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ADJUVANT CHEMOTHERAPY RESPONSE ON STAGE IB3, IIA2, AND IIB CERVICAL CANCER PATIENT AT PROF. DR. I.G.N.G NGOERAH GENERAL HOSPITAL IN 2021-2022

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ABSTRACT

Cervical cancer has become attention and health problem due to increased number of case and death. There are various type of cervical cancer treatments. In Prof. Dr. I.G.N.G. Ngoerah General Hospital, neoadjuvant chemotherapy is used to reduce tumor size before surgery is performed on IB3, IIA2, IIB stage cervical cancer due to limited radiotherapy device. This study aims to investigate neoadjuvant chemotherapy response on IB3, IIA2, IIB stage cervical cancer. Data of patient characteristic and chemotherapy response were collected from patient medical record. The data was processed using univariate analysis. The IB3 stage has highest successful response proportion (70%), followed by IIA2 stage (64,3%), then IIB (54%). Elderly patients (> 50 years old) have worse response compared to young patients (< 50 years old). Based on age, the highest percentage of complete chemotherapy responses was in the age range of 40-49 years (17%). Based on the parity group, the lowest parity group had the highest complete chemotherapy response (14%). There were 41% of patients with a poor response in the SCC group and 43% of patients with a poor response in the non-SCC group. When viewed from the degree of differentiation, the group with a good degree of differentiation has the highest percentage of complete responses (29%). The group with the largest tumor size which is above 7 cm had the highest percentage of poor chemotherapy response (67%).

Keywords: Neoadjuvant chemotherapy, cervical cancer, chemotherapy response.

INTRODUCTION

Cervical cancer has become the center of attention and health problems in recent decades. This cancer is a type of dangerous malignant tumor that often occurs in women caused by the Human Papilloma Virus (HPV) virus. The morbidity and mortality rates of cervical cancer tend to increase [1]. The number of women that affected by cervical cancer has increased around 10-40% in past 30 years [2].

According to recent data, the number of cervical cancer case and death was estimated around 570,000 and 311,000 in 2018 [3]. Furthermore, cervical cancer takes second place in cancer with highest mortality rate [4]. In Indonesia, based on data from the Ministry of Health 2019, cervical cancer is already in the second highest number of cancers with a prevalence of 23 people in 100,000 population with an average number of deaths of 14 people in 100,000 population [5].

One of problem in treating cervical cancer is the controversy on choice of treatment especially on IB3, IIA2, and IIB stage. There are various treatment of cervical cancer including radical hysterectomy surgery, chemoradiation, and chemotherapy followed by radical hysterectomy. At Prof. Dr. I.G.N.G. Ngoerah General Hospital, IB3, IIA2, and IIB stage cervical cancer treatment is carried out with chemotherapy because of the limited number of chemoradiation equipment. Neoadjuvant chemotherapy is type of chemotherapy that given with purpose to reduce tumor size before surgery is performed [6]. The chemotherapy agent that used as neoadjuvant chemotherapy at Prof. Dr. I.G.N.G. Ngoerah General Hospital is paclitaxel-carboplatin. Based on those problem, this study aims to provide information about neoadjuvant chemotherapy response among stage IB3, IIA2, and IIB cervical cancer patients at Prof. Dr. I.G.N.G. Ngoerah General Hospital.

MATERIALS AND METHODS

This study was a descriptive observational study using a cross-sectional design, in which data were collected at a single point in time from existing medical records. The study was conducted at the Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, over a nine-month period from February to October 2023. The study population consisted of patients diagnosed with

stage IB3, IIA2, and IIB cervical cancer (bulky tumors), and the sampling method used was total sampling, including all patients who met the inclusion and exclusion criteria during the study period. The inclusion criteria were patients with stage IB3, IIA2, or IIB cervical cancer who received three cycles of neoadjuvant chemotherapy with paclitaxel-carboplatin between January 1, 2021, and December 31, 2022, while the exclusion criteria were patients with incomplete medical records or those who did not complete the three planned cycles of neoadjuvant chemotherapy. Data were collected retrospectively using a structured data collection form from patients' medical records, including variables such as cancer stage, age, parity, histopathological type, tumor size, degree of differentiation, and response to neoadjuvant chemotherapy. Cancer staging was determined based on the FIGO 2018 classification, while chemotherapy response was assessed using the RECIST 1.1 criteria (Complete Response, Partial Response, Stable Disease, and Progressive Disease). All variables were categorized according to predefined operational definitions: age was grouped into <30, 30–39, 40–49, 50–59, and ≥60 years; parity into 0–2, 3–4, and ≥5; tumor size into 4–4.9 cm, 5–5.9 cm, 6–6.9 cm, and ≥7 cm; histopathological type into squamous cell carcinoma and non-squamous cell carcinoma; and degree of differentiation into well, moderate, and poor differentiation. The instruments used in this study were patients' medical records and a data collection sheet (data matrix), and data collection was performed by reviewing the medical records of eligible patients during the study period. All collected data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) version 25, and the results were presented in the form of tables and narrative descriptions. This research has been approved by the Research Ethics Commission of FK Unud/RSUP Prof. Dr. I G.N.G. Ngoerah Denpasar via an ethical letter number 580/UN14.2.2.V.II.14/LT/2023.

