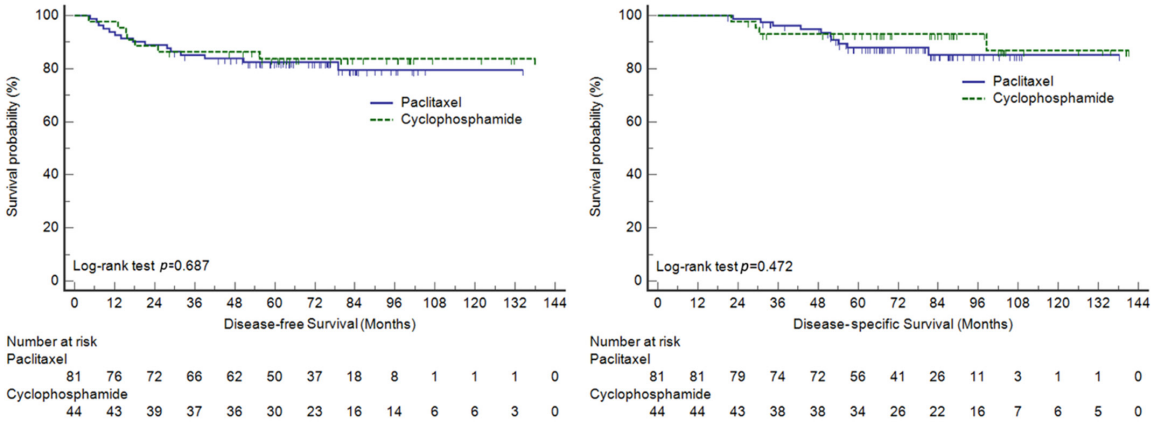

Figure 2. Kaplan-Meier analysis of disease-free survival (left) and disease-specific survival (right) in patients treated with paclitaxel versus cyclophosphamide in stage I/II patients.

under investigation for potential benefit in selected subgroups.

In elderly patients with advanced ovarian cancer, the comparative effectiveness of platinum-based combinations has been explored in limited studies. In two sequential trials analyzed by Trédan et al., patients aged ≥70 years receiving PTX-carboplatin had more favorable baseline characteristics but showed no survival advantage over CTX-based therapy [18]. The lack of benefit from PTX in this population may reflect age-related pharmacokinetic changes and poorer treatment tolerance, leading to frequent dose reductions and early discontinuation. In contrast, our study focused on a younger early-stage cohort (mean age, 50 years) and found no significant difference in survival outcomes between CTX- and PTX-based regimens among patients aged <50 or ≥50 years, suggesting that treatment efficacy was not age-dependent in this setting. However, subgroup analysis results from other early-stage studies have been inconsistent. For example, Chen et al. (mean age, 49 years) reported poorer 5-year DFS and DSS in patients aged >50 receiving

