

Post-chemotherapy response of *by*

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Post-chemotherapy response of paclitaxel and carboplatin regimens in advanced stage cervical cancer types of histopathology squamous cell carcinoma and adenocarcinoma

Yohanes Adhitya Prakasa Sukoco Putra^{1*}, Meitria Syahadatina Noor²,
Ferry Armanza³, Hariadi Yuseran³, Renny Aditya⁴

¹Obstetric and Gynecology Resident, Faculty of Medicine, Universitas Lambung Mangkurat, Ulin General Hospital, Banjarmasin, Indonesia;
²Public Health Science, Faculty of Medicine, Universitas Lambung Mangkurat, Banjarmasin, Indonesia;
³Gynecology Oncologist, Department of Obstetric and Gynecology, Ulin General Hospital, Banjarmasin, Indonesia;
⁴Social Obstetric, Department of Obstetric and Gynecology, Ulin General Hospital, Banjarmasin, Indonesia;

*Corresponding author:
Yohanes Adhitya Prakasa Sukoco Putra;
Obstetric and Gynecology Resident,
Faculty of Medicine, Universitas
Lambung Mangkurat, Ulin General
Hospital, Banjarmasin, Indonesia;
yohanesadhitya@yahoo.com

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ABSTRACT

Background: Cervical cancer incidence in South Borneo was placed 10th in Indonesia. South Borneo Department of Health revealed 1,930 patients diagnosed with cervical cancer in 2019. The main therapy for advanced cervical cancer was radiotherapy, chemotherapy, and combination. This study aims to demonstrate that paclitaxel plus carboplatin regimens have a better post-chemotherapy response in patients with advanced cervical cancer squamous cell carcinoma than adenocarcinoma.

Methods: This study used an analytical observational method with a cross-sectional approach. The sample size was taken during the period during which this study was conducted from January 2015 to December 2020 and was taken by total sampling and divided into 2 groups consisting of patients with advanced cervical cancer, squamous cell carcinoma, and adenocarcinoma histological types. Data were analyzed using SPSS version 21.0 for Windows.

Results: A total of 202 individuals made up the study's sample, including 54 (26.8%) adenocarcinomas, 148 (73.2%) patients with advanced cervical cancer, and patients with various histological kinds of squamous cell carcinoma. About 107 (52.9%) patients provided complete responses, whereas up to 95 (47.1%) patients provided incomplete responses.

Conclusion: Squamous cell carcinoma, the histological type of cervical cancer, responds to treatment better than adenocarcinoma.

Keywords: Post-chemotherapy response, squamous cell carcinoma, adenocarcinoma

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INTRODUCTION

A malignancy of the uterine cervix is cervical cancer. The most prevalent type of cancer and the major cause of death worldwide is cervical cancer.¹ According to data from GLOBOCAN 2020, cervical cancer is placed in 7th place globally for incidence and 9th on mortality cause.^{1,2}

Cervical cancer incidence in South Borneo was placed 10th in Indonesia. South Borneo Department of Health revealed that 1,930 patients were diagnosed with cervical cancer in 2019.³ Ulin Hospital, Banjarmasin, which depicted an increase in cervical cancer incidence yearly. In 2018, cervical cancer was diagnosed in 1,447 patients.³

Cervical cancer seriously impacts

women, such as losing the ability in sexual intercourse. This is the fear cervical cancer patients often experience and causes a decreased quality of life.^{4,5}

The main therapy of advanced cervical cancer was radiotherapy, chemotherapy, or chemoradiation, a combination of chemotherapy and radiotherapy.^{6,7} However, not all developing countries have access to radiotherapy, the main management of cervical cancer. Inaccessible radiotherapy rendered to chemotherapy administration as the means to replace radiotherapy; this led to cervical cancer undertreatment. This condition also happens in Indonesia, where not all hospitals have access to radiotherapy as cervical cancer therapy, increasing the case fatality rate. Treatment for advanced

cervical cancer by chemotherapy only gave rise to undertreatment cases. Ulin hospital, Banjarmasin, is one of the referral hospitals in Borneo for cervical cancer treatment. The problem that may arise is the limited availability of radiotherapy facilities causes the patient to wait longer. Due to that, therapy given to patients are more likely to be chemotherapy, causing undertreatment.^{4,8,9}

The chemotherapy for advanced cervical cancer was in combination with platinum and taxane groups. The platinum drug class was often used as cisplatin or carboplatin; the taxane group usually given was paclitaxel. Several studies stated both groups were used as first-line therapy.^{4,9}

One of the obstacles that may surface is that advanced-stage cervical cancer

patients need radiotherapy as the main management; however, it is unavailable. Therefore, they were only given chemotherapy without radiotherapy. Based on those mentioned above, this study aims to prove the post-chemotherapy response of paclitaxel and carboplatin regimen in advanced-stage cervical cancer patients, which squamous cell carcinoma was found from histopathology was better compared to adenocarcinoma at Ulin hospital, Banjarmasin.