RESULTS

Patients Characteristic

The characteristics of stage IB3 cervical cancer patients including age, number of parities, histopathology type, degree of differentiation, and size of cancerous tumors are shown in table 1. Based on age, the age group of 40-49 years ranks highest as people with stage IB3 cervical cancer (60.0%). Based on the number of parities, the largest parity group is parity 0-2 (50.0%). Based on histopathology, the SCC type has a higher frequency (60.0%) than non-SCC (40.0%). Based on the level of differentiation, the level of good differentiation ranks highest (50.0%).

Table 1. Stage IB3 patient characteristic

Characteristics	N	Percentage (%)
Age (years)		
30-39	3	30,0
40-49	6	60,0
50-59	1	10,0
≥60	0	0,0
Total	10	100
Parity		
0-2	5	50,0
3-4	3	30,0
≥5	2	20,0
Total	10	100
Histopathologic type		
Non-SCC	4	40,0
SCC	6	60,0
Total	10	100,0
Differentiation		
Baik	5	50,0
Moderat	1	10,0
Buruk	4	40,0
Total	10	100,0
Tumor size		
4-4,9 cm	3	30,0
5-5,9 cm	2	20,0
6-6,9 cm	2	20,0
≥7 cm	3	30,0
Total	0	100,0

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The characteristics of stage IIA2 cervical cancer patients are shown in table 2. Based on age, the age group of 40-49 years ranks highest as people with stage IIA2 cervical cancer (42.9%). Based on the number of parities, the largest parity group is parity 3-4 (57.1%). Based on histopathology, the SCC (squamous carcinoma) type has a higher frequency (78.6%) than non-SCC (21.4%). Based on the level of differentiation, the level of poor differentiation ranks highest (50.0%).

Table 2. Stage IIA2 patient characteristic

Characteristics	N	Percentage (%)
Age (years)		
≤20	1	7,1
30-39	3	21,4
40-49	6	42,9
50-59	2	14,3
≥60	2	14,3
Total	14	100,0
Parity		
0-2	5	35,7
3-4	8	57,1
≥5	1	7,1
Total	14	100,0
Histopathologic type		
Non-SCC	3	21,4
SCC	11	78,6
Total	14	100,0
Differentiation		
Baik	4	28,6
Moderat	3	21,4
Buruk	7	50,0
Total	14	100,0
Tumor size		
4-4,9 cm	2	14,3
5-5,9 cm	5	35,7
6-6,9 cm	3	21,4
≥7 cm	4	28,6
Total	14	100,0

The characteristics of stage IIB cervical cancer patients is shown in table 3. Based on age, the age group of 50-59 years ranks highest as people with stage IIB cervical cancer (45.9%). Based on the number of parities, the largest parity group is parity 3-4 (48.6%). Based on histopathology, the SCC type has a higher frequency (81.1) than non-SCC (18.9%). Based on the level of differentiation, the level of poor differentiation ranks highest (56.8%).

Table 3. Stage IIB patient characteristic

Characteristics	N	Percentage (%)
Age (years)		
30-39	3	8,1
40-49	12	32,4
50-59	17	45,9
≥60	5	13,5
Total	37	100,0
Parity		
0-2	12	32,4

3-4	18	48,6
≥5	7	18,9
Total	37	100,0
Histopathologic type		
Non-SCC	7	18,9
SCC	30	81,1
Total	37	100,0
Differentiation		
Baik	8	21,6
Moderat	8	21,6
Buruk	21	56,8
Total	37	100,0
Tumor size		
4-4,9 cm	7	18,9
5-5,9 cm	13	35,1
6-6,9 cm	12	32,4
≥7 cm	5	13,5
Total	37	100,0

Chemotherapy Response

Partial chemotherapy response was highest in all staging groups. The highest frequency of complete response belongs to the IB3 stage group. Meanwhile, the lowest complete response frequency belongs to the stage IIA2 group. The overall chemotherapy response of each stage can be seen in tables 4-6.

