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Short Communication

Comparison of PD-L1, CTR-1, VEGF, and p53 expression in sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy

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Abstract

The current standard treatment for ovarian cancer is a combination of cytoreductive surgery and platinum-based chemotherapy; however, many patients develop resistance, leading to a high recurrence rate. The aim of this study was to analyze the expression of PD-L1, CTR-1, VEGF, and p53 in epithelial ovarian cancer (EOC) patients, comparing those sensitive and resistant to platinum-based chemotherapy. A cross-sectional study was conducted among EOC patients who underwent surgery and platinum-based chemotherapy between 2020 and 2023 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, with evaluations performed six months post-chemotherapy. The expression of PD-L1, CTR-1, VEGF, and p53 were measured using immunohistochemistry (IHC) and compared between chemotherapy-sensitive and resistant patients. A total of 65 patients were included: 31 resistant and 34 sensitive cases. The results showed higher PD-L1 expression in the resistant group compared to the sensitive group (mean combined positive score (CPS) of 0.46±0.29 vs 0.17±0.09, $p<0.001$). The CTR-1 expression was lower in the resistant group (immunoreactive score 2.90±1.30) compared to the sensitive group (immunoreactive score 6.82±2.68) with $p<0.001$. VEGF and p53 expression were also higher in the resistant group (6.68±2.59 vs 2.76±1.10 and 64.68±13.54% vs 30.15±13.06%, respectively) compared to the sensitive group, with both having $p<0.001$. The study suggests that increased expression of PD-L1, VEGF, and p53 and decreased CTR-1 expression are associated with platinum-based chemotherapy resistance among EOC patients. Therefore, these biomarkers might have the potential for predicting treatment responses and understanding resistance mechanisms.

Keywords: Ovarian cancer, PDL-1, CTR-1, VEGF, p53

Introduction

Ovarian cancer is one of the leading causes of death among women under the age of 70 in many countries [1]. It ranks as the third most common gynecological cancer, following cervical and uterine cancers, yet it has the highest fatality rate among cancers of the female reproductive system [1]. In 2020, an estimated 21,750 new cases of ovarian cancer were reported in the United States, resulting in approximately 13,940 deaths [2]. Similarly, Europe recorded 29,000 ovarian cancer-related deaths during the same period [2]. The projections for 2040 suggest a substantial increase in ovarian cancer mortality [3]. This worrying trend is attributed to several factors,

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Received: September 1, 2024 - Accepted: December 19, 2024 - Published online: January 6, 2025

including the often-asymptomatic nature of tumor growth, delayed symptom onset, and the lack of effective screening methods, which lead to late-stage diagnoses [3]. Notably, more than 70% of patients diagnosed at Stage III or IV experience disease recurrence within five years, earning ovarian cancer the grim reputation of a "silent killer" [4].

The current standard treatment for ovarian cancer involves a combination of cytoreductive surgery and platinum-based chemotherapy [5]. However, the high rates of recurrence and the development of treatment resistance highlight the limitations of these approaches. This has created an urgent need for more advanced therapeutic strategies. At the forefront of ongoing research are novel pharmaceutical agents that primarily target molecular pathways involved in cancer cell proliferation, tumor suppression, and modulation of the immune response [6]. Key emerging therapies include anti-angiogenic agents, growth factor signaling inhibitors, poly adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors, and folate receptor inhibitors [7]. Additionally, immunotherapeutic strategies are being extensively evaluated in clinical trials [7].

Specific molecular targets, such as programmed death-ligand 1 (PD-L1), copper transporter 1 (CTR-1), vascular endothelial growth factor (VEGF), and p53, play a pivotal role in addressing resistance and recurrence in ovarian cancer. Although immunotherapy use remains limited, early results are promising [8,9]. Biomarkers, including PD-L1, CTR-1, VEGF, and p53, are key for predicting treatment responses and understanding resistance mechanisms. This research lays the groundwork for developing more effective, personalized treatments for ovarian cancer patients [10,11]. The aim of this study was to compare the expression of PD-L1, CTR-1, VEGF, and p53 between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy.

