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DETERMINANTS OF ANEMIA OCCURRENCE IN CERVIX CA PATIENTS UNDERGOING CHEMOTHERAPY

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ABSTRACT
Chemotherapy causes the death of some cells that have been formed from the process of DNA, RNA or protein synthesis. The myelosuppressive effects of long-term chemotherapy treatment will continue throughout the therapy cycle such as infection, septicemia and spontaneous bleeding and worsening of anemia. This study aims to determine the factors that influence the occurrence of anemia in cisplatin chemotherapy patients. This study used an analytical observational design with a retrospective cross-sectional approach (medical records). The population was 394 patients with a sample of 136 with a simple random sampling technique. Data were obtained from medical records and supporting examination results, then summarized and tabulated according to the coding. Data analysis used the chi square test. The results of this study obtained 86 patients who experienced anemia and as many as 136 cases of anemia with 35 patients experiencing recurrent anemia. The p value in the chi-square test for age with the occurrence of anemia was (p = 0.026), the p value in the chemotherapy series (p = 0.011), the p value in leukopenia with anemia (0.000), the p value in thrombocytosis (p = 0.004). The use of chemotherapy with cisplating has a significant relationship with anemia in patients with Ca Cervix IIIA - IVA. The use of chemotherapy with cisplatin has a significant relationship between age, leukopenia levels, thrombocytosis levels, and the series of chemotherapy used in the occurrence of anemia. So that chemotherapy can cause damage to the spinal cord, so that it fails to produce red blood cells, white blood cells, and platelets in the blood.

Keywords: anemia; cervical ca; chemotherapy; determinants

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INTRODUCTION

Health problems in the world and the cause of high morbidity and mortality rates in developed countries are cancer, the most dominant disease with an incidence of 19.3 million cases with a death rate of up to 10 million people in 2020 and this figure has increased compared to 2018. Cancer is defined as a disease with certain genes that control the process of cell regeneration in the human body becoming damaged and growing into abnormal cells (Anggriani *et al.*, 2023). Developing countries are the target of cancer, and one of them is Indonesia. In 2011, Indonesia was alert to deaths and morbidity caused by cancer, in that year the proportion of deaths caused by cancer reached 13% of total deaths from all age groups, and was in third place after CVD and Communicable, maternal, perinatal and nutritional conditions (28%) (Lasari, Amalia and Sarmila, 2021).

Based on GLOBOCAN data, a project of the International Agency for Research on Cancer (IARC), in 2018 there were 18.1 million new cases of cancer and 9.6 million deaths from

cancer worldwide. The incidence of cervical cancer ranks fourth in cancer incidence in women in the world after breast cancer, colorectal cancer and lung cancer. (Vera Novalia, 2023). Global Cancer Observatory 2018 data from the World Health Organization (WHO) states that cervical cancer is the second most common type of cancer in Indonesia with 32,469 cases or equivalent to 9.3% of the total cases (Anggriani *et al.*, 2023). Based on GLOBOCAN data in 2018, cervical cancer ranked third as the cause of cancer death with data of 18,729 deaths occurring in Indonesia. According to GLOBOCAN in IARC in 2020, cancer cases in Indonesia increased by 36,633 (17.2%) with 234,511 death (Vera Novalia, 2023). Based on Medical Record data at the Oncology Polyclinic in 2020, there were 432 new patient visits for Cervical Cancer with 297 cases of stage III and 5 cases of stage IV from a total of 4974 cases of Cervical Cancer. This causes Cervical Cancer to become a very feared disease because the early stages of this disease do not cause significant symptoms, while significant symptoms appear at high stages so that they have a worse prognosis.

