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Hematological and biochemical toxicity analysis of chemotherapy in women diagnosed with cervical cancer

Análise de toxicidade hematológica e bioquímica da quimioterapia em mulheres diagnosticadas com câncer do colo do útero

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ABSTRACT

Introduction and objective: We verified the main hematological and biochemical alterations during the chemotherapy treatment for women with cervical cancer. **Material and method:** A retrospective, analytical and cross-sectional test was performed. The sample consisted of 39 medical records of women who underwent chemotherapy in the period from January to December 2016. The effects of hematological toxicities were evaluated according to erythrogram, leukogram, and platelet parameters, in relation to biochemical toxicities, using levels of serum marker (urea, creatinine, transaminases). **Results:** It was evidenced that among the chemotherapy protocols used, cisplatin showed a leukogram and plateletgram of 1.06 and 2.09 chances, respectively, for the development of leucopenia and thrombocytopenia during treatment. **Conclusion:** It was not possible to identify the degree of toxicity of the adverse effects of the treatment, because when these effects were registered in the medical record, they appeared without description, making it difficult to evaluate the degree of toxicity presented.

Key words: neoplasm; antineoplastic; hematology; toxicity.

RESUMO

Introdução e objetivo: *Foram verificadas as principais alterações hematológicas e bioquímicas durante o tratamento quimioterápico de mulheres com câncer do colo uterino.* ***Material e método:*** *Um teste retrospectivo, analítico e transversal foi realizado. A amostra foi composta por 39 prontuários de mulheres que realizaram quimioterapia no período de janeiro a dezembro de 2016. Os efeitos das toxicidades hematológicas foram avaliados segundo os parâmetros de eritrograma, leucograma e plaquetograma em relação às toxicidades bioquímicas, por meio dos níveis séricos de marcadores (ureia, creatinina e transaminases).* ***Resultados:*** *Entre os protocolos quimioterápicos utilizados, a cisplatina apresentou leucograma e plaquetograma de 1,06 e 2,09 chances, respectivamente, para o desenvolvimento de quadro de leucopenia e trombocitopenia durante o tratamento.* ***Conclusão:*** *Não foi possível identificar o grau de toxicidade dos efeitos adversos do tratamento, pois quando esses efeitos foram registrados no prontuário, apareceram sem descrição, o que dificultou a avaliação do grau de toxicidade apresentado.*

Unitermos: *neoplasia; antineoplásico; hematologia; toxicidade.*

RESUMEN

Introducción y objetivo: *Se detectaron los principales cambios hematológicos y bioquímicos durante el tratamiento quimioterapéutico de mujeres con cáncer del cuello uterino.* ***Material y método:*** *Se realizó un estudio retrospectivo, analítico y transversal. La muestra se compuso de 39 historiales de mujeres sometidas a quimioterapia en el período de enero a diciembre de 2016. Se evaluaron los efectos de las toxicidades hematológicas según los parámetros de eritrograma, leucograma y plaquetograma con respecto a las toxicidades bioquímicas, mediante los niveles séricos de indicadores (urea, creatinina, transaminasas).* ***Resultados:***

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Se ha comprobado que entre los protocolos de quimioterapia utilizados, el cisplatino presentó leucograma y plaquetograma de 1,06 y 2,09 chances, respectivamente, para el desarrollo de un cuadro de leucopenia y trombocitopenia durante el tratamiento. ***Conclusión:*** *No se pudo identificar el grado de toxicidad del tratamiento, pues cuando eses efectos fueron registrados en el historial, aparecieron sin descripción, dificultando la evaluación del grado de toxicidad presentado.*

Palabras clave: *neoplasia; antineoplásico; hematología; toxicidad.*

INTRODUCTION

In Brazil, in 2018, according to the National Cancer Institute [Instituto Nacional do Câncer (INCA)], there were an estimated 16,370 new cases of cervical cancer, with an estimated rate of 15.43 cases per 100,000 women. According to the regional incidence in Brazil, not taking into account non-melanoma skin tumors, cervical cancer stands out first in the North region with 25.62 cases per 100,000 women. In the Midwest and Northeast regions, they hold the second position with rates of 18.32/100 thousand and 20.47/100 thousand, respectively, in the Southeast region, it is the fourth most incident (9.97/100 thousand), and the fourth in the South (14.07/100 thousand). In the state of Pernambuco alone, an estimated 1,030 new cases are reported[1]. The predominant age range is 20 to 29 years, increasing the index at a peak of 45 to 49 years, which is the fourth most frequent cause of cancer death in women[2].