Methods

Study design, setting, and sampling

A case-control study was conducted at the Department of Obstetrics and Gynecology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2020 to December 2023. The study included epithelial ovarian cancer (EOC) patients who underwent surgery followed by platinum-based chemotherapy (paclitaxel-carboplatin chemotherapy) during this period. Participants were selected using consecutive sampling. Histopathological assessments were performed on all cases to evaluate the tumor characteristics. Treatment outcomes were assessed six months after the completion of chemotherapy, and divided the patients into resistant or sensitive to chemotherapy. Furthermore, the immunohistochemical assessments were conducted to assess the expression of PD-L1, CTR-1, VEGF, and p53 between these two groups.

Patients and chemotherapy response assessment

This study included patients diagnosed with EOC with three subtypes: clear cell, endometrioid, and serous ovarian cancer. All patients had undergone complete surgical staging and received six cycles of paclitaxel-carboplatin chemotherapy (a platinum-based regimen) with a paclitaxel dose of 175 mg/m^2 and a fixed carboplatin dose calculated using an area under the curve (AUC) of 6. The patients were then divided into two groups based on their response to chemotherapy: chemotherapy-resistant and chemotherapy-sensitive based on Response Evaluation Criteria in Solid Tumors criteria (RECIST) criteria, a standardized guideline to assess the response to chemotherapy. Chemotherapy-sensitive patients were defined as those whose disease progressed or recurred within six months of completing chemotherapy, while chemotherapy-resistant group consisted of patients who showed no evidence of progression or recurrence within six months post-chemotherapy. The evaluation was made through clinical examination, ultrasound, or computed tomography (CT) scans, and had no history of other malignancies.

Data collection

Eligible patients were recruited and key demographic and clinical characteristics were collected. Patients were then grouped based on key demographic and clinical characteristics. Age was categorized into three groups: patients under 50 years, those aged 51–60 years, and patients over

60 years. Cancer stages were defined according to the International Federation of Gynecology and Obstetrics (FIGO) staging system, encompassing stages IC through IIIC [3]. Stage IC is defined by the involvement of both ovaries, with the presence of malignant ascites and/or tumors on the surface of one or both ovaries. Stage IIA is characterized by tumor involvement in one or both ovaries with pelvic extension, while stage IIB involves extension to the uterus and/or fallopian tubes. Stage IIIA indicates that the cancer has spread to the peritoneal cavity without visible tumors on the surface of the organs, whereas Stage IIIB includes visible peritoneal tumors smaller than 2 cm in diameter. Stage IIIC denotes the most advanced disease, with tumor involvement in one or both ovaries, accompanied by peritoneal implants outside the pelvis, malignant ascites, and/or metastasis to regional lymph nodes.

The collection of tumor tissue samples was conducted from each patient for histopathological and immunohistochemical analysis during the surgery (complete surgical staging) before the chemotherapy was initiated. Based on histopathological subtypes, the cancers were classified into three main categories: clear cell carcinoma, endometrioid carcinoma, and serous carcinoma [8,9]. Clear cell carcinoma was recognized for its clear cells on histological examination and is associated with a more aggressive clinical course. Endometrioid carcinoma, frequently linked to endometriosis, is characterized by glandular architecture, while serous carcinoma is characterized by the production of serous fluid and often presents at an advanced stage, indicating a generally poor prognosis [8,9].

Immunohistochemistry (IHC) of biomarkers

The expression of the biomarkers PD-L1, CTR-1, VEGF, and p53 was evaluated using IHC from paraffin-embedded cancer tissues. All IHC analyses were performed using tools and reagents from BioLegend (BioLegend, San Diego, USA), following the manufacturer's protocols. Briefly, antigen retrieval was performed by treating the sections with 0.025% trypsin at 37°C for 6 minutes. The sections were subsequently incubated with primary antibodies against PD-L1 (1:100), CTR-1 (1:100), VEGF (1:100), and p53 (1:100) for 25–30 minutes. Biotinylation was then performed using a biotinylated secondary antibody, followed by the addition of horseradish peroxidase (HRP) polymer. The immunoreactivity was visualized using a diaminobenzidine (DAB) substrate in a darkened environment to ensure optimal development. Finally, the sections were counterstained with Mayer's hematoxylin, dehydrated, and mounted with coverslips.

