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ORIGINAL

Relationship between Serum Vascular Endothelial Growth Factor-A Levels and Response to Chemotherapy in Cervical Cancer

Relación entre los niveles séricos del factor de crecimiento endotelial vascular A y la respuesta a la quimioterapia en el cáncer de cuello uterino

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ABSTRACT

Introduction: cervical cancer ranks second in gynecological cancer worldwide. 62-82 % of cervical cancer patients present at an advanced stage and respond poorly to treatment. Assessment of chemotherapy response requires examination of the biomarker Vascular endothelial growth factor-A (VEGF-A), which is the main regulator of the abnormal angiogenesis process.
Objectives: this study aims to analyze the relationship between serum VEGF-A levels and the response to neoadjuvant chemotherapy in cervical cancer patients.
Methods: this research is Quasi-Experimental, pretest and posttest without control. Total sample: 30 stages IIIB cervical cancer patients underwent a pretest before cisplatin chemotherapy by measuring cervical lesions using ultrasound and serum VEGF-A levels using ELISA. 3 weeks after the third cycle of chemotherapy, a posttest examination is carried out like the pretest examination.
Results: the results showed a significant reduction in serum VEGF-A levels and cervical lesion diameter after chemotherapy (p=0,032), (p=0,000). In response to neoadjuvant chemotherapy, 21 patients responded negatively, and 9 responded positively. High levels of VEGF-A before chemotherapy gave a negative response (p=0,042) and low levels of VEGF-A after chemotherapy gave a positive response (p=0,049).
Conclusions: this study concludes that there is a relationship between high serum VEGF-A levels before chemotherapy with a negative response and low serum VEGF-A levels after chemotherapy with a positive response in cervical cancer patients.

Keywords: Cervical Cancer; VEGF; Neoadjuvant Chemotherapy; Chemotherapy Response; Diameter Of Cervical Lesion.

RESUMEN

Introducción: el cáncer de cuello uterino ocupa el segundo lugar entre los cánceres ginecológicos a nivel mundial. Entre el 62 % y el 82 % de las pacientes con cáncer de cuello uterino se presentan en una etapa avanzada y responden mal al tratamiento. La evaluación de la respuesta a la quimioterapia requiere el examen del biomarcador Factor de crecimiento endotelial vascular A (VEGF-A), que es el principal regulador del proceso de angiogénesis anormal.
Objetivos: este estudio tiene como objetivo analizar la relación entre los niveles séricos de VEGF-A y la respuesta a la quimioterapia neoadyuvante en pacientes con cáncer de cuello uterino.
Métodos: esta investigación es Cuasi-Experimental, pretest y postest sin control. Muestra total: 30 pacientes con cáncer de cuello uterino en estadio IIIB se sometieron a una prueba previa antes de la quimioterapia con cisplatino midiendo las lesiones cervicales mediante ultrasonido y los niveles séricos de VEGF-A mediante

ELISA. 3 semanas después del tercer ciclo de quimioterapia, se realiza un examen post-test como el examen previo a la prueba.
Resultados: los resultados mostraron una reducción significativa en los niveles séricos de VEGF-A y el diámetro de la lesión cervical después de la quimioterapia (p=0,032), (p=0,000). En respuesta a la quimioterapia neoadyuvante, 21 pacientes respondieron negativamente y 9 respondieron positivamente. Los niveles altos de VEGF-A antes de la quimioterapia dieron una respuesta negativa (p=0,042) y los niveles bajos de VEGF-A después de la quimioterapia dieron una respuesta positiva (p=0,049).
Conclusiones: este estudio concluye que existe una relación entre niveles séricos altos de VEGF-A antes de la quimioterapia con una respuesta negativa y niveles séricos bajos de VEGF-A después de la quimioterapia con una respuesta positiva en pacientes con cáncer de cuello uterino.

Palabras clave: Cáncer de Cuello Uterino; VEGF; Quimioterapia Neoadyuvante; Respuesta a la Quimioterapia; Diametro de Lesión Cervical.