METHODS

This research used an analytical observational method with a cross sectional approach. The sample size was determined by total sampling and divided into 2 groups: patients with advanced cervical cancer, histological kinds of squamous cell carcinoma, and adenocarcinoma. The study's time frame was from January 2015 to December 2020. The sampling method in this study was carried out by total sampling based on inclusion and exclusion criteria. Inclusion criteria for this study were patients with diagnosis of advanced cervical cancer, patients with advanced cervical cancer with anatomical pathology results of squamous cell carcinoma and adenocarcinoma, and patients with advanced cervical cancer with histopathological types of squamous cell carcinoma and adenocarcinoma who underwent chemotherapy regimens of paclitaxel and carboplatin as many as 6 series of chemotherapy for 6 months and no difference in chemotherapy regimen dose in this study.

Exclusion criteria were patients with advanced cervical cancer with other cancers (double primary) such as ovarian cancer, vaginal cancer, or vulvar cancer, cervical cancer patients who had undergone surgery, and patients with advanced cervical cancer who had radiotherapy. Identification of response to chemotherapy was obtained from physical examination data such as clinical tumor size by clinical measurement using centimeters in medical records reviewed by a gynecologic oncologist. The results of this study will be analyzed using the Chi-Square test for each category with a 95% confidence level (95% CI) with an alpha value of 0.05 ($\alpha = 0.05$) with SPSS version

21.0 for Windows.

RESULTS

A total of 202 advanced-stage cervical cancer squamous cell carcinoma and adenocarcinoma patients enrolled in this study. They were given chemotherapy at Ulin hospital, Banjarmasin, from 2015 until 2020.

Based on a medical record search, a total of 202 subjects were enrolled according to inclusion and exclusion research criteria. The decision was based on age, parity, cervical cancer stage, histopathology result, tumor size, and differentiation degree. These characteristics data are listed in Table 1.

Table 1 displays the characteristics of the subjects included in the study. In this

study, the age group 20 – 29-year-old had the least number of patients, 7 patients with a percentage of 3.6%. The age group with the highest number of patients was 40 – 49-year-old with 75 patients (37.1%) (Table 1).

Total parity was also described in Table 1 in which nulliparity has the least of only 4 patients (2.2%). Patients with 4 or more parity have the most patients of 70 patients (34.6%). The cervical cancer stage was also depicted in the characteristics table. Advanced stage IIIA cervical cancer had the lowest number of patients, with only 18 or 8.9%. Meanwhile, advanced stage IIIB was the greatest number of patients, with 136 patients or 67.3% (Table 1).

In this study, squamous cell carcinoma was found more compared to adenocarcinoma. Adenocarcinoma

Table 1. Characteristics of advanced-stage cervical cancer patients (IIB-IIIB) squamous cell carcinoma and adenocarcinoma who were given chemotherapy at Ulin hospital, Banjarmasin, from 2015 to 2020.

Characteristics	Total (N=202)	Percentage (%)
Age (years old)		
20-29	7	3.6
30-39	34	16.8
40-49	75	37.1
50-59	68	33.6
≥ 60	18	8.9
Parity		
0	4	2.2
1	25	12.3
2	59	29.2
3	44	21.7
≥ 4	70	34.6
Stage		
IIB	48	23.8
IIIA	18	8.9
IIIB	136	67.3
Histopathology		
Squamous Cell Carcinoma	148	73.2
Adenocarcinoma	54	26.8
Tumor size (cm)		
≤ 4	75	37.1
> 4	127	62.9
Differentiated		
Well	53	26.2
Moderate	139	68.8
Poor	10	5.0

Table 2. Comparison of post-chemotherapy response on advanced-stage cervical cancer (IIB-IIIB) squamous cell carcinoma and adenocarcinoma.

