UNIVERSA MEDICINA

September-December, 2016 *Vol.35 - No.3*

Paclitaxel-carboplatin chemotherapy induced hematologic toxicities among epithelial ovarian cancer patients

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ABSTRACT

BACKGROUND

Epithelial ovarian cancer (EOC) is one of the most common cancers diagnosed in Indonesian women. A combination of paclitaxel and carboplatin is used to treat EOC as standard chemotherapy which is known to have hematologic toxicities. This study aimed to investigate the effect of combined paclitaxel-carboplatin chemotherapy on hematologic status in EOC patients managed at Dr. Hasan Sadikin General Hospital, Bandung, West Java.

METHODS

All patients with confirmed pathological diagnosis of EOC at Dr. Hasan Sadikin General Hospital in the period of 2013 to 2014 were registered. Only patients with complete hematologic data before and after chemotherapy were collected and compared using the paired non-parametric Wilcoxon and McNemar tests.

RESULTS

In total there were 147 patients with EOC (median age 46 ± 12 years), with the most dominant pathological diagnosis of mucinous (32.7%) and serous (29.3%) types. Only 33 patients had hematologic data before the initiation of chemotherapy. There was a significant decrease after chemotherapy including hemoglobin level (12.0 vs 10.9 g/dL, p=0.013), erythrocyte count (4.53 vs 3.74 million/μL, p<0.001), leukocyte count (7,700 vs 4,000/mm^3 p<0.001) and platelet count (343,000 vs 215,000/mm^3, p<0.001). Interestingly, anemia cases after chemotherapy were predominant (87.9%) compared with erythopenia, leukopenia, thrombocytopenia i.e. 39.4%, 57.6%, and 27.3% respectively.

CONCLUSIONS

This study confirmed the hematologic toxicities after paclitaxel-carboplatin chemotherapy in EOC patients treated in Hasan Sadikin General Hospital, West Java. The hemoglobin concentration may serve as prognostic factor. Further studies directed to other factors such as genetic factor for polymorphisms may be encouraged to explore the decrease of the hematologic indices.

Keywords: Anemia, erythropenia, leukopenia, thrombocytopenia, epithelial ovarian cancer, paclitaxel-carboplatin

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Univ Med 2016;35:165-70
DOI: 10.18051/UnivMed.2016.v35.165-170
pISSN: 1907-3062 / eISSN: 2407-2230

INTRODUCTION

Epithelial ovarian cancers (EOC) are still burdening female health nowadays. The World Health Organization estimated that this type of cancer accounted for 151,905 female deaths worldwide in 2012.[1] In Indonesia, EOC, together with other ovarian cancers are placed in the third rank of the most prevalent gynecologic cancers, next to breast and cervical cancers.[2] There are several risk factors associated with EOC, for example age older than 50 years, no pregnancy and lactation history and family history of breast and ovarian cancers.[3]

Management of EOC consists of explorative surgery and chemotherapy.[3] The standard regimen for EOC is intravenous paclitaxel 175 mg/m^2 and carboplatin area under curve is 7.5 for six cycles.[3] These regimen components, especially carboplatin have several side effects in bone marrow, resulting in suppression of hematopoiesis. Common hematologic toxicities developing in patients include anemia, thrombocytopenia, and leukopenia.[4] These side effects are mediated by the formation of DNA-protein cross-linking that further disrupts cell-cycle regulation and suppresses cell growth.[5]

Chemotherapy is a standardized process performed at Dr. Hasan Sadikin Hospital, Bandung. There is a need for research on the hematologic impact of the paclitaxel- carboplatin combined therapy in EOC patients.

Therefore, the aim of this study was to explore EOC patients treated in Dr. Hasan Sadikin General Hospital, Bandung and to investigate the effect of the paclitaxel-carboplatin regimen.

METHODS

Research design

This study employed an analytical retrospective cohort study design conducted using medical records of patients treated in Dr. Hasan Sadikin General Hospital, Bandung. The medical records were collected in the period of January 2013 to December 2014.

Research subjects

All subjects with a pathological diagnosis of EOC were recruited for this study. Other types of ovarian cancer including malignant granulosa cell tumor and teratoma were excluded. Clinical, laboratory and chemotherapy data including the number of chemotherapy cycles were recorded.

Laboratory analysis

As for laboratory data, hematologic findings were collected before the initiation of chemotherapy and after chemotherapy of 6 cycles. Anemia was defined at a Hb concentration of <12.0 g/dL, erythropenia at an erythrocyte count of <3.6 million/μL, leukopenia at a leukocyte count of <4400/mm^3 and thrombocytopenia at a platelet count of <150,000/mm^3. Only patients with complete hematologic data and number of chemotherapy cycles were included.