Table 4. Neoadjuvant chemotherapy response of IB3 cervical cancer patients.

Chemotherapy Response	**N**	**%**
Complete	2	20,0
Partial	5	50,0
Stable	1	10,0
Progressive	2	20,0
Total	10	100,0

Table 5. Neoadjuvant chemotherapy response of IIA2 cervical cancer patients.

Chemotherapy Response	**N**	**%**
Complete	2	14,3
Partial	7	50,0
Stable	3	21,4
Progressive	2	14,3
Total	14	100,0

Table 6 Neoadjuvant chemotherapy response of IIB cervical cancer patients.

Chemotherapy Response	**N**	**%**
Complete	2	5,4
Partial	18	48,6
Stable	15	40,5
Progressive	2	5,4
Total	37	100,0

Based on age, the highest percentage of complete chemotherapy responses was in the age range of 40-49 years (17%). Based on the parity group, the lowest parity group had the highest complete chemotherapy response (14%). When viewed from the degree of differentiation, the group with a good degree of differentiation has the highest percentage of complete responses (29%). The distribution of size and type of histopathology varies considerably in each response group. The overall chemotherapy response based on age, parity, histopathology type, differentiation, and tumor size can be seen in tables 7-11.

Table 7. Neoadjuvant chemotherapy response based on age.

		Chemotherapy response			
		Complete	*Partial*	*Stable*	*Progressive*
		n (%)	n (%)	n (%)	n (%)
Age	<29	0 (0%)	1 (100%)	0 (0%)	0 (0%)
	30-39	1 (11%)	5 (56%)	1 (11%)	2 (22%)
	40-49	4 (17%)	10 (42%)	6 (25%)	4 (17%)
	50-59	1 (5%)	10 (50%)	9 (45%)	0 (0%)
	>60	0 (0%)	5 (57%)	3 (43%)	0%

Table 8. Neoadjuvant chemotherapy response based on parity.

		Chemotherapy response			
		Complete	*Partial*	*Stable*	*Progressive*
		n (%)	n (%)	n (%)	n (%)
Parity	0-2	3 (14%)	16 (73%)	2 (9%)	1 (5%)
	3-4	3 (10%)	11 (38%)	11 (38%)	4 (14%)
	>5	0 (0%)	3 (30%)	6 (60%)	1 (10%)

Table 9. Neoadjuvant chemotherapy response based on histopathologic type.

		Chemotherapy response			
		Complete	*Partial*	*Stable*	*Progressive*
		n (%)	n (%)	n (%)	n (%)
Histophatologic type	SCC	12 (11%)	23 (49%)	15 (32%)	4 (9%)
	Non-SCC	1 (7%)	7 (50%)	4 (29%)	2 (14%)

Table 10. Neoadjuvant chemotherapy response based on differentiation.

		Chemotherapy response			
		Complete	*Partial*	*Stable*	*Progressive*
		n (%)	n (%)	n (%)	n (%)
Differentiation	Poor	1 (3%)	8 (25%)	17 (53%)	6 (19%)
	Moderate	0 (0%)	10 (83%)	2 (17%)	0 (0%)
	Good	5 (29%)	12 (71%)	0 (0%)	0 (0%)

Table 11. Neoadjuvant chemotherapy response based on tumor size.

		Chemotherapy response			
		Complete	*Partial*	*Stable*	*Progressive*
		n (%)	n (%)	n (%)	n (%)
Tumor size	4-4,9	1 (8%)	7 (58%)	4 (33%)	0 (0%)
	5-5,9	2 (10%)	12 (60%)	5 (25%)	1 (5%)
	6-6,9	2 (12%)	8 (47%)	5 (29%)	2 (12%)
	>7	1 (8%)	3 (25%)	5 (42%)	3 (25%)