Histopathology	Response (N=202)		Total	p	PR
	Complete (N=107)	Incomplete (N=95)			
SCC, n (%)	96	52	148 (73.2)	0.000*	7.217
AdenoCa, n (%)	11	43	54 (26.8)		

PR: Prevalence Ratio; AdenoCa: Adenocarcinoma *Statistically significant if p-value less than 0.05

was found in only 54 patients; however, squamous cell carcinoma was discovered in 148 patients. When compared based on percentage alone, adenocarcinoma was found in only 26.8%, while squamous cell carcinoma was discovered in 73.2% (Table 1).

Tumor size and differentiation were also seen in this study. Tumor size was classified into 2 groups: 4 centimeters or less and more than 4 centimeters. Tumor-sized 4 centimeters or less were detailed in 74 (37.1%) patients, while tumor-sized more than 4 centimeters were reported in 127 (62.9%) patients (Table 1).

The well-differentiated tumor was obtained in 53 (26.2%) patients. In this study, most patients have moderately differentiated in 139 (68.8%) patients. The least amount was poorly differentiated in 10 (5.0%) patients (Table 1).

Table 2 describes the comparative analysis of the post-chemotherapy response between squamous cell carcinoma and adenocarcinoma. Chi-square analysis concluded a significant difference with a p-value of 0.000 ($p < 0.005$). This result showed that post-chemotherapy response in advanced-stage cervical cancer squamous cell carcinoma was better compared to adenocarcinoma. The analysis revealed PR of 7.217 demonstrated that advanced-stage cervical cancer squamous cell carcinoma patients who received chemotherapy for 6 series in 6 months using paclitaxel and carboplatin tended to give 7.217 times higher therapeutic response compared to adenocarcinoma with the same regimens (Table 2).

DISCUSSION

Patient characteristics are age, fertility rate, staging, histopathologic type, tumor size, and differentiation. The biggest age

range group is 40-49 years old, consisting of 75 patients (37.1%). Meanwhile, the smallest age range group is 20-29 years old, consisting only of 7 patients (3.6%). This result is supported by the previous study in 2019, which found that cervical cancer patients have a mean of 49 years of age with an age range of 24-69 years.¹⁰ Similar study was done by a previous study and the result stated that most cervical patients are 45-49 years old.¹¹ Because of the repeated trauma on the cervix that usually happens in a sexually active patient, cervical cancer was mainly found in the sexually active age group. In a woman over 35 years old, the squamocolumnar junction will move from the outside to the inside of the cervical canal, causing proliferation and, if uncontrolled, causing cell dysplasia that leads to malignancy.¹²

About 70 patients (34.6%) have given birth to 4 or more babies, while only 4 (2.2%) patients have never given birth. The meta-analysis study done by Tekalegn Y et al., in 2021 also found a similar result where women that gave birth to 3 children or more had a 2.4 times higher possibility of having cervical cancer compared to women that gave birth less than 3 times.¹³ This is also supported by a previous study that found a higher birth rate increase the risk of cervical cancer occurred.¹⁴ Having more than 4 times childbirth is one of some risk factors for cervical cancer because when in childbirth, a trauma happens to the cervix, causing easier infection of HPV. Hormonal reaction and decreased immunity in pregnancy also contribute to HPV infection.^{15,16}

In this study, most patients (136 patients or 67.3%) were classified as stage III B, whereas only 18 patients (8.9%) were classified as III-A. The same result can be seen in a study by Mabuchi S et al., where most of the cervical cancer

patients were classified as III B.¹⁷ In 2019, a previous study also showed that more than half (58%) of the patients were classified as III B.¹⁰ The reason is that most of the women with cervical cancer are asymptomatic, so it is diagnosed when the cancer is already in a higher stage.³ Cervical cancer aggressivity can be seen from its stage. Epithelial cell polarization and basal membrane affect the cancer aggressivity called *Epithelial Mesenchymal Transition* (EMT). Phenotype changes from epithelial cells to mesenchymal cells play an important role in the progressivity and metastasis of cancer. EMT caused loss of epithelial markers such as E-cadherin, claudin, occluding, plakophilin, cytokeratin, and desmoplakin resulting in mesenchymal marker production such as Vim1/Vimentin, SNAI, N-cadherin, Zeb1, and Zeb2. An increase of regulation in HPV oncoprotein expression on the epithelial cells will increase the regulation of the mesenchymal gene. HPV and FGF directly contribute to the induction of EMT by triggering phenotype and molecular changes in keratinocytes. Induced EMT will prevent E-cadherin and induce Vim1 expression. Astrocyte Elevated Gene-1 (AEG-1) expression in cervical cancer cells will significantly induce the aggressivity of the cancer cells. Overexpression of AEG-1 will decrease the E-cadherin regulation but increase the Vim1 regulation. Hypoxia in cervical cancer will result in proteomic change and induce the expression of Lysyl Oxidase (LOX), a hypoxia-responsive gene. High LOX expression will increase the Vim1 expression and decrease the E-cadherin regulation so that it will cause morphological changes to mesenchymal cells in cervical cancer. These conditions will affect the increase of aggressivity of cervical cancer.¹⁸

