

Effect of paclitaxel-cisplatin chemotherapy towards hemoglobin, platelet, and leukocyte levels in epithelial ovarian cancer patients

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ABSTRACT

Paclitaxel-cisplatin combination chemotherapy as first-line treatment of epithelial ovarian cancer (EOC) is known to cause myelosuppression that leads to decreased hemoglobin, platelet and leukocyte levels. This study aims to evaluate the side effect of paclitaxel-cisplatin chemotherapy in EOC patients with hematologic status at Sanglah General Hospital, Denpasar. Observational retrospective research was conducted from February to May 2018. Samples were EOC patients who underwent six cycles of paclitaxel-cisplatin chemotherapy at Sanglah General Hospital, Bali-Indonesia from January 2015 to May 2018. Side effects of chemotherapy were seen from hemoglobin, platelet, and leukocyte data before and after six cycles of chemotherapy. Hematologic data were analyzed and compared using Paired *T*-test with a level of confidence of 95% using the STATA version 14 software. Mean value of three hematologic parameters decreased after six cycles, including hemoglobin levels were 12.05–10.69 g/dl (p -value = 0.282); platelet levels were 378.5–326.9 g/dl (p -value = 0.569) and leukocyte levels were 11.32–8.28 g/dl (p -value = 0.517). There were differences of hemoglobin, platelet, and leukocyte levels before the first and after the sixth cycle of chemotherapy. Low side effects of paclitaxel-cisplatin were observed in this study (Anemia grade 1).

INTRODUCTION

Epithelial ovarian cancer (EOC) is a type of ovarian cancer that has more common prevalent rate when compared with non-EOC; it is about 90% of ovarian cancer cases (Berek and Hacker, 2005). EOC is the sixth most common cancer that causes death among women due to its gynecologic malignancies (McGuire *et al.*, 2000). EOC in Indonesia is placed in the third rank among the other most prevalent gynecologic cancers; the first and second ranks are breast cancer and cervical cancer (Charles *et al.*, 2016).

Treatment of EOC consists of the combination of cytoreductive surgery, combination of taxane chemotherapy, and platinum-based chemotherapeutic drugs (Kim *et al.*, 2012). Paclitaxel belongs to taxane group that is derived from the bark of the Pacific yew tree, *Taxus brevifolia* Nutt (Kampan *et al.*, 2015). Paclitaxel combined with cisplatin (platinum-containing agents) is now used as the first-line treatment for ovarian cancer. Paclitaxel-cisplatin chemotherapy is shown to improve therapeutic response rate, including complete or partial clinical response with the percentage of 38.7% and 42.7%, respectively (Bois *et al.*, 2003). In Sanglah General Hospital (Bali, Indonesia), paclitaxel-cisplatin combined chemotherapy is a therapy used in the treatment of EOC patients (Medical Committee, 2004).

Paclitaxel-cisplatin shows efficacy in eradicating ovarian cancer cells; however, these chemotherapeutic drugs also cause side effects. Combination of paclitaxel-cisplatin causes myelosuppression through their mechanism of action in bone marrow cells (Kumar *et al.*, 2010; Wilson *et al.*, 2007).

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Myelosuppression leads to decreased hemoglobin, platelet level, and leukocyte level, so patients experience anemia, thrombocytopenia, and leukopenia (Bois *et al.*, 2003). There have been various studies evaluating myelosuppression effects of paclitaxel-cisplatin chemotherapy on ovarian cancer patients carried out outside Bali-Indonesia. But until now, Bali has a lack of data about the side effect of paclitaxel-cisplatin chemotherapy on the hematologic status of ovarian cancer patients, especially on EOC patients. This study aims to evaluate the side effect of paclitaxel-cisplatin chemotherapy in the hematologic status of EOC patients at Sanglah General Hospital, Denpasar-Bali.

MATERIALS AND METHODS

Materials

The materials include collected data sheets of hemoglobin, platelet, leukocyte, and medical records of EOC patients who received paclitaxel-cisplatin chemotherapy from January 2015 to May 2018.

Methods

This study is observational retrospective research that has obtained a certificate of ethical clearance (Number: 159/UN.14.2/KEP/2018) and research permit (Number: LB.02.01/XIV.2.2.1/9396/2017) from Ethics Commission Research and Development of Faculty of Medicine, Udayana University/General Hospital Sanglah Denpasar. The study was conducted by collecting medical records of patients from January 2015 to May 2018. All subjects with EOC (stages I–IV) were recruited for this study. Patients were selected based on the inclusion criterion of patients with EOC at Sanglah Hospital who received six cycles of chemotherapy with paclitaxel-cisplatin from January 2015 to May 2018. The exclusion criterion was patients with EOC who have a history of bone marrow disorder. This study was conducted by recording hemoglobin, platelets, and leukocytes levels data from EOC patients that fulfilled inclusion criteria. Data were taken before the first and after the sixth chemotherapy. The data were analyzed using paired *T*-test. All data processing was conducted using STATA version 14 software. The value of hemoglobin, platelet, and leukocyte before and after paclitaxel-cisplatin chemotherapy was stated to have significant differences when it showed $p < 0.05$.