PD-L1 expression was quantified by counting the number of stained cells associated with each antibody, and the combined positive score (CPS) was calculated using the formula: CPS=(number of PD-L1-staining cells (tumor cells, lymphocytes, macrophages)/total number of viable tumor cells)×100. The expression levels of CTR-1 and VEGF were determined using the immunoreactive score (IRS), a semi-quantitative method that combines both the intensity of staining and the percentage of positive cells to generate a numerical score. The final IRS score was calculated by multiplying the intensity score by the percentage score, resulting in a value ranging from 0 to 12. For p53 expression, the expression level was represented as the percentage of stained cells relative to the total number of cells.

Statistical analysis

Analysis of variance (ANOVA) was conducted to identify factors associated with chemotherapy-resistant and chemotherapy-sensitive. The normality and homogeneity of variance were assessed using the Shapiro-Wilk test and Levene's test, respectively. The expression levels of PD-L1, CTR-1, VEGF, and p53 between two groups (sensitive and resistant EOC patients to platinum-based chemotherapy) were compared using logistic regression analysis. Data analysis was performed using SPSS version 26.0 (IBM, Chicago, USA) and a p-value of <0.05 was considered statistically significant.

Results

Characteristics of the patients

A total of 65 patients with EOC were included in the study, and their characteristics are presented in **Table 1**. Among these, 31 cases (47.7%) were classified as resistant to treatment, while 34 cases

(52.3%) were classified as sensitive. The characteristics of the ovarian cancer cases in relation to resistance status are summarized in **Table 1**. The mean age of patients with resistant tumors was 57.35±8.11 years, while those with sensitive tumors had a mean age of 55.85±8.82 years. Clear cell carcinoma was more prevalent in the resistant compared to the sensitive group (29.0% vs 11.8%). Endometrioid carcinoma was observed in 22.6% of resistant cases and 26.5% of sensitive cases, while serous carcinoma was found in 48.4% and 61.8% of resistant and sensitive cases, respectively. Approximately 10% of resistant cases were classified as stage 1C, compared to 20.6% of sensitive cases. Other stage distributions were similar between the groups, with no notable differences. All characteristics between resistant and sensitive groups had no significant differences (**Table 1**).

Table 1. Characteristics of patients with epithelial ovarian cancer based on resistance status to platinum-based chemotherapy

Characteristics	Description/category	Resistance status		*p*-value
		Resistant (n=31)	Sensitive (n=34)	
Total		31 (47.7%)	34 (52.3%)	
Age (years)	Mean±SD	57.35±8.11	55.85±8.82	0.494
	Median (min-max)	57.00 (44–71)	55.50 (42–70)	
	<50	8 (25.8%)	12 (35.3%)	0.533
	51-60	12 (38.7%)	9 (26.5%)	
	>60	11 (35.5%)	13 (38.2%)	
Histopathological subtype	Clear cell carcinoma	9 (29.0%)	4 (11.8%)	0.219
	Endometrioid carcinoma	7 (22.6%)	9 (26.5%)	
	Serous carcinoma	15 (48.4%)	21 (61.8%)	
Cancer stage	IC	3 (9.7%)	7 (20.6%)	0.917
	IIA	2 (6.5%)	2 (5.9%)	
	IIB	4 (12.9%)	3 (8.8%)	
	IIC	1 (3.2%)	1 (2.9%)	
	IIIA	7 (22.6%)	7 (20.6%)	
	IIIB	7 (22.6%)	9 (26.5%)	
	IIIC	7 (22.6%)	5 (14.7%)	

