Evaluation of CA 125, BUN, and Creatinine Serum in Ovarian Cancer Patients Receiving Paclitaxel-Cisplatin Chemotherapy Treatment

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Abstract: The effectiveness and side effects of paclitaxel-cisplatin chemotherapy were assessed from the patient's treatment progress and toxicity level. The objective was to evaluate these two criteria through the assessment of CA 125, BUN, and creatinine serum in patients as an approach to overcome the data limitation at Sanglah General Hospital. Observational retrospective research with patients who had epithelial ovarian cancer (EOC) at Stages I, II, III, and IV was conducted from February-March 2018. Patients' blood samples were checked before the first and after the sixth cycle of chemotherapy. The data were processed with the Shapiro-Wilks normality test. As for the abnormally distributed data, they were analyzed statistically using the Wilcoxon test in SPSS. The mean values of CA 125 before the first and after the sixth chemotherapy cycles were 9,429.6 ± 1,5978.7 U/ml and 31.65 ± 36.07 U/ml, respectively (*p*-value= 0109). The mean values of BUN parameter were 10.63 ± 2.95 mg/dl and 14.83 ± 7.176 mg/dl (*p*-value= 0.315), respectively. The creatinine serums were averagely 0.693 ± 0.0929 mg/dl and 0.78 ± 0.2053 mg/dl (*p*-value= 0.417), respectively. There were differences in the levels of CA 125, BUN, and creatinine serum before the first and after the sixth cycles.

1 INTRODUCTION

Indonesia had the third highest incidence of ovarian cancer cases in Asia in 2012 (Raezi *et al.,* 2016). In 2014, ovarian cancer was the second most common gynecological cancer in women at Sanglah Hospital (Dhitayoni and Budiana, 2017). Chemotherapy is a therapy given to ovarian cancer patients by administering cytotoxic drugs either in single or in combination regimens (Braybrooke, 2011). According to PERMENKES RI No. 72 in 2016 on the Standards of Pharmaceutical Services in Indonesian Hospitals, a pharmacist is obliged to monitor the effectiveness and safety of the chemotherapy given to the patients by preparing the cytostatic compound and calculating the accurate dosage according to the chemotherapy protocol (Direktorat Jenderal Bina Kefarmasian dan Alat Kesehatan, 2016). Paclitaxel combined with a platinum-based regimen is known to be the most frequently used chemotherapy regimen for epithelial ovarian cancer (EOC) patients. The paclitaxel-cisplatin combination is currently the first-line regimen for ovarian cancer patients. Three trials have established the paclitaxel-cisplatin combination therapy as the standard regimen in advanced EOC patients. Therefore, this regimen is used at Sanglah

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General Hospital (Ozols *et al.,* 2000). The regimen efficacy can be evaluated by CA 125, i.e., an ideal tumor marker of epithelial ovarian cancer (Gupta and Lis, 2009). Aside from its therapeutic effects, chemotherapy triggers various side effects, particularly on renal function. The use of paclitaxel-cisplatin for cervix cancer at Sanglah General Hospital has been proved to elevate BUN level and decreases creatinine serum after the third cycle of chemotherapy (Noviyani *et al.,* 2016). However, the data of the therapeutic effect and side effect of a paclitaxel-cisplatin regimen for ovarian cancer treatment at Sanglah General Hospital remain limited. Hence, this research aimed to evaluate the difference in the levels of CA 125, BUN, and creatinine serum of EOC patients before the first cycle and after the sixth cycle of chemotherapy.

2 MATERIALS AND METHODS

2.1 Materials

The source of the research material was patients' medical records from January 2017 to May 2018. All data were obtained from a collecting form and summarized using a data summary form. This research used a set of computer unit containing SPSS software.

2.2 Methods

This observational retrospective research was located at Sanglah General Hospital, Denpasar, Bali and conducted from January to March 2018. The research subject was selected with consecutive sampling. The research commenced following the approval granted by the Research and Development Ethics Commission, Faculty of Medicine/Sanglah General Hospital, Denpasar [Ethical Clearance number: 87/UN.14.2/KEP/2017].

The inclusion criterion was EOC patients at Stage I, II, III, or IV who had consented to the collection of their CA 125, BUN, and creatinine serum data for research purposes. The exclusion criterion was patients with renal dysfunction before the chemotherapy started. The information obtained from the data collecting form was summarized and analyzed afterward.

2.3 Data Analysis

The summarized data were analyzed statistically in SPSS. The data were processed with the Shapiro-Wilks normality test. The data with normal distribution were analyzed with a dependent t-test, while the abnormally distributed ones were later examined using the Wilcoxon test with a 95% confidence level (*p= 0.05). The conditions before the first and after the sixth cycle were concluded as significantly different if the *p-value of the collected data was <0.05.