There are several risk factors that are related to neoplasm, social and environmental factors and life habits, such as low socioeconomic conditions, sexual activity before the age of 18, the plurality of sexual partners, tobacco use, prolonged use of contraceptives oral, are the main ones[3].

For cancer treatment, there are five therapeutic modalities: surgery, radiotherapy, chemotherapy, hormone therapy, and immunotherapy, which can be used separately or in combination. The chemotherapy, the most used therapy, has a higher incidence of cure of many tumors, including the most advanced cases, besides being the therapy that increases the survival of cancer patients[4].

Polychemotherapy is described as "the use of more than one antineoplastic agent in combination". Three rules should be observed in the administration of polychemotherapy: the drugs used must have different mechanisms of action, different toxicities, and should be effective when used alone. For the preparation of polychemotherapy schemes or protocols, based on these criteria, two or more agents administered at regular intervals are associated[5,6].

Because they lack specificity, when chemotherapeutics drugs affect normal cells, they trigger common side effects, which determine the cost-benefit of the treatment, to the point of interfering with the hematopoietic tissue, causing damage to the quality of life of these patients. It is essential to recognize, prevent and control these effects in order to achieve good care[6,7].

According to Fuchs and Wannmacher (2017)[8], the toxicity of chemotherapy can be divided into twelve types: gastrointestinal toxicity, cardiotoxicity, hepatotoxicity, pulmonary toxicity, neurotoxicity, reproductive dysfunction, bladder and renal toxicity, metabolic alterations, dermatological toxicity, allergic reactions, and anaphylaxis. Fatigue and hematological toxicity are the most lethal.

Hematologic toxicity is the one with the greatest repercussion, encompassing events such as anemia, febrile neutropenia, thrombocytopenia, and leukopenia. It is related to the fact that hematopoiesis is a process characterized by high mitotic activity and rapid cell proliferation that produces short-cycle cells. This feature makes the bone marrow extremely susceptible to the effects of these drugs. It is a dose-limiting factor of chemotherapy, responsible for the need on improvement between programmed applications[2,8,9].

In parallel, chemotherapeutic drugs may cause other adverse effects, including disorders in the serum biochemistry of patients, which, in most cases, is associated with the use of several antineoplastic agents during treatment, from varying degrees of transient elevation of enzymes, such as altered levels of urea, creatinine, bilirubin, transaminases, and electrolytes, with the clinical manifestation corresponding to mild and moderate changes that can be reversed with temporary interruption of protocol used, in severe cases, they may be irreversible, which makes it important to monitor these enzymes[10].

Due to these manifestations, the patient undergoing chemotherapy should be monitored for renal and hepatic function, because chemotherapeutics agents cause metabolic alterations, which are often associated with other factors and clinical situations[10,11]. Thus, this study aimed to demonstrate the hematological and biochemical toxicity profiles of patients with cervical cancer under chemotherapy.

MATERIAL AND METHOD

This is a retrospective, analytical and cross-sectional field study involving patients diagnosed with cervical cancer undergoing chemotherapy treatment at a center of oncology in the city of Caruaru, Agreste Pernambucano, Brazil, performed from January to December 2016. We analyzed the results of the examinations that were performed routinely in the service that were obtained from the charts of patients in chemotherapy treatment, with no the need to formal consent request. The initiation of the study occurred after approval by the ethics committee (CAAE: 59121916.6.0000.5203) of the Centro Universitário Tabosa de Almeida.

In the development of the present study, a description of the results of the complete blood count and biochemical examinations of the patients was performed, considering each protocol individually, and describing each alteration found during the treatment.

The study included the charts of patients with cancer of the uterine cervix that underwent chemotherapy during the study period and chemotherapy cycles greater than two. The exclusion criteria were medical records with a history of renal diseases and those that were incomplete with regard to exams results.