INTRODUCTION

Cervical Malignant Growth is the fifth most normal disease universally and the second most normal gynecological disease in ladies all through the world with passings coming to 55 % of the number of malignant growth deaths.[1] human papillomavirus (HPV) contamination is the primary component causing cervical cancer.[2] Based on data obtained from Dr Soetomo Regional General Hospital Surabaya (2022) Cervical cancer cases reached 464 cases with the highest stage IB amounting to 298 cases. 62-82 % of cervical cancer patients are diagnosed at an advanced stage and are a group of cervical cancer growth that is at high risk, resulting in poor treatment reactions.[1]

The International Federation of Gynecology and Obstetrics (FIGO) recommends that the treatment modality for locally advanced cervical cancer (LACC) stages IB3, II, III, IVA with a lesion size of more than 4 cm, which is called a bulky lesion, is chemoradiation. At Dr Soetomo Regional General Hospital, due to limited radiotherapy facilities, the treatment option for locally advanced cervical cancer is to provide neoadjuvant chemotherapy and wait in line for radiation. Providing treatment to locally advanced cervical cancer patients at Dr Soetomo Regional General Hospital is slightly different from FIGO's recommendations.[3]

Neoadjuvant chemotherapy aims to reduce the size of the tumor volume and shrink large lesions on the cervix before surgery or radiation for locally advanced cervical cancer. 2-3 cycles of neoadjuvant therapy help increase the rate of surgical resection chemotherapy.[2,4] The gold standard evaluation of chemotherapy response is assessed based on the size of the cervical tumor. Evaluation of chemotherapy response can be classified based on Response Evaluation Criteria in Solid Tumors (RECIST). Clinical response assessment is only based on surface response findings, so it will face obstacles in assessing chemotherapy response. One way to assess the response to chemotherapy treatment is tumor marker examination.[5] Vascular Endothelial Growth Factor-A (VEGF-A) is a significant biomarker that is a key signal that causes tumor angiogenesis, namely the process of forming new blood vessels in tumors that originate from blood vessels that already exist in the body. thereby helping the growth and spread of tumors. VEGF and its receptors are one of the important factors involved in the process of tumor angiogenesis.[6,7,8]

Past exploration expressed that checking VEGF levels can be utilized to evaluate the reaction to radiation treatment with a responsiveness of 80 % and a particularity of 75 %.[5] The benefit of using a serum VEGF biomarker is that it takes samples non-invasively from the patient and can see changes in the VEGF biomarker by repeating the test during treatment.[8] Based on these data, This study aims to analyze the relationship between serum VEGF-A levels and the response to neoadjuvant chemotherapy in cervical cancer patients.

METHODS

Design, Population, and Sample

This type of research is Quasi-Experimental and non-randomized with a (pre-test and post-test) research design with no control design. The examination populace was 30 patients with stage IIIB cervical malignant growth who came to the gynecology oncology facility at Dr Soetomo Regional General Hospital Clinic, Surabaya. The research subjects were selected according to the inclusion criteria in the study, namely patients with stage IIIB cervical cancer, who had never received treatment for their cancer and had no contraindications to chemotherapy. Exclusion criteria in the study were patients found to have a tumor or other cancer other than cervical cancer, the patient refused to participate in the study, and did not complete 3 series of chemotherapy. The research sampling method used consecutive sampling on patients who met the inclusion and exclusion criteria.

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Procedure and Analysis

This research was conducted from October 2023 to January 2024 in the cancer service development center room, gynecological oncology clinic, clinical pathology laboratory, Diagnostic Center building, and radiology installation at Dr Soetomo Regional General Hospital, Surabaya.

Research subjects get clarification and motivation behind the assessment by marking a Data assent and informed assent. the exploration Subjects then Went through a pretest Assessment, in particular estimating the size of cervical cancer utilizing abdomen ultrasound (Philips)and taking venous blood to determine serum VEGF-A levels using the Enzyme-linked immunosorbent assay (ELISA) Bioassay Technology Laboratory (E0050Hu). Next, all subjects received neoadjuvant cisplatin chemotherapy for 3 cycles. 3 weeks after receiving the 3rd cycle of chemotherapy, a posttest examination was carried out with the same examination as the pretest. Evaluation of response to chemotherapy uses Response evaluation criteria in solid tumors (RECIST) and is divided into four classifications, namely: progressive disease, stable disease, partial response, and complete response.