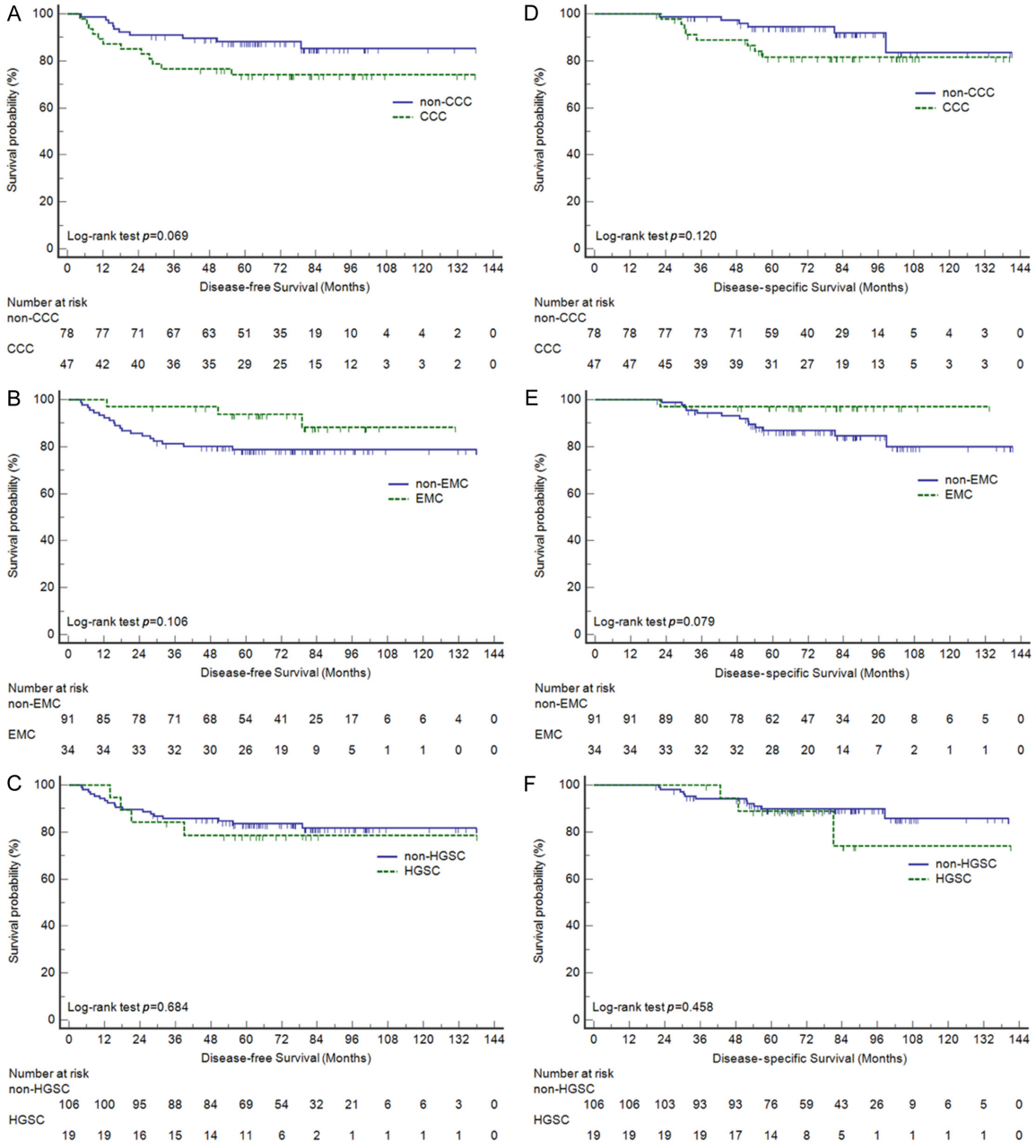

Figure 3. Kaplan-Meier curves of disease-free survival (A-C) and disease-specific survival (D-F) stratified by histologic subtype: clear cell carcinoma (CCC), endometrioid carcinoma (EMC), and high-grade serous carcinoma (HGSC) in stage I/II patients.

CTX-platinum [19]. This variability in age-related outcomes highlights the need for further validation in homogeneous early-stage cohorts.

Comparative studies on CTX and PTX regimens in high-risk early stage EOC

The role of CTX in platinum-based adjuvant chemotherapy for high-risk early-stage EOC has been investigated in several studies [19-21]. Garcia-Saenz et al. reported similar 5-year relapse-free survival (73% vs. 71%) and DSS (84% vs. 76%) between non-taxane and taxane-based regimens, with no statistically significant differences [20]. A Taiwanese retrospective study also demonstrated comparable 5-year DFS and overall survival between platinum-PTX and platinum-CTX regimens across

Table 4. Multivariate Cox regression analyses of factors associated with disease-free survival (DFS) and disease-specific survival (DSS) in stage I-II patients (n = 125)

Factors	DFS			DSS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, years						
(≥50 vs. <50)	1.54	0.58-4.12	0.386	0.91	0.26-3.04	0.877
FIGO stage						
(II vs. I)	3.39	1.02-11.20	0.046	3.89	0.94-17.99	0.082
Histology						
(CCC vs. non-CCC)	2.40	0.63-9.20	0.200	2.92	0.63-19.11	0.235
(EMC vs. non-EMC)	0.35	0.06-2.27	0.274	0.54	0.04-4.94	0.608
(HGSC vs. non-HGSC)	0.46	0.07-3.18	0.430	0.71	0.06-6.95	0.790
Platelet, 10^4/uL						
(≥40 vs. <40)	0.69	0.19-2.56	0.583	1.15	0.25-4.21	0.856
CA-125, U/mL						
(≥35 vs. <35)	6.68	0.83-53.49	0.074	6.26	0.69-833.15	0.254
C/T regimen						
(Paclitaxel vs. Cyclophosphamide)	2.58	0.81-8.24	0.111	2.06	0.47-9.19	0.347