DISCUSSION

Partial response ranks highest as neoadjuvant chemotherapy response in each stage group. If the complete and partial response frequencies of each stage are compared, the higher the stage level, the lower the frequency of complete and partial responses. These results are in accordance with research conducted by Gupta et al which showed that the use of neoadjuvant chemotherapy has a lower effectiveness in stage IIB cervical cancer than IB3 and IIA2 when compared to radiotherapy [7]. This study found that neoadjuvant chemotherapy still has beneficial effect especially on the lower stage of cervical cancer. However, according to a literature review by Miriyala et al, neoadjuvant chemotherapy could not be considered as standard therapy for cervical cancer. Similar as this current study, Miriyala et al reported that the around 25-30% cervical cancer patient that received neoadjuvant chemotherapy have poor response. Chemoradiation is still considered as standard therapy [8]. However, recent study found there is no significant difference between neoadjuvant chemotherapy followed by surgery and chemoradiation treatment in patient overall survival rate in early stages cervical cancer (stage IB2-IIB). These findings suggest that the use of neoadjuvant chemotherapy is still recommended in early stages of cervical cancer. However further study is still required [9].

Based on age groups, the percentage of patients with good chemotherapy response (complete and partial) in the age group under 50 years is higher than the age group over 50 years. Even all patients in the age group under 29 years have a good chemotherapy response. In a study conducted by Daiku et al, a comparison of chemotherapy effectiveness responses was carried out in chemotherapy patients who were divided into ages under 75 years and over 75 years. From the study, the group of patients over the age of 75 years had worse therapeutic outcomes [10]. Those finding suggest that age is one of contributory factor of chemotherapy response. The reason of this phenomenon possibly caused by the poor ability of elderly patient body to tolerate toxicity of chemotherapy agent [11]. Older patient also tends to have more advanced stage of cancer due to accumulation risk factor including carcinogenic agent exposure and declined immune system function [12]. Paclitaxel-carboplatin is also hepatotoxic [13]. Decline in liver function in aging could worse this side effect [14].

Based on parity, this study shows that the amount of parity has an influence on the chemotherapy response of cervical cancer patients. There were 70% of adverse responses (stable and progressive) in the patient group with parity above 5, as many as 52% of bad responses in the patient group with parities of 3-4, and 14% of bad responses in the patient group with parity of 0-2. Based on these results, the higher the parity number, the worse the chemotherapy response obtained. However, there are currently no other studies examining the effect of parity on chemotherapy response in cervical cancer patients. This relationship is possibly caused by an association not causation. According to a systematic review and meta-analysis conducted by Tekalegn et al, the number of parities has a positive correlation with an increased risk of cervical cancer [15].

Based on the degree of differentiation, patients with poor degrees of cancer differentiation tend to have poor chemotherapy response. The highest percentage of patients with poor chemotherapy response belonged to the group of patients with a degree of poor cancer differentiation (72%). The lowest percentage of patients with poor chemotherapy response belonged to a group of patients with a good degree of cancer differentiation (0%). This finding is in line with research conducted by Luo et al, where cervical cancer patients with a low degree of cancer differentiation had a poorer prognostic response to adjuvant chemotherapy therapy [16]. Matsuo et al found that low levels of tumor cell differentiation correlated with an increase in the clinical stage of cervical cancer. Based on this correlation, the low level of cancer cell differentiation can be one of the considerations in determining patient prognosis [17]. Based on the pathogenesis of cancer, in general, cancer cells are cells that undergo mitosis so quickly that they lose the opportunity to differentiate. Therefore, the low level of differentiation is one of the hallmarks of cancer [18].

When viewed from the type of histopathology group. The group of patients with SCC had a slightly better chemotherapy response compared to the group of patients with non-SCC. There were 41% of patients with a poor response in the SCC group and 43% of patients with a poor response in the non-SCC group. The percentage of patients with a complete response in the SCC group (11%) was higher than in the non-SCC group (7%). When compared with the results of other studies, there was no significant difference in chemotherapy response between groups of cervical cancer patients with SCC and non-SCC types at stages I-IIA2. Significant response differences between the two histopathology groups were only seen in patients with higher stages, namely IIB-IV [19].

In this study there was no linear increase between tumor size and decreased chemotherapy response. However, the group with the largest tumor size, which is above 7 cm, has the highest percentage of poor chemotherapy response (67%). Research by Baron et al. showed that tumor sizes above 5 cm play a role in the poor response of neoadjuvant chemotherapy [20].

CONCLUSION

Effectiveness of neoadjuvant chemotherapy usage on cervical cancer patient depend on several factor including cancer

stage, patient age, tumor differentiation degree, and tumor size. Lower cancer stage has better outcome. Based on age, young patient (< 50 years old) have better therapy outcome compared to old patient (> 50 years old). When viewed from the degree of differentiation, the group with a good degree of differentiation has the best outcome. Based on tumor size, large tumor size contributes for bad therapy outcome.

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