RESULTS AND DISCUSSION

Ovarian cancer stage classification (Table 1) showed two patients with phase III ovarian cancer (66.67%) and one patient with phase I ovarian cancer (33.33%). Ovarian cancer can hardly be detected at an early stage because of its unspecific symptoms, so 70% of its cases are diagnosed during advanced stages (Yurkovetsky *et al.*, 2010). Survival of ovarian cancer patients depends on the stage of diagnosis; therefore, early detection is important to reduce mortality (Raul-Hain *et al.*, 2011). According to McLemore *et al.* (2010), screening techniques using transvaginal ultrasound and CA 125 monitoring can be performed in early detection of ovarian cancer. However, a study conducted by Modugno (2004) showed that those screening techniques did not show reductions in mortality and morbidity of ovarian cancer patients.

Table 1. Patients characteristics.

Characteristics	Amount (N = 3)	%
FIGO Stage		
I	1	33.33
III	2	66.67
Parity		
Nulliparity (P ₀)	1	33.33
Primiparity (P ₁)	-	-
Multiparity (≥P1)	2	66.67
Histopathological classification		
Mucinous	1	33.33
Serous	2	66.67
Age		
30–45 years	1	33.33
46–60 years	2	66.67
Level of education		
Elementary School	1	33.33
Junior High School	-	-
Senior High School	-	-
None	2	66.67
Job		
Housewife	1	33.33
Farmer	1	33.33
None	1	33.33

Based on the parity parameter of the patients (Table 1), multiparity women (66.67%) were common than nulliparity women (33.33%). Another study by Gea *et al.* (2016) on Ovarian Cancer Overview at RSUP Prof Dr. RD Kandou Manado from January 2013 to December 2015, found that most ovarian cancer patients were multiparity (68.42%), followed by primiparity (24.21%) and nulliparity (7.37%) women. It was the same findings found by researchers. This was incompatible with the previous study showing that parous women had a lower risk of ovarian cancer than nulliparous women (Pike *et al.*, 2004). Increased risk of ovarian cancer among parous women may be due to high ovulation cycle which caused the cumulative effect of any minor trauma to the ovarian epithelium that led to the malignant transformation of the cell (Mahdavi *et al.*, 2006).

Histopathological classification (Table 1) shows that the most histopathologic type of patients was serous (66.67%) followed by mucinous (33.33%). This result was also found in the research conducted by Chang *et al.* (2018) that showed the most common types of EOC histopathology were (1) serous (43.3%), (2) clear cell (22.8%), (3) endometrioid (17.3%), and

Table 2. Hemoglobin levels before and after six cycles of paclitaxel-cisplatin chemotherapy.

	N	Hemoglobin Level (g/dl)		p
		Mean	SD	
Before chemotherapy I	3	12.05	0.79	0.282
After chemotherapy VI	3	10.69	0.85	

Table 3. Platelet levels before and after six cycles of paclitaxel-cisplatin chemotherapy.

	N	Platelet Level (10 ³ /μl)		p
		Mean	SD	
Before chemotherapy I	3	378.5	205.02	0.569
After chemotherapy VI	3	326.9	105.65	

(4) mucinous (11.2%). Of all patients, the most common EOC patients are 46–60 years old (Table 1). Aging increased risk of ovarian cancer from 15.7 to 54 per 100,000 women with ages from 40 to 79 years (Partridge and Barnes, 1999). Table 1 showed that two patients never got formal education (66.67%) and one patient finished primary school program. Their jobs were farmer (33.33%), housewife (33.33%), and one of them did not work (33.33%).

Differences in hemoglobin, platelets, and leukocytes levels before the first and after the sixth chemotherapy were because of how paclitaxel and cisplatin were cytotoxic drugs that induced myelosuppression by directly impairing hematopoiesis in the bone marrow (Kumar *et al.*, 2010; Wilson *et al.*, 2007). Paclitaxel causes myelosuppression by binding strongly with bone marrow cells' microtubules, thus preventing depolymerization. This process later causes mitosis inhibition then apoptosis in cell division (Anderson *et al.*, 2002). Whereas cisplatin binds covalently with bone marrow cells' DNA to form intra and interstrand cross-links DNA that causes DNA damage during replication (Perry, 2008). Mechanism of those chemotherapeutic drugs resulted in a decrease of hemoglobin, platelets, and leukocytes levels (Wilson *et al.*, 2007).

Grade 0 of thrombocytopenia and leukopenia was found in this study (Tables 3 and 4). The highest side effect observed was anemia grade 1 with a mean value of 10.69 g/dl after the sixth chemotherapy (Table 2). According to Gynecologic Oncology Group, anemia grade 1 referred to hemoglobin with a range between 10.0 and 12.0 g/dl. Cisplatin-induced nephrotoxicity that led to anemia through decreased renal production of erythropoietin. Erythropoietin is a cytokine produced in the kidneys that stimulate erythropoiesis in patients. Impaired erythropoiesis will decrease the production of red blood cells and hemoglobin levels (Rodgers *et al.*, 2012).

CONCLUSIONS

There were differences of hemoglobin, platelet, and leukocyte levels before the first and after the sixth cycle of paclitaxel-cisplatin chemotherapy. Low side effects of paclitaxel-cisplatin (anemia grade 1) made these chemotherapeutic drugs highly recommended for EOC patients' therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

Table 4. Leukocyte levels before and after six cycles of paclitaxel-cisplatin chemotherapy.

	N	Leukocyte Level (10 ³ /μl)		p
		Mean	SD	
Before chemotherapy I	3	11.32	7.23	0.517
After chemotherapy VI	3	8.28	5.03	

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