CCC = clear cell carcinoma; C/T = chemotherapy; DFS = disease-free survival; DSS = disease-specific survival; EMC = endometrioid carcinoma; HGSC = high grade serous carcinoma; HR = hazard ratio; n = number.

Table 5. Multivariate Cox regression analyses of factors associated with disease-free survival (DFS) and disease-specific survival (DSS) in stage I patients (n = 95)

Variables	Comparison	n (%)	DFS		DSS	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
Histology	CCC	39 (41.1)	5.27 (1.16-49.97)	0.082	5.73 (0.54-783.69)	0.321
	Non-CCC	56 (58.9)	1		1	
	EMC	29 (30.5)	0.98 (0.13-10.81)	0.983	1.21 (0.06-177.92)	0.921
	Non-EMC	66 (69.5)	1		1	
CA-125[a]	≥35	62 (78.5)	12.68 (1.51-1655.80)	0.110	4.70 (0.45-644.23)	0.357
	<35	17 (21.5)	1		1	
C/T regimen	PTX	52 (54.7)	1.72 (0.54-5.64)	0.377	1.91 (0.40-9.06)	0.443
	CTX	43 (45.3)	1		1	

[a]total n = 79. CCC = clear cell carcinoma; C/T = chemotherapy; CTX = cyclophosphamide; DFS = disease-free survival; DSS = disease-specific survival; EMC = endometrioid carcinoma; HR = hazard ratio; n = number; PTX = Paclitaxel.

early-stage subgroups (IA/IB, IC, and II) [21]. Our findings are consistent with these studies, indicating that CTX is not inferior to PTX in platinum-based adjuvant chemotherapy for high-risk early-stage EOC.

Nevertheless, subgroup analyses from previous studies have yielded inconsistent results. Hsieh et al. reported that patients with CCC had significantly better survival outcomes with taxane-based regimens compared to non-taxane regimens [21]. In our cohort, CCC and EMC were the two most common histologic subtypes, particularly among earlier cases. Therefore, we performed subgroup analyses specifically focusing on CCC and EMC, which are more prevalent in East Asian populations. Importantly, DFS and DSS were comparable between the CTX and PTX groups in patients with either CCC or EMC, reinforcing that CTX-based regimens are not inferior to PTX in these predominant histologic subtypes.

Biologic basis for the comparable efficacy of CTX and PTX across clear cell and endometrioid subtypes

The comparable efficacy of CTX- and PTX-based regimens in our cohort may reflect histotype-specific chemosensitivity. Compared with

HGSC, which is typically sensitive to both platinum and taxane due to *TP53* mutation and genomic instability [22, 23], CCC and EMC harbor distinct molecular alterations that influence drug response. CCC frequently carries AT-rich interactive domain-containing protein 1A (*ARID1A)* mutations and activation of the PI3K/AKT-mTOR pathway, both linked to reduced sensitivity to microtubule-targeting agents such as PTX [24, 25]. Similarly, EMC exhibits PTEN loss, *PIK3CA* or *ARID1A* mutations [26, 27], and occasional β-tubulin III overexpression, which may limit taxane efficacy while maintaining susceptibility to DNA-damaging agents [28, 29]. CTX, through DNA alkylation and inter- or intra-strand cross-linking by its active metabolite phosphoramide mustard, induces double-strand DNA breaks and apoptosis [30, 31]. This DNA-directed mechanism, independent of microtubule stabilization, may remain active in tumors with taxane-resistant molecular profiles, providing a biologic rationale for the comparable outcomes observed in these subtypes.