A validated research instrument composed of two parts was used: identification of the patients (age, occupation, tobacco use, ethnicity, and the chemotherapy protocols performed); and description of the hematological and biochemical profile of the 2^{nd}, 4^{th}, 6^{th} cycles as well as the identification of hematological alterations and the biochemical measurements of urea, creatinine, transaminase [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] of each cycle studied in the various protocols, regardless of any variable. The results were analyzed by the Chi-square test, using the PRISM program, version 6.0, considering a 95% confidence interval.

RESULTS

The sample consisted of 45 medical records of women submitted to cervical cancer treatment between January and December 2016. From these, six women were excluded from the study due to presenting incomplete medical record data regarding chemotherapy treatment, recording of tests results or for giving up treatment. Among the records analyzed, two cases of febrile neutropenia occurred during chemotherapy treatment.

Among the 39 charts from patients that concluded treatment in the referred period, the age ranged from 29 to 87 years, the mean age was 53.5 with standard deviation of ± 16.96. Data regarding age, marital status, occupation, ethnicity, smoking, are presented below (**Table 1**). A numerical prevalence of women between 40-59 years old (33.2%) and married (46.1%) can be noted; 30.7% were retired. Non-smokers and non-alcoholics (56.5% and 64.1%) also prevailed.

The protocols applied were thus distributed: a total of 21/39 (53.8%) received cisplatin; 11/39 (28.2%) received paclitaxel and carboplatin (PC); 4/39 (10.2%) received carboplatin, cisplatin, and paclitaxel (CCP); 3/39 (7.7%) received cisplatin and paclitaxel (CP). Regarding the 2^{nd}, 4^{th}, 6^{th} cycles of chemotherapy, 7/39 (18%) performed the monthly chemotherapy cycles, 23/39 (58.9%) weekly cycles, and 9/39 (23.0%) every 21 days.

Hematologic toxicity encompasses events such as anemia, febrile neutropenia, thrombocytopenia, and leukopenia. The association between exposure to the risk factor and outcome was analyzed to evaluate the risk of developing the disease among those exposed in relation to the non-exposed (**Table 2**). After analyzing the results of the complete blood counts, according to the medical

TABLE 1 – Distribution of biological variables according to the parameters analyzed, Caruaru, Pernambuco, 2018

Characteristics	*n*	%
Age group		
20-39 years	11	28.9
40-59 years	13	33.2
60-79 years	12	30.7
> 80 years	3	7.7
Marital status		
Single	14	46.1
Married	18	20.2
Divorced	2	5
Widow	5	12.8
Occupation		
Seamstress	1	2.5
Domestic worker	11	28.5
Teacher	2	5
Farmer	8	20.5
Retired	12	30.7
Craftsman	1	2.5
General services	1	2.5
Merchant	3	7.5
Ethnicity		
Yes	14	35.9
No	25	64.1
Smoking		
Yes	17	43.5
No	22	56.5

TABLE 2 – Analysis of complete blood count results, Caruaru, Pernambuco, 2018

Protocols	Erythrogram			Leukogram			Plateletgram		
	n	%	OR	*n*	%	OR	*n*	%	OR
Cisplatin									
Positive	13	(61.9)	1.03	12	(57.1)	1.06	12	(57.1)	2.09
Negative	8	(38.1)		9	(42.9)		9	(42.9)	
PC									
Positive	7	(63.6)	1.3	5	(45.4)	0.53	7	(63.6)	1.13
Negative	4	(36.4)		6	(54.6)		4	(36.4)	
CCP									
Positive	1	(25)	0.5	2	(50)	0.75	0	(0)	0
Negative	3	(75)		2	(50)		4	(100)	
CP									
Positive	2	(66.6)	2.8	3	(100)	0	0	(0)	0
Negative	1	(33.3)		0	(0)		3	(100)	

PC: paclitaxel and carboplatin; CCP: carboplatin, cisplatin, and paclitaxel; CP: cisplatin and paclitaxel; OR: odds ratio.

records, 24/39 (61.5%) of the women in the erythrogram showed a decrease in the number of red blood cells, in relation to the leukogram, about 22/39 (56.4%) presented a decrease in total numbers of leukocytes. As for platelet 19/39 (48.7%), there was a decrease in the number of platelets.

It was seen that women who used the CP protocol had a 2.8 chance of developing anemia compared to those who used the CCP that is in the protection factor, presenting a 0.5 chance of developing anemia due to the use of the antineoplastic.