SD: standard deviation

Comparison of PDL-1 expression based on chemotherapy sensitivity

PD-L1 negative expression suggests chemotherapy sensitivity, characterized by the absence of staining or a clear cell membrane (**Figure 1A**). In contrast, PD-L1 positive expression is indicative of chemotherapy resistance, as demonstrated by brown staining on the tumor cell membrane, highlighted by white arrows (**Figure 1B**). The analysis of PD-L1 expression in relation to resistance status is presented in **Table 2**. The mean PD-L1 expression score for resistant cases was 0.46±0.29, while sensitive cases exhibited a mean PD-L1 expression of 0.17±0.09. The mean of PD-L1 expression was statistically significant between resistant and sensitive groups with $p<0.001$ (**Table 2**).

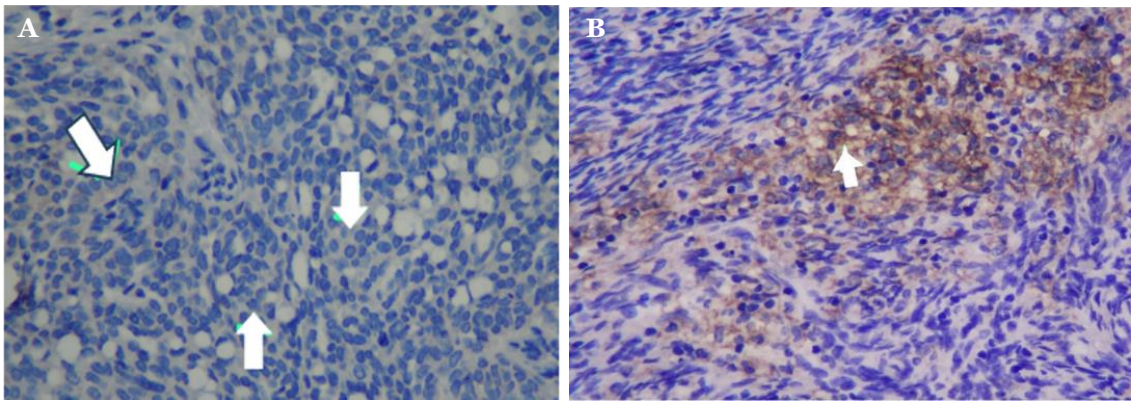

Figure 1. Comparison of programmed death-ligand 1 (PDL-1) expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy. (A) Negative staining for PDL-1; (B) positive staining for PDL-1, demonstrated by brown staining. Magnification of 400 times.

Comparison of CTR-1 expression based on chemotherapy sensitivity

CTR-1 positive cells were observed as brown staining within the cytoplasm of tumor cells. CTR-1 positive cells were found in chemotherapy-sensitive specimens at 400× magnification (**Figure 2**). In contrast, negative CTR-1 expression (chemotherapy-resistant specimens) had unstained cytoplasm.

Table 2. Comparison of programmed death-ligand 1 (PDL-1) expression scores between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy

Resistance status	n	PD-L1 expression (combined positive scores)			*p*-value
		Mean±SD	Median	Min-max	
Resistant	31	0.46±0.29	0.50	0.01–0.90	<0.001
Sensitive	34	0.17±0.09	0.00	0.00–0.50	

The comparison of CTR-1 expression (based on IRS score) between two groups in relation to chemotherapy resistance is summarized in **Table 3**. In resistant cases, the mean CTR-1 expression score was 2.90±1.30, with a median score of 2.00 and a range of 2 to 6. In contrast, sensitive cases had a significantly higher mean expression score of 6.82±2.68 (p<0.001).