Statistical analysis

Descriptive statistics for clinical data and histopathological category of EOC were shown as frequencies. McNemar and Wilcoxon tests were used to determine the association of the hematologic status before and after chemotherapy. For the statistical analyses, the SPSS 22.0 software package (SPSS Inc. Chicago. IL) was used.

Ethical clearance

The ethical clearance required for this study was granted by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran - Dr. Hasan Sadikin General Hospital, Bandung (No. 3010/UN6.C.C1/PP/2015).

RESULTS

In total, there were 147 women with a median age of 46 years and an age range of 14 to 81 years, among whom more than half (59.2%) were younger than 50 years, i.e. the cut-off point of menopausal age in Indonesia. The most common histopathological types found in these

patients were the mucinous and serous types, comprising 32.7% and 29.3%, respectively. Many of the subjects were lost to follow up; some of them refused to undergo chemotherapy management or did not have complete hematologic laboratory data, resulting in only 33 patients with complete laboratory and chemotherapy data who were further analyzed in this study. Of these EOC patients, most (54.5%) were diagnosed before the age of 50 years and were already in stage III (51.5%). Only 12 of 33 patients completed the six cycles of chemotherapy, while others underwent only three to five cycles (Table 1). There was no documentation in the medical records regarding the cause of early termination of the chemotherapy.

The hematologic findings were not normally distributed, except for erythrocyte counts. Therefore the hemoglobin, leukocyte and platelet counts were presented as mean and standard deviation, whereas the erythrocyte count was presented as median and range. The hemoglobin level and the erythrocyte, leukocyte and platelet counts decreased significantly after chemotherapy as depicted in Table 2.

Using categorical laboratory references, the distribution of patients with anemia, erythropenia, leukopenia, and thrombocytopenia also decreased significantly as shown in Table 3. Interestingly, after chemotherapy there was a predominant increase in anemia in 20 of 33 patients (60.6%), while erythropenia, leukopenia, and thrombocytopenia increased only in 13/33 (39.4%), 19/33 (57.6%), and 9/33 (27.3%) of patients, respectively (Table 3).

Table 1. Characteristics of epithelial ovarian cancer patients with complete hematologic data (n=33)

Characteristic	n (%)
Age group (years)	
<50	18 (54.5)
50-59	9 (27.3)
≥60	6 (18.2)
Location of primary tumor	
Bilateral	9 (27.3)
Right	11 (33.3)
Left	7 (21.2)
Unclear	6 (18.2)
Histopathological classification	
Mucinous	12 (36.4)
Serous	12 (36.4)
Endometrioid	4 (12.1)
Clear cell	1 (3.0)
Mixed	1 (3.0)
Undifferentiated	3 (9.1)
Parity	
Nulliparous	5 (15.2)
Primiparous (1)	12 (36.4)
Multiparous (2-4)	13 (39.4)
Grand multiparous (>4)	3 (9.1)
Abortion	
0	27 (81.8)
1	4 (12.1)
2	2 (6.1)
FIGO stage	
I	4 (12.1)
II	5 (15.2)
III	18 (54.5)
IV	3 (9.2)
Recurrent	3 (9.1)

*FIGO=International Federation of Gynecology and Obstetrics

The age at clinical presentation of EOC was analyzed to determine whether it was associated with the decrease in all post-chemotherapy hematologic findings, but the results showed no association (data not shown).

Table 2. Difference of hematologic findings between pre- and post-chemotherapy

Hematologic findings	Chemotherapy				p
	Pre		Post		
	Median	Range	Median	Range	
Hemoglobin, (g/dL)	12.0	(5.5 - 14.6)	10.9	(5.6 - 13.9)	0.013*
Erythrocyte count (million/µL)	4.53	(2.05 - 6.46)	3.74	(1.91 - 5.19)	<0.001*
Leukocyte count (/mm^3)	7.7	(2.10 - 18.90)**	4.0	(2.8 - 7.8) **	<0.001*
Platelet count (/mm^3)	343	(125 - 771)**	215	(87 - 606) **	<0.001*

*p values were statistically significant. Analysis conducted using Wilcoxon test. Significance level p=0.05
**Values were x1.000

Table 3. Chemotherapy induced anemia, erythropenia, leukopenia and thrombocytopenia in adults

Hematologic status	Chemotherapy		p
	Pre (n)	Post (n)	
Hemoglobin			
Low (anemia)	16	29**	0.001*
Normal	17	4	
Erythrocyte count			
Low (erythropenia)	5	13**	0.039*
Normal	28	20	
Leukocyte count			
Low (leukopenia)	1	19**	<0.001*
Normal	32	14	
Platelet count			
Low (thrombocytopenia)	1	9**	<0.001*
Normal	32	24	