The cisplatin protocol was the only chemotherapy in the leukogram evaluation that presented 1.06 chances in patients who developed leukopenia during the treatment. On the other hand, the CP, PC and CCP protocol did not show an association between the use of the protocol and the chances of developing the disease.

The risk of thrombocytopenia among women who used cisplatin is a 2.09 chance of developing the disease higher than the women who used other protocols. The CP and CCP protocols were not associated.

The analysis of the correlation of the use of the antineoplastic protocol with the laboratory finding (**Table 3**) reported by the results of the complete blood count were not significant by the Chi-square test, considering a significance level of 5%.

Biochemical toxicity

We can observe that from the 39 records, 14/39 (35.9%) presented an increase in the creatinine measurement, about 19/39 (48.7%) presented an increase in urea. Among transaminases, 17/39 (43.6%) presented an increase in AST, and 21/39 (53.8%) presented an increase in ALT.

TABLE 3 – RR of using the various protocols × hematological changes, Caruaru, Pernambuco, 2018

Protocols	Anaemia		Leukopenia		Trombocytopenia	
	RR	*p*	RR	*p*	RR	*p*
Cisplatin	1.63	0.15	1.32	0.12	0.93	0.9
PC	1.6	0.3	0.02	0.12	0	0.12
CCP	0.67	0.09	1.2	0.6	0	0.9
CP	1.5	0.6	1	0.12	1	0.9

RR: relative risk; PC: paclitaxel and carboplatin; CCP: carboplatin, cisplatin and paclitaxel; CP: cisplatin and paclitaxel.

Table 4 shows the analysis of the results of the biochemical tests (creatinine, urea, AST, and ALT), in relation to the antineoplastic protocols used. It was found that regarding nephrotoxicity in the cisplatin protocol, five (12.8%) presented alterations in creatinine measurement, and eight (20.5%) changes in urea. Regarding the evaluation of the probability of the women who used this protocol in developing some type of nephrotoxic alteration is minimal. In the verification of hepatotoxicity, it was observed that nine (23%) presented an increase in AST and 11 (28.2%) presented an increase in ALT.

From the 11 patients who received the PC protocol, in the investigation of nephrotoxicity seven (17.9%) presented alterations in creatinine and seven (17.9%) in the urea measurements, the possibility of having a renal alteration is 2.33, increasing the chance of risk.

In the liver profile, the CCP protocol was administered in four of the 39 patients only, where one (2.5%) presented an increase in creatinine level and two (5.2%) an increase in the urea level. Analyzing the likelihood of these patients developing some type of kidney disease, odds ratio (OR) = 1.05 was observed, and no

TABLE 4 – Analysis of biochemical results, Caruaru, Pernambuco, 2018

Protocols	Creatinine			Urea			AST			ALT		
	n	%	OR	*n*	%	OR	*n*	%	OR	*n*	%	OR
Cisplatin												
Positive	5	12.8	0.31	8	20.5	0.96	9	23	0.93	11	28.2	0.88
Negative	16	41		13	33.3		12	30.7		10	25.6	
PC												
Positive	7	17.9	5.25	7	17.9	2.33	5	12.8	1.11	7	17.9	1.75
Negative	4	10.2		4	10.2		6	15.3		4	10.2	
CCP												
Positive	1	2.5	0.39	2	5.2	1.05	1	2.5	0.39	1	2.5	0.25
Negative	3	7.7		2	5.2		3	7.7		3	7.7	
CP												
Positive	1	2.5	0.88	2	5.2	2.23	2	5.2	2.8	2	5.2	1.78
Negative	2	5.2		1	2.5		1	2.5		1	2.5	

AST: aspartate aminotransferase; ALT: alanine aminotransferase; OR: odds ratio; PC: paclitaxel and carboplatin; CCP: carboplatin, cisplatin and paclitaxel; CP: cisplatin and paclitaxel.

association was observed. Regarding hepatic measures, one (2.5%) presented an increase in AST and two (5.2%) presented an increase in ALT, so the probability of occurrence of liver disease risk is OR = 0.25 with a decrease in risk.

In the CP protocol, one (2.5%) patient presented an increase in creatinine and two (5.2%) presented an increase in urea measurement, with an OR = 2.23 with a probability of developing renal diseases. Two (5.2%) patients presented an increase in AST and ALT and presented OR = 1.78 for the development of liver diseases related to the protocol.