Chemotherapy treatment is one of the therapies for cancer that is done by giving cytostatic drugs either intravenously or orally. These chemotherapy drugs have toxic effects or systemic dysfunction with varying degrees of severity because the drugs not only destroy cancer cells, but also healthy body cells. The body cells that are attacked are mainly cells that divide rapidly such as mucous membranes, hair follicles, bone marrow (Sri Wahyuni *et al.*, 2022). Anemia is a common finding in patients with cancer, with the percentage of anemia occurring between 30-90%. Causes of anemia in cancer patients include metabolic and nutritional disorders, chronic diseases, kidney disorders, blood loss, decreased production due to bone marrow disease, peripheral destruction due to autoimmune disorders, drug-induced red blood cell aplasia, and chemotherapy-induced anemia. Chemotherapy can cause anemia through inhibition of normal hematopoiesis and cytokine action. Chemotherapeutic agents cause anemia directly by interfering with hematopoiesis, including the synthesis of red blood cell precursors in the bone marrow. The nephrotoxic effects of certain cytotoxic agents (platinum-containing) can also cause anemia by decreasing erythropoietin production. (Febriani and Rahmawati, 2019). A preliminary study conducted previously explained that the administration of therapy carried out at Dr. Soetomo Hospital, Surabaya, especially for patients with stage III Cervical Cancer was slightly different, which should have been chemoradiation, but patients at Dr. Soetomo Hospital were given chemotherapy first for 3-4 cycles while waiting for the radiation schedule. Chemotherapy before radiation is expected to inhibit the growth of cancer cells. The type of chemotherapy used at Dr. Soetomo Hospital, Surabaya is Cisplatin because the response produced is considered better than other types. The administration of chemotherapy before radiation is due to limited equipment and the large number of Cervical Cancer patients who receive radiation.

The myelosuppressive effects of certain cytotoxic agents tend to accumulate over the course of therapy, resulting in worsening anemia with increasing cycles of chemotherapy. An increased incidence of grade 2 and 3 anemia is also associated with further cycles of chemotherapy. Other factors that may be considered when evaluating the risk of chemotherapy-induced anemia include the nadir Hb level, the time required to reach the nadir Hb level, and whether the Hb measurement was performed before or after the nadir level (Febriani and Rahmawati, 2019). Based on this, the occurrence of anemia in Ca patients is important to be handled, especially in patients receiving therapy. Therefore, this study aims to analyze factors related to the occurrence of anemia in Ca Cervix stage IIIA-IVA patients undergoing cisplatin chemotherapy, with the hope that comprehensive anemia treatment can be carried out based on the condition of the disease.

METHOD

This study design uses an analytical observational design method with a retrospective cross-sectional approach (medical records) of patients with cervical cancer III A - IVA who underwent chemotherapy. The population in this study were patients with cervical cancer stage IIIA - IVA who received Cisplatin chemotherapy at Dr. Sutomo Hospital, Surabaya, totaling 394 people. This study uses total sampling with a random sampling technique. The sample size was 86 people with 35 patients experiencing recurrent anemia so that the number of anemia cases in this study was 136. The data collection technique used in this study was using the medical record data observation technique. Data processing used the chi-square analysis test on the variables. This study has been approved by the Health Research Ethics Committee of Dr. Soetomo Hospital, Surabaya on November 13, 20222 with letter number 1126 / LOE / 301.4.2 / XI / 2022.

RESULTS

Table 1.
Cross tabulation table between age and the incidence of anemia in cervical cancer patients undergoing cisplatin chemotherapy

Category Age	Types of Anemia						Remarks p
	Light		Currently		Heavy		
	∑	%	∑	%	∑	%	
30-45 years	14	25	31	55,4	11	19,6	0,022
46-66 years	25	31,3	26	32,5	29	33,3	

Based on the cross-tabulation results above, it was found that more than half (55.4%) of respondents aged 30-46 years experienced moderate anemia, and almost half of respondents (33.3%) aged 46-66 years experienced severe anemia. After statistical testing using chi square, the p value was obtained = 0.022 (p> 0.05), meaning that there was no significant relationship between age and the incidence of anemia in Ca Cervix patients with cisplatin chemotherapy.

Table 2. Cross tabulation table between leukopenia and the incidence of anemia in cervical cancer patients undergoing cisplatin chemotherapy

Category Leukopenia	Types of Anemia						Remarks p
	Light		Currently		Heavy		
	∑	%	∑	%	∑	%	
With Leukopenia	3	11,1	7	25,9	17	63,0	0,000
Not Leukopenia	36	33,0	50	45,9	23	21,1	

Based on the cross-tabulation results above, it was found that most (63.0%) respondents with leukopenia experienced severe anemia (17 respondents), and almost half (50%) of respondents without leukopenia experienced moderate anemia (50 respondents). After statistical testing using chi square, a p value of 0.000 (p <0.05) was obtained, meaning that there was a significant relationship between leukopenia and the incidence of anemia in cervical cancer patients with cisplatin chemotherapy.