Adverse effects of paclitaxel limit its use despite proven efficacy

Although platinum-PTX doublets improve outcomes in advanced ovarian cancer, concerns remain regarding its adverse effects. GOG 111 showed that PTX carries higher risks of severe hypersensitivity, neutropenia, alopecia, and neurotoxicity compared to CTX [9]. A European-Canadian trial of cisplatin-PTX versus cisplatin-CTX in 680 patients with advanced EOC reported higher rates of hypersensitivity (4% vs. 1%) and grade 3-4 neurotoxicity (19.6% vs. 1%) in the PTX group [8]. Minor hypersensitivity reactions occur in approximately 40% of patients receiving PTX regimen; notably, 3% experience life-threatening reactions despite premedications. Neurotoxicity occurs in 60-80% of patients, with severe symptoms in 2-33% [32]. Currently, no effective treatments or preventive measures are available. Conversely, the CTX group had higher rates of grade 3-4 thrombocytopenia, nausea, and vomiting [8]. Nausea and vomiting are generally manageable and preventable with supportive medications. CTX-induced thrombocytopenia was rarely associated with complications, and overall risk differences between the two groups were modest.

Limited prognostic value of CA125 in early-stage epithelial ovarian cancer

While the comparable efficacy between PTX and CTX regimens supports treatment flexibility based on toxicity considerations, our analysis also revealed that traditional prognostic markers showed limited utility in early-stage disease. Pretreatment CA125 levels were not significantly associated with prognosis in either univariate or multivariate analysis for both DFS and DSS, indicating that CA125 levels do not influence outcomes in early-stage disease. This may reflect the cohort's histological composition, predominantly stage I-II cases with CCC and EMC, and relatively few HGSC - the subtype most strongly associated with CA125 elevation. Given that clear cell and endometrioid tumors typically produce less CA125 in early stages [33, 34], the lack of independent prognostic significance of pretreatment CA125 is both biologically plausible and clinically relevant. This aligns with multiple studies demonstrating that tumor marker levels in stage I and II were not correlated with survival [35], whereas CA125 prognostic value is primarily observed in advanced-stage disease and high-grade serous histology [36]. Recent studies have also shown that CA125 dynamic changes, particularly half-life rather than pretreatment levels, were the most important independent prognostic factors in EOC [37].

Lack of prognostic impact of thrombocytosis in early-stage disease

Similarly, elevated platelet count did not demonstrate independent prognostic significance in our early-stage EOC cohort. Thrombocytosis is frequently observed in advanced-stage (FIGO III-IV) ovarian cancer and is positively associated with tumor burden [38, 39]. It is also an independent predictor of poor survival, with hazard ratios ranging from 1.4 to 2.0 in this population [40]. In contrast, its prognostic role in early-stage disease remains unclear, as most studies have focused on advanced tumors with elevated interleukin-6 (IL-6) and thrombopoietin levels [41]. Moreover, most evidence is based on HGSC, with limited data in clear cell and endometrioid subtypes, which predominated in our cohort and differ biologically [2, 42]. This lack of prognostic impact is biologically plausible, as IL-6 - induced thrombopoietin-driv-

en thrombocytosis is more evident in advanced-stage disease with greater tumor burden and has been primarily described in serous histology [41]. Our findings suggest that FIGO stage remains the key prognostic factor in high-risk early-stage EOC with predominant clear cell and endometrioid histology, while routine pre-treatment CA125 and platelet counts may offer limited prognostic utility in this population.

Limitations

This retrospective, single-institution study is subject to potential selection bias and may limit the generalizability of the findings. The relatively small number of stage II patients reduced statistical power and precluded reliable subgroup analysis. Moreover, the modest sample size restricted detailed age-stratified analyses (e.g., across finer age bands or including older patients), potentially masking subtle age-specific differences in regimen efficacy that may emerge in broader populations. Treatment allocation was non-randomized, with more stage II patients receiving PTX, likely reflecting both physician preference and limited case numbers, which also constrained the feasibility of propensity score matching. Additionally, the absence of toxicity profiles and patient-reported outcomes limited our ability to assess regimen tolerability, and the current lack of ongoing clinical trials comparing CTX-platinum and PTX-platinum regimens in early-stage disease further underscores the need for prospective studies to evaluate safety and efficacy endpoints. Although histologic subtype and FIGO stage were considered in our analysis, future multicenter prospective studies are warranted to validate these findings and further explore molecular or immunologic predictors of treatment response.