In the analysis of the association test and the relative risk (**Table 5**), it was verified that there is no association regarding the use of the antineoplastic protocol with the biochemical alterations found.

TABLE 5 – Association and RR of using the various protocols × biochemical changes, Caruaru, Pernambuco, 2018

Protocols	Urea		Creatine		AST		ALT	
	RR	*p*	RR	RR	*p*	*p*	RR	*p*
Cisplatin	1	0.9	0.84	0.5	0.76	0.12	1	0.2
PC	1.1	0.7	0.84	0.4	0.78	0.6	1.26	0.2
CCP	0.98	0.9	0.4	0.6	0.46	0.3	0.42	0.5
CP	1.26	0.5	0.52	0.3	1.13	0.12	1.4	0.7

AST: aspartate aminotransferase; ALT: alanine aminotransferase; RR: relative risk; PC: paclitaxel and carboplatin; CCP: carboplatin, cisplatin and paclitaxel; CP: cisplatin and paclitaxel.

DISCUSSION

In the sociodemographic profile in the present study we observed that most of the women were from the 40-59 years age group, the mean age was 53.5. Although the age is recognized as one of the risk factors for the development of cervical cancer, the literature describes that the incidence of cancer development predominates in the 20-29 years age group, however, in the present study patients younger than 45 years of age represents 28.2% of the total sample, which corroborates with some authors[12-14].

Regarding the chemotherapy protocols adopted in the service in question, we observed that they are those standardized and indicated by the scientific literature and we perceive the service's concern in adapting the protocols to the patients in the best possible way, into an individualized manner, as we could verify with the chemotherapy protocols modified due to the general state of the patient, as well as the neoplasm staging[2].

Many chemotherapeutic agents are used in the treatment of cervical cancer, as platinum-based agents (cisplatin and carboplatin), taxanes (paclitaxel), topotecan, vinorelbine, gemcitabine, ifosfamide, as well as monoclonal antibodies (bevacizumab). Although effective, these agents show side effects that may compromise the treatment and quality of life of these patients[15].

A similar study performed with women with breast cancer undergoing chemotherapy also pointed to the occurrence of anemia, neutropenia, thrombocytopenia in the treatment period in which protocols are based on the cisplatin use[16]. The study by Nam *et al*. (2013)[17] compares the main toxicity rates between the treatment of cervical cancer with cisplatin associated with radiotherapy and carboplatin associated with radiotherapy showing that the protocol with carboplatin confers a greater degree on the development of thrombocytopenia. In our study, we found that carboplatin associated with cisplatin and paclitaxel did not present a greater risk of developing thrombocytopenia when compared to cisplatin alone.

Studies mention that the increase in urea measurement in the PC protocol may be related to both cisplatin and cyclophosphamide since both have a nephrotoxic effect[4]. When compared to the risk of renal toxicity between carboplatin and cisplatin, studies show that nephrotoxicity of carboplatin has a lower incidence than cisplatin[18, 19]. In our study, we observed that the association of cisplatin with carboplatin and paclitaxel reduced nephrotoxicity when compared to CP and CP/PC protocols, which we can assume that the association of the drugs allows a reduction in the concentration of administered drugs with a consequent decrease in the renal toxicity.

Some studies have shown that renal and hepatic function is a risk factor for nephrotoxicity and drug-induced hepatotoxicity, another study of the same name noted a significant progression in serum creatinine in treatment, characterizing acute nephrotoxicity caused by cisplatin, with toxicity related to the cumulative dose[4, 20].

Although the study by Porras, Nogueda, and Chacón (2018)[5] reports that the combination therapy increases the risk in the development of hematological toxicity, the present study observes that the patients who used the CCP protocol were the ones that were less likely to develop hematological diseases and lower rates when compared to the use of cisplatin alone.

CONCLUSION

It was observed that there was an expressive decline in hemoglobin indices regardless of the protocol used, due to hematologic toxicity induced by chemotherapy. All these changes

manifest after chemotherapy, which alerts for the need for follow-up and possible changes in therapy.

It should be noted here that, in the analysis of hematological alterations, other alterations possibly presented by the patients were not associated with possible comorbidities. Knowing that the cancer patient is complex, this fact may represent a limitation of the study. Another limitation is the lack of periodic literature on the subject, which reduces the discussion on the issue.

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