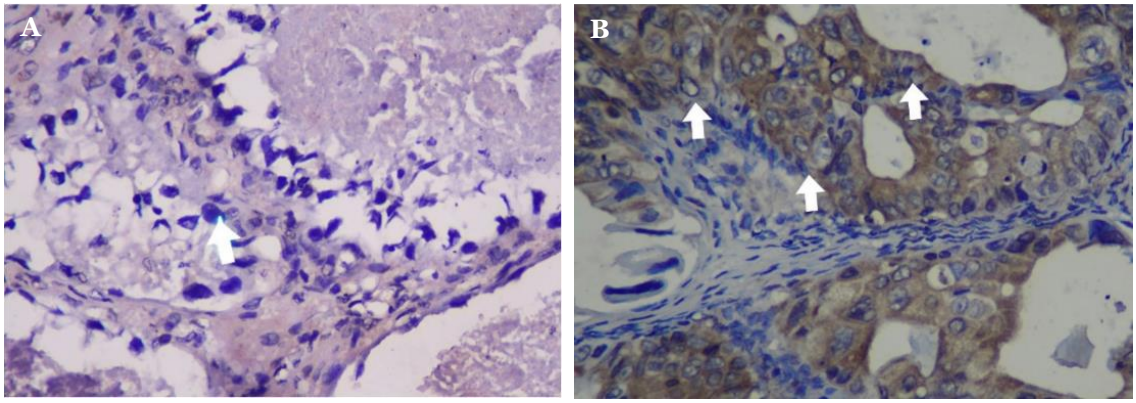

Figure 2. Comparison of copper transporter 1 (CTR-1) expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy. (A) Negative staining for CTR-1; (B) positive staining for CTR-1, demonstrated by brown staining. Magnification of 400 times.

Table 3. Comparison of copper transporter 1 (CTR-1) expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy

Resistance status	n	Immunoreactive score (IRS) of CTR-1 expression			*p*-value
		Mean±SD	Median	Min-max	
Resistant	31	2.90±1.30	2.00	2–6	<0.001
Sensitive	34	6.82±2.68	6.00	2–12	

Comparison of VEGF expression based on chemotherapy sensitivity

In this study, negative VEGF expression (chemotherapy-sensitive specimens) was characterized by a clear, unstained cytoplasm, while VEGF-positive cells were observed as brown staining in the cytoplasm of tumor cells in chemotherapy-resistant specimens (**Figure 3**). Comparison of VEGF expression (based on IRS scores) between two different chemotherapy sensitivity groups is presented in **Table 4**. Our data indicated that the VEGF expression was significantly higher in the resistant group, with a mean expression score of 6.68±2.59, compared to sensitive group, which had a mean expression score of 2.76±1.10 (p<0.001) (**Table 4**).

Table 4. Comparison of vascular endothelial growth factor (VEGF) expression score between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy

Resistance status	n	Immunoreactive score (IRS) of VEGF expression			*p*-value
		Mean±SD	Median	Min-max	
Resistant	31	6.68±2.59	6.00	2–12	<0.001
Sensitive	34	2.76±1.10	2.00	2–6	

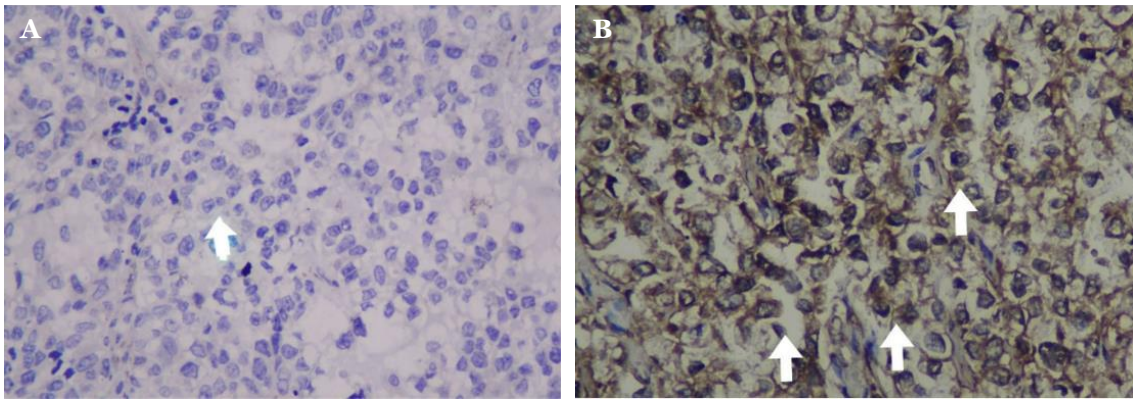

Figure 3. Comparison of vascular endothelial growth factor (VEGF) expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy. (A) Negative staining for VEGF; (B) positive staining for VEGF, demonstrated by brown staining. Magnification of 400 times.