Table 3.
Cross tabulation table between thrombocytosis and the incidence of anemia in cervical cancer patients undergoing cisplatin chemotherapy

Category Thrombocytosis	Types of Anemia						Remarks p
	Light		Currently		Heavy		
	∑	%	∑	%	∑	%	
Thromboytosis	12	20,3	21	35,6	26	44,1	0,004
Not Thromboytosis	27	35,1	36	46,8	14	18,2	

Based on the cross-tabulation results above, it was found that most (44.1%) respondents with thrombocytosis experienced severe anemia (26 respondents), and most (46.8%) respondents with non-thrombocytosis conditions experienced moderate anemia (36 respondents). After statistical testing using chi square, a p value of 0.004 (p <0.05) was obtained, meaning that there was a significant relationship between thrombocytosis and the incidence of anemia in cervical cancer patients with cisplatin chemotherapy.

Table 4.
Chi-Square test table of chemotherapy series on the incidence of anemia in cervical cancer patients undergoing cisplatin chemotherapy

Category series kemoterapi	Types of Anemia						Remarks p
	Light		Currently		Heavy		
	∑	%	∑	%	∑	%	
After series 1	21	34,4	26	42,6	14	23	0,011
After series 2	11	28,9	20	52,6	7	18,4	
After series 3	5	20	8	32	12	48	
After series 4	2	16,7	3	25	7	58,3	

Based on the Spearman rank test table above, the p value was obtained = 0.011 (p <0.05) so that there was a significant relationship between the chemotherapy series and the incidence of anemia in Cervical Cancer patients with cisplatin chemotherapy.

DISCUSSION

The results of this study found that most of the Ca Cervix patients who experienced anemia were aged 46-66 years. After cross-tabulation with the predetermined anemia criteria, it was found that more than half of the respondents aged 30-46 years experienced moderate anemia, and more than half of the respondents aged 46-66 years experienced moderate anemia. After statistical testing using chi-square, there was a significant relationship between age and the incidence of anemia in Ca Cervix patients with cisplatin chemotherapy. These results are in line with previous research conducted by Stauder in 2018. The study explained that anemia that occurs in pre-elderly ages can occur due to bone marrow failure syndrome, decreased erythropoietin production in the kidneys, and nutritional deficiencies in the process of inflammation (Stauder *et al.*, 2018) so the incidence of anemia is more common in pre-elderly ages, namely 45-59 years. As age increases, the quality of the human body decreases, this was conveyed by Suryaningsih in 2016, there was a difference in the decrease in hemoglobin levels in the blood before and after chemotherapy for Cervical Cancer patients over the age of 45 years. This is also related to the body's response, which with increasing age, the body's response to chemotherapy is reduced, so patients over the age of 45 years are more susceptible to anemia, both with and without chemotherapy. Age over 45 years with Cervical Cancer disease are at greater risk of anemia due to the chronic disease conditions experienced. The mechanism of anemia in chronic diseases is due to the presence of cytokines from the inflammatory process produced by the bone marrow which will inhibit the erythropoiesis process. The results of this study showed that most respondents with leukopenia experienced severe anemia, and most respondents with no leukopenia experienced

moderate anemia. After statistical testing using chi-square, a significant relationship between leukopenia and the incidence of anemia in patients with cervical cancer with cisplatin chemotherapy. These results are in line with research conducted by Audina in 2019. That decreased hematopoietic cell production due to marrow suppression is one of the side effects of cisplatin chemotherapy, causing leukocyte levels in the blood to decrease due to cisplatin (Audina *et al.*, 2019). In a study conducted by Johanis in 2018, a significant relationship was found between leukocyte levels and hemoglobin levels in the blood. This is due to problems with the bone marrow which functions to produce white blood cells and red blood cells (Johanis & Hajat, 2018).