*p values were statistically different. Analysis conducted using McNemar test. Significance level p=0.05
**Low hematologic counts after chemotherapy

DISCUSSION

Our study explored the hematologic findings before and after paclitaxel-carboplatin chemotherapy among patients with epithelial ovarian cancer (EOC) and confirmed that there was a significant decrease in hematologic findings such as anemia, erythropenia, leukopenia, and thrombocytopenia. These findings are coherent with studies in advanced EOC cases, either using conventional or dose-dense paclitaxel-carboplatin regimen.[4,7] The paclitaxel-carboplatin regimen is known to have a lower incidence of high-grade neutropenia in EOC chemotherapy compared to its alternative regimen, docetaxel and carboplatin.[8] In our study we did not perform neutrophil counts; however, the hemoglobin level was significantly reduced after chemotherapy. Hemoglobin levels before chemotherapy have proposed to have prognostic value in terms of progression-free survival time for EOC patients.[9] The paclitaxel-carboplatin regimen is also used in other neoplasm cases, notably non-small cell lung cancer (NSCLC) and urothelial cancer, and has been associated with febrile neutropenia.[10] Furthermore, anemia, neutropenia, and thrombocytopenia are the most frequently observed toxicities after paclitaxel-carboplatin chemotherapy in advanced urothelial cancer patients in Japan.[11] These hematologic toxicities are also observed in NSCLC, and in addition, the paclitaxel-carboplatin regimen has been revealed to produce more severe anemia and neutropenia in Asian than in non-Asian patients.[12]

As hematopoietic stem cells undergo senescence, many lesions and mutations are accumulated in their DNA, producing exhaustion in stem cell division.[7] This underlying mechanism may be responsible for the more severe hematologic toxicities of cytotoxic chemotherapy regimens, for example cyclophosphamide-doxorubicin in breast cancer and bevacizumab-paclitaxel-carboplatin in NSCLC.[13,14] However, an association between age and severity was not documented in these studies, and another study in NSCLC cases with paclitaxel-carboplatin chemotherapy also yielded similar results.[15]

The hematologic toxicities occurring in EOC patients after having received paclitaxel-carboplatin chemotherapy are influenced by several factors, i.e. from the regimen itself and patient background. Paclitaxel exerts its cytotoxic effects by depolymerizing microtubules, thus arresting the cell cycle and inducing apoptosis.[16] However, paclitaxel only induces minimal hematologic toxicities when administered alone.[16] Carboplatin used in this regimen has a myelosuppressive effect via the mechanism of DNA-protein damage in bone marrow by means of crosslinking between them, thus resulting in decreased numbers of erythrocytes, leukocytes, and platelets, as well

as other toxic effects (neurotoxicity, ototoxicity, and nephrotoxicity).[17,18] It also seems that carboplatin may increase serum TNF-α, suppressing the development of hematologic progenitor cells.[19]

Currently, genetic polymorphisms are being investigated to determine their association with paclitaxel-carboplatin hematologic toxicity, depending on race and ethnicity. The single nucleotide polymorphisms 2677G>T/A and 3435C>T of *ABCB1* genes have been associated with neutropenia in paclitaxel chemotherapy in EOC cases in some studies,[20,21] but no association has been found in others.[22,23] Some studies in NSCLC have demonstrated that polymorphisms in drug-transporter genes *(ABCB1* and *ABCG2),* DNA-repair pathway genes (*ERCC4* and *XCC*), and apoptosis pathway genes (*CASP 8* and *CASP10*) are associated with thrombocytopenia, neutropenia, and severe hematologic toxicity, respectively, due to paclitaxel-carboplatin effects.[24-26]

One limitation of this study is the small sample size which was not appropriate to the estimated sample size due to incomplete data. Another limitation is inadequate hematologic data in each of the chemotherapy cycles, which limits statistical analysis; however, the decreasing trend in the hematologic data might be used to generalize the findings.

CONCLUSION

In conclusion, the decrease in hematologic data such as anemia, leukopenia, and thrombocytopenia after paclitaxel-carboplatin chemotherapy were confirmed in EOC patients treated in Dr. Hasan Sadikin General Hospital. The hemoglobin concentration may serve as prognostic factor. In addition, further studies are needed on genetic background factors that may play a role in the decrease in hematologic data.

CONFLICT OF INTEREST

Competing interest: No relevant disclosures.

ACKNOWLEDGEMENT

This research is part of a Progress Grants 2014 study conducted under the Oncology Working Group, Faculty of Medicine, Universitas Padjadjaran.

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