Comparison of P53 expression based on chemotherapy sensitivity

P53 expression was identified as brown staining in the nuclei of tumor cells in chemotherapy-resistant specimens, while chemotherapy-sensitive specimens exhibited negative p53 expression, characterized by visible blue nuclei (**Figure 4**). Comparisons of p53 expression scores based on the chemotherapy resistance are summarized in **Table 5**. Resistant cases had a mean p53 expression of 64.68±13.54%, while the chemotherapy-sensitive group had a significantly lower mean expression (30.15±13.06%, $p<0.001$) (**Table 5**).

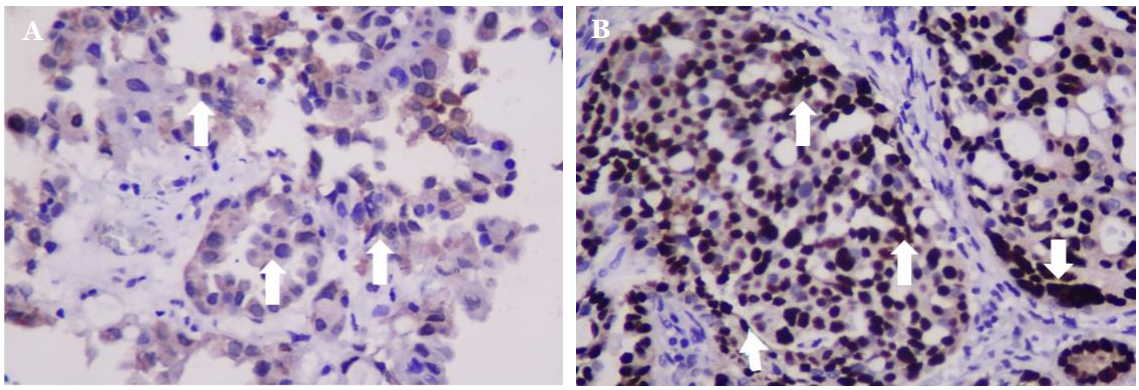

Figure 4. Comparison of p53 expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy. (A) Negative staining for p53. (B) Positive staining for VEGF, demonstrated by brown staining. Magnification of 400 times.

Table 5. Comparison of p53 expression between sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy

Resistance status	n	p53 expression			*p*-value
		Mean±SD	Median	Min-max	
Resistant	31	64.68±13.54%	70.00	20–80	<0.001
Sensitive	34	30.15±13.06%	30.00	10–55	

Discussion

This study was conducted to compare the expression levels of PD-L1, CTR-1, VEGF, and p53 between platinum-based chemotherapy-sensitive and -resistant EOC patients. Our findings indicated that the expressions of PD-L1, VEGF, and p53 were significantly increased in chemotherapy-resistant EOC patients, whereas CTR-1 expression was significantly decreased in these cases.

The finding of the high PD-L1 expression was associated with resistance to chemotherapy aligned with the established role of PD-L1 in ovarian cancer progression [16]. PD-L1 acts as a

binding site between PD-1 and its ligand expressed on ovarian cancer cells, leading to the dysfunction, neutralization, and exhaustion of T lymphocytes [16]. This mechanism allows cancer cells to evade recognition by the host's immune system. Studies found that the expression of PD-1 in ovarian cancer was associated with poor prognosis and highlighted the tumor's ability to evade immune surveillance. PD-1 expression was predominantly observed in high-grade serous ovarian cancer [17].