Responses are categorized into positive responses, namely Partial response and Complete response, while negative responses are Progressive disease and Stable disease. The method used to obtain data/information uses test, observation, and documentation techniques. Data analysis was carried out using SPSS 23. The Data is displayed in the form of a Frequency Distribution and Analytical table with Shapiro Wilk. T-test and correlation using the chi-square test. The significance level uses a probability value of 5 % (0,05).

Ethical Approval Number: 0795/KEPK/X/2023.

RESULTS

Characteristics of research subjects

The characteristics of the subjects of this research are presented in table 1 below:

Table 1. Characteristics of research subjects (October 10, 2023, Surabaya)

Category	Description	Amount
Age	20 – 40 years	5 (16,7 %)
	40 – 60 years	20 (66,7 %)
	> 60 years	5 (16,7 %)
Education	No school	1 (3,3 %)
	elementary school	16 (53,3 %)
	Junior high school	4 (13,3 %)
	Senior high school	8 (26,7 %)
	Bachelor	1 (3,3 %)
Parity	0-2	15 (50,0 %)
	3-4	12 (40,0 %)
	>4	3 (10,0 %)
Histology	*Squamous cell carcinoma*	25 (83,3 %)
	Adenocarcinoma	5 (16,7 %)

The characteristics of the research subjects showed that the highest number of cervical cancers was between the ages of 40-60 years, amounting to 20 subjects (66,7 %). The highest level of education is elementary school, with 16 subjects (53,3 %). The highest number of parity 0-2 was 15 subjects (50,0 %), Characteristics of research subjects with cell type (histology) in cervical cancer Squamous cell carcinoma amounted to 25 subjects (83,3 %), and Adenocarcinoma cell type amounted to 5 subjects (16,7 %)

Frequency of Response to Chemotherapy

The results of the chemotherapy response examination 3 weeks after chemotherapy cycle 3 in the study are presented in table 2:

Table 2. Frequency of response to chemotherapy (January 10, 2024, Surabaya)

	Category	Frequency (%)
Positive Response	Complete response	2 (6,7 %)
	Partial response	7 (23,3 %)
Negative response	Stable disease	18 (60,0 %)
	Progressive disease	2(10,0 %)

The results of chemotherapy response examination 3 weeks after chemotherapy cycle 3 in this study showed 2 subjects (10,0 %) with Progressive disease response, 18 subjects (60,0 %) with stable disease response, 7 subjects (23,3 %) with Partial response, and 2 subjects (6,7 %) with complete response. The response to neoadjuvant chemotherapy was then further categorized into positive response (Complete response and Partial response) and negative chemotherapy response (Stable disease and Progressive disease).

Serum VEGF-A Levels Before and After Neoadjuvant Chemotherapy

The results of data analysis using the T-test show that cervical cancer patients who were given neoadjuvant chemotherapy are presented in table 3:

Table 3. Serum VEGF-A levels (January 10, 2024, Surabaya)

Group	N	Mean serum VEGF-A levels	Median	SD	P
Pretest	30	92,57	89,80	13,895	0,032
Postets	30	84,75	82,70	16,509	

The results of data analysis using the T-test showed that cervical cancer patients who were given neoadjuvant chemotherapy showed that the value of serum VEGF-A levels before chemotherapy was higher (92,57) than after neoadjuvant chemotherapy (84,75) with a value of p=0,032 (p<0 .05). The result of this study demonstrates that there is a significant distinction in Serum VEGF-A levels in cervical disease patients when neoadjuvant chemotherapy. It tends to be reasoned that neoadjuvant chemotherapy is powerful in decreasing serum VEGF-A levels.

Diameter of Cervical Lesions Before and After Neoadjuvant Chemotherapy

The results of data analysis using the T-test showing cervical cancer patients before being given neoadjuvant chemotherapy are presented in table 4.