Histopathology characteristics in this study are squamous cell carcinoma and adenocarcinoma. Most histopathological results were squamous cell carcinoma with 148 (73.2%) patients, compared to adenocarcinoma, which was only 54 (26.8%) patients. The same result was found in a previous study that showed 81.8% of histopathological test results came back as squamous cell carcinoma.¹⁹ A study by Shafiq A in 2019 had a similar result where squamous cell carcinoma is more common

at 73% compared to adenocarcinoma at only 27%.²⁰ The most common histological kind of cervical cancer, squamous cell carcinoma, was found in 2020, according to a previous study by Titiloye NA et al.²¹ Because HPV can infect squamous cells more easily than other types of cells, type 16 HPV is more closely associated with the development of squamous cell carcinoma than type 18 HPV-caused cervical adenocarcinoma, squamous cell carcinoma is a more common type of cervical cancer histopathological result than adenocarcinoma.²² Histopathological type of squamous cell carcinoma happens more commonly than adenocarcinoma because squamous cell carcinoma originates from the squamocolumnar junction, while adenocarcinoma originates from the endocervical columnar.²³

This study also observed the tumor size. Tumor size is divided into 4 cm or less and more than 4 cm. About 127 (62.9%) patients had a tumor-sized more than 4 cm, while 75 (37.1%) patients had a tumor size of 4 cm or less. A previous study also found that the most common tumor sizes observed were tumor sizes of more than 4 cm, which was 49.7 percent.²⁴ A previous study by Shafiq A in 2019 stated that a tumor size of 4 cm was found in 52.7 percent compared with a tumor size of less than 4 centimeters.²⁰ Post-chemotherapy response was also affected by tumor size. The larger the size of the tumor will affect the level of hypoxia of tumor cells. This hypoxic condition will cause changes in the response of tumor cells to hypoxic stress so that tumors become more adaptive, induce growth factors, and activate anti-apoptotic mediators to increase cell survival. Hypoxic conditions will also cause HIF-1 α activation, which will activate VEGF. This mechanism causes a decrease in chemotherapy response through various mechanisms, including angiogenesis, disruption of cell microtubule mechanisms, and activation of anti-apoptotic mediators. It will cause a decrease in cell apoptosis and increase tumor cell survival.²⁵

Most of the differentiation results are moderate differentiation, with 139 (68.8%) patients, while poor differentiation is the least with only 10 patients (5%). A previous study conducted found the same results

where moderate differentiation is the most differentiation type.²² A previous study in 2019 got the same results where 60% of differentiation is moderately differentiated among other differentiations.²² A previous study by Titiloye NA et al., in 2020 found that moderate differentiation was 52 percent compared to other differentiations.²¹ Weak VEGF expression was found in well-differentiated cells and moderate VEGF expression was found in moderate differentiation, while poor differentiation resulted in high VEGF expression. VEGF expression level will affect tumor cell angiogenesis. High levels of VEGF expression will lead to an increase in tumor cell angiogenesis. Angiogenesis is essential for tumors to be able to grow. Changes in the tumor microenvironment resulting from tumor growth and tumor hypoxia conditions will cause an angiogenic switch through HIF-1 α activity. This process will increase the regulation of pro-angiogenic factors and decrease the regulation of anti-angiogenic factors. VEGF is a potent angiogenic factor. High VEGF will cause several conditions, including the angiogenesis process, disruption of cell microtubule dynamics, and the activation of anti-apoptotic mediators such as Bcl xL, XIAP, and survivin.

