Cluster of Differentiation as Predictor of Therapy Response to Neoadjuvant Chemotherapy in Advanced Stage Cervical Cancer

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ABSTRACT

Cervical cancer is the third leading cause of death of women worldwide and number one in developing countries. On the Gynecology Division of Oncology Dr. Mohammad Hoesin Hospital Palembang administration of neoadjuvan chemotherapy is used as a therapy in advanced stage cervical cancer. Decreased CD4 cell value in the human body indicates a decrease in white blood cells or lymphocytes that play a role in fighting infections that enter the human body. This study aims to determine the value of CD4 in advanced cervical cancer at Dr. Mohammad Hoesin Hospital, Palembang. A case series study was undertaken in January to September 2017 at Dr. Mohammad Hoesin Hospital Palembang. There were 30 patients with advanced cervical cancer who meets the inclusion criteria. The frequency and distribution of data are described in tabular form. The effectiveness of NAC was analyzed using Paired T Test/Wilcoxon. Assessment of CD4 as a predictor of NAC therapy response was seen from the values of sensitivity and specificity. Data analysis using SPSS version 18.0. In this study, there were 30 patients with advanced cervical cancer. Mean age was 47.93 ± 9.537 years with age range 32-72 years and the highest stage was 3B (63.3%). With statistical analysis, there were no differences in age, height, stage and type of therapy between patients with positive and negative treatment response (p > 0.05). In addition, there was difference in the value of mass (p = 0.000) and the mass width (p = 0.000) before and after NAC therapy. There was no difference in CD4 values before and after NAC therapy series I (p = 0.072) but there are difference in CD4 values after NAC series II therapy (p = 0.021) The CD4 values after NAC series I therapy had a sensitivity of 82.14% and a specificity of 100% while the CD4 values after NAC II series therapy had a sensitivity of 89.29% and a specificity of 100%. It can be concluded that the CD4 cell value of patients with advanced cervical cancer increasing with Neoadjuvant Chemotherapy (NAC) therapy and can be used as a predictor of treatment response in patients with advanced cervical cancer.

Keywords: Advanced stage, CD4, cervical carcinomancer, NAC, predictors

INTRODUCTION

Cervical cancer is the third leading cause of death of women worldwide and number one in developing countries. WHO report shows that cases of cervical cancer are on the rise worldwide, where an estimated 10 million new cases per year and will increase will be 15 million cases by 2020 [1, 2].

Management of cervical cancer is radical hysterectomy, chemotherapy, radiation or combination of chemotherapy and radiation. neoadjuvant (NAC) chemotherapy in advanced cervical cancer is still a debate up to now and has not been included in the therapy recommendations by various international oncology organizations. Various studies reported increased survival of patients with advanced

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cervical cancer who received neoajuvan chemotherapy followed by radical surgery compared to primary radiation [3].

CD4 (Cluster of Differentiation) is a marker on the surface of human white blood cells, especially lymphocyte cells. CD4 cell counts in people with reduced immune systems become very important, because the decrease in CD4 values in the human body indicates a decrease in white blood cells or lymphocytes that should play a role in fighting infections that enter the human body [4].

This study aims to analyze the relationship between CD4 values as a predictor of treatment response in patients with advanced cervical cancer who have received neoadjuvant chemotherapy at Dr. Mohammad Hoesin Hospital Palembang [4].

MATERIALS AND METHODS

A descriptive research in the form of serial cases was undertaken January to September 2017 at Dr. Mohammad Hoesin Hospital Palembang. There were 30 patients with advanced cervical cancer who meets the inclusion criteria. The protocol has been approved of Ethic Committe, Faculty of Medicine Sriwijaya University.

The diagnosis of advanced cervical cancer is done by clinical staging by obstetrician and gynecology specialist of oncology consultant then the blood sampling from the vein is aseptically done and processed using Hemocytometry to know the value of T-CD4 lymphocytes. samples are checked at three times when the stage of cervical cancer was enforced, before patients undergo NAC series 2 and before patients undergo NAC series 3.

The frequency and distribution of data are described in tabular form. The effectiveness of NAC was analyzed using Paired T Test/Wilcoxon. Assessment of CD4 as a predictor of NAC therapy response was seen from the values of sensitivity and specificity. Data analysis using SPSS version 18.0.

RESULTS

The general characteristics of the study subjects are shown in Table 1. 93.3% Out of 30 patients had positive therapeutic response where 2 patient (6.7%)with complete response and 26

patient(87,7%) with partial response. whereas patients with negative therapy response (stable disease) only found as many as 2 people (6.7%). Patients who received NAC did not have progressive disease, meaning that with NAC giving a good response for patients with advanced cervical cancer.

Table 1: General Characteristics of Research Subjects

| Characteristic | Total | Treatment Response | | p value |
		Positive	Negative	
Age (years), mean±SD	47.93 ± 9.537	47,54 ± 9,48	53.50 ± 12.02	0.402 [a]
Age, n (%)				
• > 50 years old	10 (33.3)	9 (32.1)	1 (50)	1.000 [b]
• ≤ 50 years old	20 (66.7)	19 (67.9)	1 (50)	
Weight (kg), mean±SD	53.07 ± 5.90	54.04 ± 4.77	39.50 ± 0.707	0.000 [a]
Height (cm), mean±SD	154.77 ± 2.50	154.89 ± 2.409	153.00 ± 4.243	0.309 [a]
BMI (kg/m²), mean±SD	22.12 ± 2.029	22.49 ± 1.485	16.91 ± 1.237	0.020 [c]
Stadium, n(%)				
• 2B	8 (26.7)	7 (25.0)	1 (50)	
• 3A	3 (10.0)	3 (10.7)	0 (0)	0.700 [d]
• 3B	19 (63.3)	18 (64.3)	1 (50)	
Therapy, n(%)				
• NAC Cisplatin-Paclitaxel	12 (40)	12 (42.9)	0 (0)	0.503 [b]
• NAC Carbo-Paclitaxel	18 (60)	16 (57.1)	2 (100)	

[a] *Independent T Test, p= 0,05;* [b] *Fisher Exact, p = 0,05;*
[c] *Uji Mann_Whitney, p = 0,05;* [d] *Pearson Chi-Square, p = 0,05*

In this study, statistical analysis showed that there were differences in the length and width of tumor mass before and after NAC therapy (p = 0.000) in which the length and width of tumor mass after NAC therapy was less than before the therapy as shown in Table 2.