Table 4. Diameter of cervical lesions before and after neoadjuvant chemotherapy (January 10, 2024, Surabaya)

Group	N	Mean the largest diameter of cervical lesions	Median	SD	P
Pre-test	30	4,97	4,78	1,550	0,000
Post-test	30	3,84	3,93	1,571,578	

The results of data analysis using the T-test showed that cervical cancer patients before being given neoadjuvant chemotherapy found that the largest diameter of the lesion was higher (4,97mm) than after neoadjuvant chemotherapy (3,84mm) with a value of p=0,000 (p<0,05) research results in This states that there is a significant difference between the size of the largest diameter of the lesion in cervical cancer patients before and after neoadjuvant chemotherapy. It can be concluded that neoadjuvant chemotherapy is very effective in reducing the diameter of cervical lesions.

Serum VEGF-A Levels Before Therapy with Chemotherapy Response

The results of the association test using the Chi-square Test, serum VEGF-A levels before neoadjuvant chemotherapy are presented in table 5:

Table 5. Serum VEGF-A levels before therapy with chemotherapy response(January 10, 2024, Surabaya)

		Chemotherapy Response				
		Response (+)	Response (-)	Total		*p-value*
VEGF levels	High VEGF Levels	3 (10 %)	16 (53,3 %)	19 (63,3 %)		
	Low VEGF Levels	6 (20 %)	5 (16,7 %)	11 (36,7 %)	2ji	0,042
Total		9 (30 %)	21 (70 %)	30 (100 %)		

The result of the association test using the Chi-square Test, serum VEGF-A levels before neoadjuvant chemotherapy showed that high VEGF-A levels had a positive chemotherapy response in 3 subjects (10 %) and a negative chemotherapy response in 16 subjects (53 %). Meanwhile, low levels of VEGF-A before chemotherapy

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showed a positive chemotherapy response in 6 subjects (20 %) and a negative chemotherapy response in 5 subjects (16,7 %) and obtained a p-value = 0,042 (p<0,05) so from this value it can be It was concluded that there was a statistically significant relationship between high serum VEGF-A levels before neoadjuvant chemotherapy and a negative chemotherapy response in cervical cancer patients.

Serum VEGF-A Levels After Therapy with Response to Chemotherapy

Table 6 shows the side effects of the affiliate test using the chi-square test, serum VEGF-A levels after neoadjuvant chemotherapy.

Table 6. Serum VEGF-A levels before therapy with chemotherapy response(January 10, 2024, Surabaya)

		Chemotherapy Response				
		Response (+)	Response (-)	Total	*p-value*	
VEGF levels	High VEGF Levels	1(3,4 %)	11 (36,6 %)	1 2(40 %)		
	Low VEGF Levels	8(26,6 %)	10 (33,4 %)	18 (60 %)	2ji	0,049
Total		9 (30 %)	21 (70 %)	30 (100 %)		

The aftereffects of the affiliation test utilizing the chi-square test, serum VEGF-A levels after neoadjuvant chemotherapy showed that high VEGF-A levels had a positive chemotherapy response in 1 subject (3,4 %) and a negative chemotherapy response in 11 subjects (36,6 %). Meanwhile, low levels of VEGF-A after chemotherapy showed a positive chemotherapy response in 8 subjects (26,6 %) and a negative chemotherapy response in 10 subjects (33,4 %) and obtained a p-value = 0,049 (p<0,05) so this value indicates a significant relationship between low serum VEGF-A levels after neoadjuvant chemotherapy and positive chemotherapy response in cervical cancer patients at Dr Soetomo Regional General Hospital.

DISCUSSION

Characteristics of Research Subjects

The after-effects of this study by Khatimah,[9] showed 35 subjects, of which 25 subjects (71,4 %) were squamous cell carcinoma type, followed by 10 subjects (28,6 %) in the adenocarcinoma group. The most common type of squamous cell carcinoma is found in around 80 % and 20 % of adenocarcinoma types, while other histological types are very rare in cervical cancer.