A study elucidated that PD-L1 contributed to the immunosuppressive tumor microenvironment [18]. Their study identified robust PD-L1 expression on tumor cells and tumor-associated macrophages in culture models. Transwell co-culture experiments revealed that ovarian cancer cells developed resistance to carboplatin after being co-cultured with macrophages [18]. While the role of PD-L1 and PD-1 interactions in T-cell suppression is well understood, limited knowledge exists regarding the involvement of PD-L1 signaling in ovarian cancer chemotherapy resistance. It was hypothesized that PD-L1 expression in ovarian cancer cells and tumor-associated macrophages correlated with carboplatin resistance [18].

This study also demonstrated that lower CTR-1 expression was associated with chemotherapy resistance. This finding was supported by previous studies showing that higher CTR-1 expression enhanced chemotherapy sensitivity [19]. CTR-1 served as the primary copper influx transporter in human cells and played a significant role as a cisplatin uptake transporter [19]. A study investigated cisplatin resistance using mutagenized wild-type yeast cells and selected mutants that thrived in the presence of cytotoxic doses of cisplatin. Mutants with CTR-1 mutations, which reduced CTR-1 expression, exhibited pronounced platinum-based chemotherapy resistance compared to other mutants [20]. To elucidate CTR-1's role in cisplatin resistance, a study assessed the absorption of a cisplatin-DNA complex and found that decreased platinum absorption, due to reduced CTR-1 expression, contributed to resistance [20]. It further demonstrated that cisplatin, similar to copper, reduced CTR-1 expression in yeast cell lines, thereby decreasing the intracellular cisplatin available to cancer cells [20].

A previous study revealed significantly lower mRNA expression of both CTR-1 and CTR-2 in ovarian cancer cells compared to normal ovarian tissue [21]. High CTR-1 expression served as a prognostic factor for improved survival, even after adjusting for age, tumor grade, stage, residual tumor, and CTR-2 mRNA expression [21]. High CTR-1 expression was significantly correlated with sensitivity to platinum-based chemotherapy and prolonged survival, whereas low CTR-1 expression and high CTR-2 expression were associated with chemotherapy resistance and shorter survival [21].

Our study revealed that elevated VEGF expression was associated with resistance to chemotherapy. VEGF, a highly specific mitogen for endothelial cells, played a pivotal role in angiogenesis, both in physiological and pathological contexts, including tumor growth [22]. Overexpression of VEGF has been consistently linked to poor prognosis in various tumor settings, particularly in ovarian cancer, where elevated serum levels of VEGF served as an independent risk factor for advanced stage and diminished survival [10,23]. A study assessed the mechanism of action of VEGF, which influenced the host response to tumors, particularly through its effects on the regulation of immune cells and fibroblasts within the tumor stroma [24]. Notably, VEGF produced by tumor cells fostered the activity of cancer stem cells, promoting increased proliferation, migration, and invasion of cancer cells, as well as augmenting the potential for chemotherapy resistance [24].

Our study found that higher p53 expression was associated with increased resistance to chemotherapy. The activation of p53 is a pivotal event in cellular regulation, influencing various processes such as cell cycle arrest, senescence, and apoptosis, which are crucial mechanisms in tumor growth and progression control [20]. As a transcription factor, p53 specifically binds DNA and regulates the transcription of diverse targets through its transactivation domain, with its transcriptional activity modulated by oligomerization [25]. In cancer contexts such as high-grade serous ovarian cancer (HGSOC), chemotherapy resistance frequently occurs, with p53 inactivation due to genetic mutations being a major contributing factor [20]. Furthermore, p53 protein aggregation was identified as a significant contributor to p53 inactivation and platinum-based chemotherapy resistance, particularly in the HGSOC cancer stem cell population [20].

However, the role of p53 in chemotherapy resistance was not always straightforward. High p53 levels are also linked to chemotherapy resistance, especially in the presence of mutations altering the pro-apoptotic balance of the p53 gene [21]. Changes in p53 function during carcinogenesis and chemotherapy could result in either a loss of p53 function or acquisition of altered function, influencing chemotherapy response [21].