The incidence of leukopenia occurs in patients with cisplatin exposure due to the influence of cisplatin which affects the function of the spinal cord in producing red blood cells and white blood cells. In this case, this study is in line with existing theories. The results of this study found that almost all respondents with thrombocytosis experienced severe anemia, and most respondents with non-thrombocytosis conditions experienced moderate anemia. After statistical testing using chi-square, it was found that there was a significant relationship between thrombocytopenia and the incidence of anemia in patients with cervical cancer with cisplatin chemotherapy. This is in line with research conducted by Zulkarnain 2017, which explains that thrombocytosis is used as a marker of poor prognosis in cervical cancer. Patients with stage Ib who have undergone operative therapy, if their platelet values increase, are also included in the poor prognosis. There is a correlation between the size of cervical cancer and thrombocytosis. Platelets are used by tumor cells to facilitate metastasis via hematogenous pathways, grow larger, and angiogenesis. Tumor cells bind to platelets and form a coating so that they cannot be detected by the immune system. The ability of tumor cells to aggregate with platelets is known as tumor cell-induced platelet aggregation (TCIPA). Tumor cells will also be protected from TNF-α due to the coating of platelets. A significant increase in IL-6 was found in cervical cancer, where IL-6 is a potent cytokine for stimulating megakaryopoiesis and megakaryocyte maturation. The increasing number of megakaryocytes produced and matured will increase the number of platelets circulating in the circulation (Zulkarnain Iskandar, Surarso Bakti, 2017).

Research conducted by Mersil in 2021 TIBC shows the ability of the protein to carry iron in the blood. High TIBC values indicate that the amount of iron bound and carried to the bone marrow is only small. If it continues, erythropoietin will continue to increase without an increase in reticulocytes. Increased erythropoietin levels are thought to cause an increase in platelets (thrombocytosis) (Mersil, 2021). This study is in line with (Audina *et al*., 2019), Cisplatin-based combination chemotherapy causes thrombocytosis (platelet count exceeds normal). This condition may be caused by a rebound phenomenon related to an increase in platelet stimulating factors such as thrombopoietin or hormone factors that are not known for sure. This thrombocytosis condition is also associated with large solid tumors.

The presence of thrombocytosis in patients with Ca Cervix is caused by the condition of exposure to cisplatin which causes damage to the spinal cord. so that these patients fail to produce red blood cells, white blood cells, and platelets in the blood, and an increase in the stage of Ca Cervix can also cause thrombocytosis. Based on the Chi-Squer test table, there is a significant relationship between the chemotherapy series and the incidence of anemia in Cervical Cancer patients with cisplatin chemotherapy with a sufficient level of correlation between the chemotherapy series and the incidence of anemia in Cervical Cancer patients with cisplatin chemotherapy. The incidence of anemia can be found after chemotherapy, some cases in Cervical Cancer patients also experience anemia before chemotherapy. Patients who

are anemic before chemotherapy can affect the prognosis in the future, this is by research conducted by Lee in 2021, patients who have at least one value below 10g/dl have a higher risk of loco-regional failure. Anemia at the beginning before chemotherapy can be caused by the stage the patient has before chemotherapy, patients who come with advanced stage IV experience anemia at the beginning twice as much as stage 1 (Lee *et al*., 2021).

Research conducted by Madedu in 2018 found that there was a decrease in hemoglobin levels in the blood of patients after chemotherapy in series 2. This is due to the presence of cisplatin which causes increased ROS production in the body. Accumulation of ROS will release cytochrome-c and mitochondria through activation of c-Jun-N-terminal kinase (JNK) and P38MAPK Cytochrome-c will then activate caspase-8, -9, and -3 (intrinsic pathway apoptosis) (Madeddu *et al*., 2018). With the presence of apoptosis, this cell causes a decrease in the hemopoietic system. Research conducted by Morrison 2018 was obtained because of the presence of cisplatin which works systemically so that it affects the bone marrow throughout the body, as a result, precursor cells and differentiation cells in the bone marrow, and mature cells in the blood circulation will be affected. Hemopoietic system cells are damaged, and apoptosis occurs so that the number of blood cells decreases (Morrison *et al*., 2018). The occurrence of anemia was found to occur in patients with exposure to cisplatin series 2. Based on observations made by researchers, the more the series of chemotherapy received by respondents, the lower the hemoglobin levels. This is due to the effect of cisplatin which can affect the bone marrow throughout the body, resulting in a decrease in erythropoiesis which causes a decrease in hemoglobin levels.

CONCLUSION

The use of chemotherapy with cisplatin has a significant relationship with anemia in patients with Ca Cervix IIIA - IVA. The use of chemotherapy with cisplatin has a significant relationship between age, leukopenia levels, thrombocytosis levels, and the chemotherapy series used in the occurrence of anemia. So that chemotherapy can cause damage to the spinal cord so that it fails to produce red blood cells, white blood cells, and platelets in the blood.

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