Frequency of Response to Chemotherapy

Based on these results, it shows that the Majority were in Stable disease, namely 18 subjects (60,0 %). These results are from Rachmanto's research.[10] where 16 subjects (53 %) who underwent neoadjuvant chemotherapy experienced a stable disease response. Evaluation of response to neoadjuvant chemotherapy requires radiological evaluation available for cervical cancer screening. Ultrasonography (USG) has many advantages, one of which is noninvasive in tumor assessment. Assessment of tumor size measurements and determining the depth of stromal infiltration, tumor location, involvement of the parametrium, bladder, and even lymph node assessment.[11]

Serum VEGF-A Levels Before and After Neoadjuvant Chemotherapy

The results of this research are in line with Priyanto,[12] stated that serum VEGF-C levels decreased significantly after administration of neoadjuvant chemotherapy (p=0,006). Srivastava[7], stated that The VEGF levels of patients before chemotherapy and after neoadjuvant chemotherapy were significantly different (p<0,001) and were significantly associated with various stages of cervical cancer (p<0,002) with various tumor sizes (p<0,001). VEGF is a glycoprotein and is involved in many stages of the angiogenic response, and plays a role in the formation of vascular networks in tumors.[13]

Diameter of Cervical Lesions Before and After Neoadjuvant Chemotherapy

The aftereffects of this examination are by Priyanto Exploration [4], which stated that the average largest cervical diameter before neoadjuvant chemotherapy was greater than after neoadjuvant chemotherapy (5,62 versus 3,50, p<0,001). Platinum-based neoadjuvant chemotherapy (NACT) before radical hysterectomy has been widely used for advanced cervical cancer (LACC), characterized as stage IB2-IIIB by the International Gynecology-Obstetrics Organization (FIGO) for many years. Most cervical cancers treated with NACT consider this treatment to be effective and can reduce tumor size and suppress micrometastases. 2-3 cycles of neoadjuvant chemotherapy in advanced cervical cancer patients can increase the rate of surgical resection chemotherapy. [2,14]

Serum VEGF-A Levels Before Therapy with Chemotherapy Response

The aftereffects of this study are by Zhang, et al.[6], the results of which showed that strong VEGF expression and high levels of VEGF-C were associated with poor survival outcomes in cervical cancer patients and were significant. The expression level of VEGF reflects the ability of tumor angiogenesis, growth, invasion, and metastasis and is related to lymph node metastasis in cervical cancer,[15] VEGF is a powerful angiogenesis-mediated factor, being a major factor in local growth and metastasis of many tumors.[16] This examination is by research by Wibisono et al.[17], who said increased expression of VEGF was associated with poor response to radiotherapy in patients with cervical adenocarcinoma. Strong VEGF expression before therapy is associated with reduced survival and poor prognosis in osteosarcoma patients.[18] Tumor cells can express VEGF by activating HIF-1α in hypoxic stress conditions. Overexpression of VEGF is associated with poor prognosis in the development of cervical cancer.[19]

Serum VEGF-A Levels After Therapy with Response to Chemotherapy

The results of this examination are by Armanza research, et al.[5] who stated that there was a significant correlation between decreased serum VEGF levels after therapy with positive radiation response (p=0,01). Post-radiation VEGF can be a demonstrative calculation of the reaction to radiation treatment in cervical malignant growth. VEGF assumes a significant part in prompting angiogenesis in a few physiological and pathological processes.[20] Research by Edianto et al.[21] said complete responses were found in 20 of 51 cervical cancers and the remainder had partial responses. 18 cases had a complete response with weak VEGF expression. VEGF has arisen as a remedial objective in a few malignancies, including cervical cancer.[22] VEGF is an important biomarker in tumor development in many cancers and is one of the angiogenesis factors that has a very large relationship with the development of cervical blood and lymphatic vessels. Radiotherapy given to cervical malignant growth and chemotherapy can fundamentally repress the arrangement of veins and lymphatic vessels in growth tissue.[23] VEGF assumes a significant part in cancer angiogenesis, and lymphangiogenesis and animates the development of veins in growth tissue, expanding the conveyance of oxygen and supplements to the cancer and in this way advancing its multiplication and metastasis.[24,25]

CONCLUSIONS

Serum vascular endothelial growth factor-A (VEGF-A) levels were significantly reduced after neoadjuvant chemotherapy and the diameter size of cervical lesions was significantly reduced after neoadjuvant chemotherapy in cervical cancer patients. High serum VEGF-A levels before neoadjuvant chemotherapy are associated with a negative chemotherapy response and low serum VEGF-A levels after neoadjuvant chemotherapy are associated with a positive chemotherapy response in cervical cancer patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

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