Low p53 protein expression in endometrial cancer could stem from various complex factors. Prolonged tissue sampling during surgical procedures could damage the p53 protein, reducing its detection in tests [22]. Additionally, specific alterations in tumor DNA could modify p53 protein levels, leading to decreased expression [26]. Although mutations in the TP53 gene are rare in low-grade endometrioid carcinoma, they are significant factors contributing to abnormal p53 accumulation and reduced activity [26]. These mutations could influence the risk of endometrial cancer recurrence and disease progression. The histological type of endometrial cancer also influences p53 expression, with estrogen-related type I cancers typically showing negative p53 expression, while non-estrogen-related type II cancers tend to exhibit positive p53 expression [27,28]. Genetic dysregulation factors, including changes in the regulation of factors such as ERβ and MDM2, and interactions with oncoproteins like HPV E6 and E6AP, may have also contributed to p53 overexpression in endometrial cancer [29]. Additionally, mutations in the TP53 gene could lead to excessive p53 protein production, considered a cellular response to DNA damage or cellular stress [30]. However, further research is needed for a comprehensive understanding of this mechanism [30,31].

Our study also investigated the interactions among the PD-L1, CTR-1, VEGF, and p53 pathways in relation to chemotherapy resistance. We observed a positive correlation between PD-L1 and VEGF, which in turn correlated with p53. All three were associated with chemotherapy resistance. Conversely, CTR-1 was negatively correlated with both p53. A previous study found a positive correlation between PD-L1 and VEGF expression [32], consistent with studies showing that PD-L1 and PD-L2 expression correlates with pro-angiogenic genes such as hypoxia-inducible factor (HIFs) and VEGF in various cancers [32]. These findings highlight a link between PD-L1, VEGF, and higher microvessel density (MVD), which is associated with poor prognosis [32,33]. A study demonstrated a correlation between p53 and CTR-1 expression in cancer patients treated with cisplatin [34]. Decreasing p53 levels enhanced CTR1 expression and cisplatin uptake, while increased p53 levels inhibited both [34]. P53 regulated CTR-1 by suppressing the nuclear translocation of specificity protein-1 (SP1), a key regulator of the CTR-1 promoter [34]. This study suggested that p53 negatively regulates CTR-1-mediated cisplatin uptake and that the p53-SP1-CTR-1 pathway may contribute to cisplatin resistance [34]. VEGF also serves as a critical prognostic factor in cancer. A study reported a significant correlation between VEGF expression and mutated p53 protein, with their combination providing strong prognostic value for disease-free survival in cancer patients, especially those receiving adjuvant therapy [35]. Both p53 and VEGF independently predicted survival, and their combination indicated an increased relapse risk in patients with high levels of both [35].

This study had several limitations. The sample size was small due to loss of follow-up, which was further compounded by the large geographic distribution of patients across East Java and eastern Indonesia, as well as the generally low socioeconomic status of participants. Additionally, difficulties in contacting patients and tracking post-therapy tumor progression hindered the evaluation.

Conclusion

Our study indicates that the expressions of PD-L1, VEGF, and p53 are significantly higher in platinum-based chemotherapy-resistant EOC patients, whereas CTR-1 expression is significantly lower compared to chemotherapy-sensitive EOC patients. Further studies are needed to explore the underlying mechanisms driving these expression patterns and their potential as predictive biomarkers for chemotherapy resistance.

Ethics approval

The protocol of the study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, reference number 0774/KEPK/IX/2023. All participants provided their consent for inclusion before the commencement of the study.

Acknowledgments

We would like to extend our gratitude to the biochemistry laboratory and anatomical pathology laboratory of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Competing interests

The authors declare that they have no conflict of interest.

Funding

This study received no external funding.

Underlying data

Data collected and analyzed in this study will be available to the corresponding author upon appropriate request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

Perbowo P, Tjokroprawiro BA, Aryati A, *et al*. Comparison of PD-L1, CTR-1, VEGF, and p53 expression in sensitive and resistant epithelial ovarian cancer (EOC) patients to platinum-based chemotherapy. Narra J 2025; 5 (1): e1419 - http://doi.org/10.52225/narra.v5i1.1419.

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