Tabel 2: Efektivitas Neoadjuvant Chemotherapy (NAC) terhadap Panjang dan Lebar Massa Tumor

Variabel	Before Therapy	After Therapy	Alteration	p value*
Lenght Mass	5.249 ± 2.018	2.893 ± 1.507	2.893 ± 1.507	0.000
Widht Mass	4.233 ± 1.841	2.424 ± 1.114	1.809 ± 1.523	0.000

* *Paired T Test, p= 0,05*

In addition, there was no difference in CD4 value before and after NAC series I therapy (p = 0.072), there was a difference in CD4 value before and after NAC series II therapy (p = 0.021) and there was no difference in CD4 value after NAC series I

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and series II therapy (p = 0.139) where the CD4 value after NAC therapy was increased.

Tabel 3: Efektivitas NAC terhadap CD4

	CD4		CD4	Alteration	p value
Before NAC Therapy	703.1± 406.5	After NAC Series I Therapy	843.9 ± 303.0	140.9± 442.7	0,072[a]
		After NAC Series II Therapy	969.4 ± 481.6	266.4 ±605.1	0,021 [a]
After NAC Series I Therapy	843.9 ±303.0	After NAC Series II Therapy	969.4 ± 481.6	125.5 ±451.6	0,139 [b]

[a]*Wilcoxon, p= 0,05*
[b]*Paired T Test, p= 0,05*

Tabel 4: Sensitivity, spesificity dan realibility CD4 value to therapy response

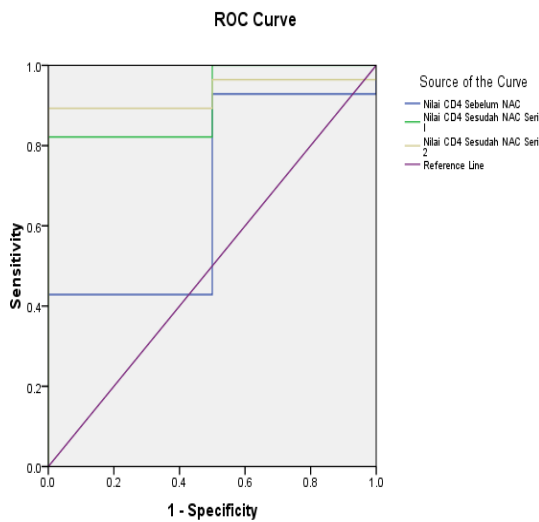| Variable	Cut Off	Sensitivity	Spesifisity	AUC	Realiability
CD4 Pre NAC	601,5 sel/ mm³	50%	50%	0.679	0,500
CD4 Post NAC seri 1	515,5 sel/ mm³	82,14%	100%	0.911	0,767
CD4 Post NAC seri 2	492 sel/ mm³	89,29%	100%	0.929	0,900

Figure 1. ROC Analysis for Predicting Response Therapy Based On CD4 Before, After Series I and After Series II (n = 30)

In this study, there was a CD4 cut-off point before therapy of 601.5 with a sensitivity of 50%, specificity 50% and AUC value 0.679. In addition, a CD4 cut-off point was obtained after NAC series I

therapy of 515.5 with a sensitivity of 82.14%, 100% specificity and AUC 0.911 value. Furthermore, the CD4 cutoff point was obtained after NAC II II therapy was 492 with sensitivity 89,29%, 100% specificity and AUC 0,929 value.

DISCUSSION

In this study there was no difference in age, stage, height and type of therapy between the two groups significantly. This means that in this study the response therapy is not influenced by age, stage, height and type of therapy. Aging is known to have an impact on the decline in immune system function, but it does not necessarily lead to a decrease in CD4 levels. In order to compensate for the decline in production of immune cells from the thymus, the naive CD4 T cells persist longer in the periphery, so CD4 levels do not appear to be significantly reduced in the elderly population, but this long-lasting CD4 indicates a significant decrease in immune function in which the ability to present APC (antigen presenting cell) is known to be much lower than CD4 which has normal half-life in adult humans [5].

There was a difference in body weight and BMI between the two groups where patients with low body weight and underweight nutritional status were more common in the negative therapy response group. BMI is related to the nutritional status of a person because the nutritional status is very influential on the function and also the status of immunity. Fat cells are a source of circulating leptin hormones in the body in line with the amount or composition of the fat cells themselves [6]. Leptin levels have a tendency to increase during the acute phase of infection [7]. CD4 cells have leptin receptors that can help CD4 cells proliferate in response to various stimuli [8]. This supports the results of this study in which all patients with treatment failure have BMT underweight.

In this study we found differences in length and width of tumor mass before and after NAC therapy where the length and width of tumor mass decreased after NAC therapy. This means that NAC therapy is effective in the treatment of advanced cervical cancer.

The CD4 AUC value before therapy has weak discrimination, after NAC series I therapy has excellent discrimination and after NAC II II

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therapy has excellent discrimination so it can be concluded that CD4 values after NAC series I and II can be used as a predictor of response therapy in patients with advanced cervical cancer.

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