Hypoxia also causes genomic instability, which increases E6 and E7 regulation so that P53 will be degraded and pRb is not activated, resulting in increased VEGF and cell survival.²³ Angiogenesis that occurs will cause abnormal neovascularization, including fragile, leaky and winding blood vessels. This neovascularization causes the distribution of chemotherapy to be disrupted. Disruption of cell microtubules results in an increase in efflux compared to the influx of cytotoxic agents, resulting in decreased cytotoxicity of chemotherapeutic agents. Activating anti-inflammatory mediators, p53 degradation, and inactivating pRb will lead to cell survival. Cells will be more adaptable to hypoxic conditions to face nutritional deficiencies or an unsupportive environment through proliferation, invasion, or metastasis.^{24,25}

In this study, the histopathological types of squamous cell carcinoma had a better response after chemotherapy than

the adenocarcinoma type with a p-value of 0.000 ($p < 0.05$). Squamous cell carcinoma type in histopathological cervical cancer was 7 times more likely to give a complete response than adenocarcinoma, as seen by the PR value of 7.217. A study by Hopkins MP et al., compared the chemotherapy response to squamous cell carcinoma and adenocarcinoma of cervical cancer and found that squamous cell carcinoma responds better to chemotherapy than adenocarcinoma.²³ A previous study had a result that supported this study where the adenocarcinoma type in cervical cancer has a poor response to chemotherapy when compared to squamous cell carcinoma.²⁴ The similar result was also found by Kfoury CFA et al., in 2019 showed squamous cell carcinoma type of cervical cancer responded more to chemotherapy than adenocarcinoma.²⁵

Various factors determine the post-chemotherapy response in cervical cancer. The most important factors in the post-chemotherapy response are Vascular Endothelial Growth Factor (VEGF) and Microvessel Density (MVD). VEGF can induce chemotherapy resistance. VEGF has a major role in the process of angiogenesis. VEGF will be activated in a hypoxic state, activating the PI3K/AKT pathway and reducing apoptosis. Decreased apoptosis will lead to increased tumor cell survival. MVD is a measuring tool used to see tumor vascularity that shows angiogenic activity so that there is a correlation between VEGF and MVD.^{23,24}

Squamous cell cervical cancer has a much lower VEGF expression compared to adenocarcinoma. Lower VEGF expression will cause lower MVD in squamous cell carcinoma cervical cancer compared to adenocarcinoma. Due to that, squamous cell carcinoma is more sensitive to chemotherapy than adenocarcinoma.¹⁹ Previous studies stated that adenocarcinoma cervical cancer has a higher VEGF expression than squamous cell carcinoma.¹⁹⁻²⁰ Meta-analysis study from Hu X in 2018 also concluded MVD impacted the therapy response and survival rate of cervical cancer patients. MVD was found to be higher in adenocarcinoma cervical cancer compared to squamous cell carcinoma.²¹ This study found several progressive post-chemotherapy

responses. These progressive responses were discovered more in adenocarcinoma compared to squamous cell carcinoma. Adenocarcinoma cervical cancer had a higher VEGF expression than squamous cell carcinoma.²⁶ This VEGF expression causes activation of MVD; therefore, MVD was also found higher in adenocarcinoma than in squamous cell carcinoma. VEGF and MVD also played main roles in angiogenesis. Due to that, higher VEGF expression and MVD will cause a higher cell tumor survival. High VEGF expression and MVD will also lead to chemotherapy resistance; therefore, the post-chemotherapy response became insensitive, resulting in a progressive response. In this study, the progressive study was categorized as an incomplete response.^{17,18,20}

There are several advantages and limitations to this study. Those advantages include this study with a period of 5 years. Therefore, it represented the population at Ulin hospital, Banjarmasin. This study was also very specific in sample selection, such as the type of histopathology and chemotherapy drugs used, so it is specific in describing the real situation. Some limitations were found in this study; for example, when compiling sample data from medical records, we found several medical records were not complete and specific; therefore, they needed to be excluded. Another limitation was that the therapeutic response was only done through clinical examination of medical records. Consequently, the therapeutic response was only evaluated through clinical evaluation, while the gold standard for the post-chemotherapy response was transvaginal ultrasonography. Suggestions for further research should improve the integrity of medical records to aid in further research. Additionally, further studies should be conducted in a prospective study design so that they can be followed or risked from the beginning until the observed effects occur.

CONCLUSION

In this study, squamous cell carcinoma cervical cancer gained a complete response, while adenocarcinoma¹ received an incomplete response. Post-chemotherapy response in paclitaxel and carboplatin in

squamous cell carcinoma cervical cancer advance stage was found to be better than adenocarcinoma.

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CONFLICT OF INTEREST

In this study, the author discloses no conflicts of interest.

FUNDING

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ETHICAL CLEARANCE

This study has received ethical committee permission with approval number 149/IX-Reg Riset/RSUD/21 from Ulin General Hospital Banjarmasin, Indonesia.

AUTHOR CONTRIBUTIONS

From the stage of proposal development, data search, and data analysis to the stage of interpretation of research data and presentation of the final report, all authors have made the same contribution to writing the report on the findings of this study.

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