Conclusion

This study demonstrates that CTX combined with platinum is not inferior to PTX-based regimens as adjuvant chemotherapy for high-risk early-stage EOC. In this predominantly stage I/II Taiwanese cohort with a high proportion of clear cell and endometrioid histologies, FIGO stage remained the key prognostic factor. Given that PTX is not reimbursed under Taiwan's National Health Insurance for early-stage patients, CTX may represent a more cost-effective alternative. For patients concerned about neurotoxicity, hypersensitivity reaction, or cost, CTX provides comparable efficacy with potentially improved tolerability and accessibility.

Acknowledgements

We thank Biostatistics Center, and Kaohsiung Chang Gung Memorial Hospital for assistance with the statistical analysis in this study. ChatGPT (OpenAI; accessed August 2025) was used to assist with English language editing (grammar and stylistic refinement). It was not used to generate scientific content, analyze data, perform statistical tests, or cite references, and no confidential or patient-level data were input. All authors critically reviewed AI-suggested edits and approved the final version.

Disclosure of conflict of interest

None.

Address correspondence to: Chen-Hsuan Wu, Department of Obstetrics and Gynecology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 833, Taiwan. Tel: +886-9-75056430; Fax: +886-7-7322915; E-mail: chenhsuan5@gmail.com

References

[1] Elsherif SB, Bhosale PR, Lall C, Menias CO, Itani M, Butler KA and Ganeshan D. Current update on malignant epithelial ovarian tumors. Abdom Radiol (NY) 2021; 46: 2264-2280.

[2] Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch 2012; 460: 237-249.

[3] Chan JK, Tian C, Teoh D, Monk BJ, Herzog T, Kapp DS and Bell J. Survival after recurrence in early-stage high-risk epithelial ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2010; 116: 307-311.

[4] Teng YH, Liu FC, Huang SY, Kuo CF and Yu HP. Epidemiology and mortality of ovarian cancer in Taiwan: a population-based study. J Clin Med 2022; 11: 5627.

[5] Trimbos JB. Surgical treatment of early-stage ovarian cancer. Best Pract Res Clin Obstet Gynaecol 2017; 41: 60-70.

[6] Colombo N, Guthrie D, Chiari S, Parmar M, Qian W, Swart AM, Torri V, Williams C, Lissoni A and Bonazzi C; International Collaborative Ovarian Neoplasm (ICON) collaborators. International collaborative ovarian neoplasm trial 1: a randomized trial of adjuvant chemothera-