3 RESULTS AND DISCUSSION

3.1 Patients' Characteristics

The number of samples collected from February to May 2018 was three. All samples fulfilled the inclusion criterion. Their characteristics are described in Table 1.

Ovarian cancer risk increases sharply after the age of 40 years old and tends to reach its peak at the age of 50-60 years old (Arania and Indri, 2015). The ovarian cancer risk elevates as the age increases until around 70 years old (Goodman *et al*., 2003). According to Table 1, the samples involved in this research are mostly of 41-60 years old.

Women need to receive education and information about gynecological health from the age of adolescence. The lack of knowledge and information about the risk factors and symptoms leads to limited awareness of ovarian cancer. The latest formal education of one of the three samples involved in this research was primary school. Meanwhile, the rest had never received any formal education at school. The low educational level of the

Table 1: Patients' Characteristics

Characteristics		Number (N=3)	Percentage (%)
Age	20-40 y.o.	1	33.3
	41-60 y.o.	2	66.7
Educational Level	No formal education	2	66.7
	Elementary school	1	33.3
Occupational Status	Farmer	1	33.3
	Employee	1	33.3
	Unemploy-ed	1	33.3
Marital Status	Married	1	33.3
	Single	2	66.7
Cancer Classification	Serous	2	66.7
	Mucinous	1	33.3
Cancer Stage	I	1	33.3
	III	2	66.7

N = Number of total samples

samples suggests that education and information about ovarian cancer are highly needed since adolescence (Rachmani *et al.*, 2012).

One of the three samples was married and had more than one child, while the other two were single and had no children. Patients who have not given birth to any children have a higher risk of developing ovarian cancer (Permuth-Wey and Sellers, 2009). One of the three samples was diagnosed with Stage I ovarian cancer and the rests were diagnosed with Stage III ovarian cancer. This condition shows that ovarian cancer is most likely diagnosed at later stages due to its ambiguous and non-specific symptoms at the early stage. Patients probably confuse them with other less severe diseases (Roett and Evans, 2009). Also, there is currently no routine and accurate test to detect early-stage ovarian cancer in general population; therefore, most women are not diagnosed until the tumors grow and metastasize to other vital parts of the body (Badgewell and Bast, 2007).

3.2 CA 125

CA 125 is a tumor marker used to diagnose ovarian cancer in women. It has the highest specificity (80%) compared to other tumor markers, such as CA 19-9 (36.4%) and CEA (8.1%) (Malati, 2007). CA 125 is secreted by abnormal epithelial cells and found in 83% of epithelial ovarian cancer patients (Liao *et al.,* 2014).

In this research, CA 125 data were collected before the first and after the sixth cycle of chemotherapy. These data showed an abnormal distribution. The results of the Wilcoxon test are shown in Table 2.

According to Table 2, there is no significant difference between the CA 125 values before the first and after the sixth cycle of chemotherapy (p*-value>0.05). A larger sample is, however, required for the next stage of this research to get a more accurate result. On the other hand, clinically, the mean values of the samples show a decreasing CA 125 before the first and after the sixth cycle of chemotherapy, i.e., 9,429.6 U/ml and 31.65 U/ml, respectively The CA 125 value of a normal individual is lower than 35 U/ml (Agarwal and Kehoe, 2010). The reduction of CA 125 value to the normal range after the sixth cycle suggests that the paclitaxel-cisplatin chemotherapy contributes to good therapeutic response in ovarian cancer patients at Sanglah General Hospital. Based on the information collected from 223 patients, Lee *et al.* (2016) explain that the CA 125 values decrease to the normal range after the first cycle of paclitaxel-cisplatin chemotherapy and normalize within three cycles of chemotherapy.

Table 2: The Results of the Wilcoxon Test of CA 125 Before the First and After the Sixth Cycle of Chemotherapy

	N	CA 125		P
		Mean	SD	
Before first cycle	3	9429.6	15978.74066	0.109 NS
After sixth cycle	3	31.6467	36.06815	

Paclitaxel works by interrupting the production of microtubules, stabilizing the existing microtubules, and inhibiting their destruction (Lacy *et al.,* 2004). It arrests the cell cycle at the G2/M phase and leads to apoptosis (Barbuti and Chen, 2015). Meanwhile, cisplatin works by binding to DNA—leading to the formation of interstrand and intrastrand crosslinks—and interrupting DNA synthesis and replication in cell proliferation (Miller *et al.,* 2010). The reduction of CA 125 value compared to the previous cycle of chemotherapy indicates good treatment response, whereas an elevated CA 125 value signifies the possibility of chemo-resistance, which prompts the replacement of ongoing regimen with another therapeutic one (Agarwal and Kehoe, 2010).