py in women with early-stage ovarian cancer. J Natl Cancer Inst 2003; 95: 125-132.
[7] Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, Franchi M, Tateo S, Zanetta G, Scarfone G, Giurgea L, Timmers P, Coens C and Pecorelli S; EORTC-ACTION collaborators. European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European organisation for research and treatment of cancer-adjuvant chemotherapy in ovarian neoplasm trial. J Natl Cancer Inst 2003; 95: 113-125.
[8] Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, Stuart G, Kaye S, Vergote I, Blom R, Grimshaw R, Atkinson RJ, Swenerton KD, Trope C, Nardi M, Kaern J, Tumolo S, Timmers P, Roy JA, Lhoas F, Lindvall B, Bacon M, Birt A, Andersen JE, Zee B, Paul J, Baron B and Pecorelli S. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000; 92: 699-708.
[9] McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL and Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334: 1-6.
[10] Bell J, Brady MF, Young RC, Lage J, Walker JL, Look KY, Rose GS and Spirtos NM; Gynecologic Oncology Group. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2006; 102: 432-439.
[11] Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, du Bois A, Kristensen G, Jakobsen A, Sagae S, Greven K, Parmar M, Friedlander M, Cervantes A and Vermorken J; Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011; 21: 419-423.
[12] Young RC, Walton LA, Ellenberg SS, Homesley HD, Wilbanks GD, Decker DG, Miller A, Park R and Major F Jr. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. N Engl J Med 1990; 322: 1021-1027.
[13] Omura G, Blessing JA, Ehrlich CE, Miller A, Yordan E, Creasman WT and Homesley HD. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. Cancer 1986; 57: 1725-1730.
[14] Bell DR, Woods RL, Levi JA, Fox RM and Tattersall MH. Advanced ovarian cancer: a prospective randomised trial of chlorambucil versus combined cyclophosphamide and cis-diamminedichloroplatinum. Aust N Z J Med 1982; 12: 245-249.
[15] Bertelsen K, Jakobsen A, Andersen JE, Ahrons S, Pedersen PH, Kiaer H, Arffmann E, Bichel P, Boestofte E, Strøyer I, et al. A randomized study of cyclophosphamide and cis-platinum with or without doxorubicin in advanced ovarian carcinoma. Gynecol Oncol 1987; 28: 161-169.
[16] Omura GA, Bundy BN, Berek JS, Curry S, Delgado G and Mortel R. Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 1989; 7: 457-465.
[17] Young RC, Brady MF, Nieberg RK, Long HJ, Mayer AR, Lentz SS, Hurteau J and Alberts DS. Adjuvant treatment for early ovarian cancer: a randomized phase III trial of intraperitoneal 32P or intravenous cyclophosphamide and cisplatin--a gynecologic oncology group study. J Clin Oncol 2003; 21: 4350-4355.
[18] Trédan O, Geay JF, Touzet S, Delva R, Weber B, Cretin J, Provencal J, Martin J, Stefani L, Pujade-Lauraine E and Freyer G; Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. Carboplatin/cyclophosphamide or carboplatin/paclitaxel in elderly patients with advanced ovarian cancer? Analysis of two consecutive trials from the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. Ann Oncol 2007; 18: 256-262.
[19] Chen CA, Chiang CJ, Chen YY, You SL, Hsieh SF, Tang CH and Cheng WF. Survival benefit of patients with early-stage ovarian carcinoma treated with paclitaxel chemotherapeutic regimens. J Gynecol Oncol 2018; 29: e16.
[20] García-Sáenz JA, Custodio A, Casado A, Vidart JA, Coronado PJ, Martín M, López-Tarruella S, Puente J, Fernández C and Díaz-Rubio E. Platinum-based adjuvant chemotherapy on moderate- and high-risk stage I and II epithelian ovarian cancer patients. Long-term single institution experience and literature review. Clin Transl Oncol 2011; 13: 121-132.
[21] Hsieh SF, Lau HY, Wu HH, Hsu HC, Twu NF and Cheng WF. Prognostic factors of early stage epithelial ovarian carcinoma. Int J Environ Res Public Health 2019; 16: 637.
[22] Hollis RL. Molecular characteristics and clinical behaviour of epithelial ovarian cancers. Cancer Lett 2023; 555: 216057.
[23] Wahl AF, Donaldson KL, Fairchild C, Lee FY, Foster SA, Demers GW and Galloway DA. Loss of normal p53 function confers sensitization to