3.3 BUN

The decomposition process of protein produces a waste product called urea. A renal function evaluation was conducted by examining the BUN value of the samples. An elevated BUN is a characteristic identified in the plasma of patients with severe renal dysfunction (Sherwood, 1996). The BUN value increases along with the

Table 3: The Results of the Dependent T-Test of BUN Values Before the Firstnd After the Sixth Cycle of Chemotherapy

	N	BUN		P
		Mean	SD	
Before the first cycle	3	10.6333	2.94845	0.315 NS
After the sixth cycle	3	14.8333	7.17658	

N= number of samples,
SD = standard deviation,
P= significant value.

Table 4: The Results of the Dependent T-Test of Creatinine Serum Before the First and After the Sixth Cycle of Chemotherapy

	N	Creatinine Serum		P
		Mean	SD	
Before the first cycle	3	0.6933	0.09292	0.417 NS
After the sixth cycle	3	0.7767	0.20526	

N= number of samples,
SD = standard deviation,
P = significant value

deterioration of renal function. Therefore, the evaluation of BUN value decides whether an ovarian cancer patient experiences renal dysfunction (Duong and Jin-Yew, 2006). Since the collected BUN data before the first and after the sixth cycle of chemotherapy showed a normal distribution, they were analyzed with a dependent t-test. The results are summarized in Table 3.

The kidneys receive approximately 25% of cardiac output and have a crucial role in absorbing drugs. The high rate of drug uptake and delivery results in a high intracellular concentration of substances. These substances are then processed in an extensive metabolism that leads to the production of reactive oxygen species and toxic metabolites (Perazella, 2009). Another study with 18 cervical cancer patients who undergo cisplatin chemotherapy shows an elevated BUN value and creatinine serum after the fifth cycle of chemotherapy (Arankumar *et al.,* 2012).

Paclitaxel likely leads to peripheral neuropathy and hematological side effects, such as neutropenia and leukopenia (Lawrenti, 2013). Meanwhile, cisplatin tends to be dominant in causing renal side effects. It accumulates in the kidneys and interacts with sulfhydryl compounds, which, thereby, increases renal membrane fragility and induces the depletion of intracellular glutathione. Renal damage is associated with acute focal tubular necrosis and the dilatation of convoluted tubules and collecting ducts. Clinically, the damage is manifested as an increase in BUN, creatinine serum, and electrolyte disturbance (Arankumar *et al.,* 2012). However, BUN values are not fully determined by patients' renal function. The other influencing factors include patients' protein intake, muscle injury, necrosis, and liver function (Duong and Jin-Yew, 2006).

3.4 Creatinine Serum

Creatinine serum is the most sensitive renal function indicator because the human body constantly produces this substance. Renal dysfunction causes an increase in creatinine serum (Ignativicius and Workman, 2006). The collected data before the first and after the sixth cycle of chemotherapy had a normal distributed. These data were then analyzed with a dependent t-test. The results are shown in Table 4.

The results showed that there was no significant difference between the creatinine serum levels before the first and after the sixth cycle of chemotherapy ($p > 0.05$). However, clinically, there was an elevated creatinine serum after the sixth cycle of chemotherapy. This elevation was still within the normal range of creatinine serum value (0.6-1.3mg/dl) (Duong and Jin-Yew, 2006). Such increase implies that paclitaxel-cisplatin causes a renal side effect on patients receiving chemotherapy. From the data of 18 patients who undergo cisplatin chemotherapy, Arankumar *et al.* (2012) conclude that the levels of the creatinine serum before the first and after the fifth cycle of chemotherapy are significantly different. They also state that the creatinine serum of the patients increases by 44.87% after the fifth cycle of the cisplatin chemotherapy (Arankumar *et al.*, 2012).

In addition to the effects of the chemotherapy, several factors can contribute to the increase of creatinine serum, such as muscular dystrophy, malnutrition, the reduction of muscle mass, and the use of several drugs like cimetidine and ascorbic acid (Indrawati *et al.,* 2011). Compared to another platinum-based agent such as carboplatin, cisplatin has a higher nephrotoxic effect caused by its lower selectiveness to tumor cells. Besides, carboplatin is a derivative of cisplatin. Therefore, carboplatin is more stable than cisplatin; however, they exhibit an equivalent activity against some types of cancer (Anderson *et al.,* 2002). To prevent any cisplatin-induced nephrotoxicity, hydration and supplementation are highly recommended for EOC patients. For patients administered with ≤ 50 mg/m^2 cisplatin, 2-4 L NS and potassium supplementation are required. In addition to this recommendation, magnesium supplementation is necessary for patients given with ≥ 50 mg/m^2 cisplatin. Meanwhile, patients receiving ≥ 100 mg/m^2 cisplatin are recommended to also take mannitol (Crona *et al.,* 2017).

4 CONCLUSION

There are differences in the levels of CA 125, BUN, and creatinine serum before the first and after the sixth cycle of chemotherapy. There are a decrease in CA 125 and elevations in BUN level and creatinine serum after the sixth cycle of chemotherapy.

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