Taxol by increasing G2/M arrest and apoptosis. Nat Med 1996; 2: 72-79.
[24] Samartzis EP, Noske A, Dedes KJ, Fink D and Imesch P. ARID1A mutations and PI3K/AKT pathway alterations in endometriosis and endometriosis-associated ovarian carcinomas. Int J Mol Sci 2013; 14: 18824-18849.
[25] Rinne N, Christie EL, Ardasheva A, Kwok CH, Demchenko N, Low C, Tralau-Stewart C, Fotopoulou C and Cunnea P. Targeting the PI3K/AKT/mTOR pathway in epithelial ovarian cancer, therapeutic treatment options for platinum-resistant ovarian cancer. Cancer Drug Resist 2021; 4: 573-595.
[26] Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih IeM, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA and Huntsman DG. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010; 363: 1532-1543.
[27] de Nonneville A, Kalbacher E, Cannone F, Guille A, Adelaïde J, Finetti P, Cappiello M, Lambaudie E, Ettore G, Charafe E, Mamessier E, Provansal M, Bertucci F and Sabatier R. Endometrioid ovarian carcinoma landscape: pathological and molecular characterization. Mol Oncol 2024; 18: 2586-2600.
[28] Dumontet C and Jordan MA. Microtubule-binding agents: a dynamic field of cancer therapeutics. Nat Rev Drug Discov 2010; 9: 790-803.
[29] Hu L, Hofmann J, Lu Y, Mills GB and Jaffe RB. Inhibition of phosphatidylinositol 3'-kinase increases efficacy of paclitaxel in in vitro and in vivo ovarian cancer models. Cancer Res 2002; 62: 1087-1092.
[30] Emadi A, Jones RJ and Brodsky RA. Cyclophosphamide and cancer: golden anniversary. Nat Rev Clin Oncol 2009; 6: 638-647.
[31] Dabbish E, Scoditti S, Shehata MNI, Ritacco I, Ibrahim MAA, Shoeib T and Sicilia E. Insights on cyclophosphamide metabolism and anticancer mechanism of action: a computational study. J Comput Chem 2024; 45: 663-670.
[32] ten Tije AJ, Verweij J, Loos WJ and Sparreboom A. Pharmacological effects of formulation vehicles: implications for cancer chemotherapy. Clin Pharmacokinet 2003; 42: 665-685.
[33] Morales-Vásquez F, Pedernera E, Reynaga-Obregón J, López-Basave HN, Gómora MJ, Carlón E, Cárdenas S, Silva-Ayala R, Almaraz M and Méndez C. High levels of pretreatment CA125 are associated to improved survival in high grade serous ovarian carcinoma. J Ovarian Res 2016; 9: 41.
[34] Zhu C, Zhu J, Qian L, Liu H, Shen Z, Wu D, Zhao W, Xiao W and Zhou Y. Clinical characteristics and prognosis of ovarian clear cell carcinoma: a 10-year retrospective study. BMC Cancer 2021; 21: 322.
[35] van Dalen A, Favier J, Burges A, Hasholzner U, de Bruijn HW, Dobler-Girdziunaite D, Dombi VH, Fink D, Giai M, McGing P, Harlozinska A, Kainz C, Markowska J, Molina R, Sturgeon C, Bowman A and Einarsson R. Prognostic significance of CA 125 and TPS levels after 3 chemotherapy courses in ovarian cancer patients. Gynecol Oncol 2000; 79: 444-450.
[36] Timmermans M, Zwakman N, Sonke GS, Van de Vijver KK, Duk MJ, van der Aa MA and Kruitwagen RF. Perioperative change in CA125 is an independent prognostic factor for improved clinical outcome in advanced ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2019; 240: 364-369.
[37] Li Z, Yin H, Ren M and Shen Y. Prognostic significance of CA125 dynamic change for progression free survival in patients with epithelial ovarian carcinoma. Med Sci Monit 2020; 26: e925051.
[38] Abu-Zaid A, Alomar O, Al-Badawi IA and Salem H. Preoperative elevated platelet count and thrombocytosis in gynecologic malignancies. Arch Gynecol Obstet 2018; 297: 1071-1072.
[39] Feng Z, Wen H, Bi R, Duan Y, Yang W and Wu X. Thrombocytosis and hyperfibrinogenemia are predictive factors of clinical outcomes in high-grade serous ovarian cancer patients. BMC Cancer 2016; 16: 43.
[40] Cozzi GD, Samuel JM, Fromal JT, Keene S, Crispens MA, Khabele D and Beeghly-Fadiel A. Thresholds and timing of pre-operative thrombocytosis and ovarian cancer survival: analysis of laboratory measures from electronic medical records. BMC Cancer 2016; 16: 612.
[41] Stone RL, Nick AM, McNeish IA, Balkwill F, Han HD, Bottsford-Miller J, Rupairmoole R, Armaiz-Pena GN, Pecot CV, Coward J, Deavers MT, Vasquez HG, Urbauer D, Landen CN, Hu W, Gershenson H, Matsuo K, Shahzad MM, King ER, Tekedereli I, Ozpolat B, Ahn EH, Bond VK, Wang R, Drew AF, Gushiken F, Lamkin D, Collins K, DeGeest K, Lutgendorf SK, Chiu W, Lopez-Berestein G, Afshar-Kharghan V and Sood AK. Paraneoplastic thrombocytosis in ovarian cancer. N Engl J Med 2012; 366: 610-618.
[42] Kurman RJ and Shih Ie M. The dualistic model of ovarian carcinogenesis: revisited, revised, and expanded. Am J Pathol 2016; 186: 733-747.