Cogitare Enfermagem

ORIGINAL ARTICLE

ASSESSMENT OF CLIMACTERIC SYMPTOMS IN YOUNG WOMEN UNDERGOING CHEMOTHERAPY*

HIGHLIGHTS

1. Amenorrhea is common in young women undergoing chemotherapy.
2. Hot flushes are common in young women undergoing chemotherapy.
3. There is no association between climacteric symptoms and the antineoplastic agent.
4. There is no association between climacteric symptoms and number of chemotherapy cycles.

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ABSTRACT

Objective: To describe the prevalence of climacteric symptoms in women undergoing cancer treatment and to analyze its relationship with the number of chemotherapy cycles. **Methods:** Cross-sectional study with 47 women undergoing chemotherapy in two cancer reference hospitals in São Luís, Maranhão, Brazil, between March 2019 and July 2020. A structured questionnaire was used containing sociodemographic variables and information on menstrual function and symptoms. Bivariate analysis and binary logistic regression were performed to assess the relationship between predictor variables and number of chemotherapy cycles. **Results:** Mean age was 31.71 years, and amenorrhea and hot flushes were the most frequent symptoms, however, unrelated to the number of chemotherapy cycles. There was no association between the presence of climacteric effects and the type of chemotherapy (p=0.15). **Conclusion:** The results reaffirmed that chemotherapy can cause climacteric symptoms, thus emphasizing the need for measures to alleviate symptoms in patients facing this problem.

DESCRIPTORS: Neoplasms; Antineoplastic Agents; Young Adult; Menopause, Premature; Women's Health.

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INTRODUCTION

Cancer is a disease that can affect individuals of all ages and is among the four leading causes of premature death in most countries[1]. In general, chemotherapy treatment affects not only tumor cells but also healthy tissue. Side effects can be diverse and, among young people, gonadotoxicity is a worrying consequence[2]. In women, antineoplastic drugs can cause decreased or insufficient ovarian reserve, leading to hypoestrogenism and, consequently, symptoms of early menopause[3-5].

The advancement of medicine and the development of new chemotherapy drugs have increased the survival of cancer patients, but toxicities are a challenge, among them toxicity related to the reproductive system. In women, this dysfunction may not occur immediately after treatment, but manifest later as early menopause. In addition to the climacteric symptoms that accompany early menopause, sexual dysfunctions such as loss of libido and pain during intercourse may also occur[6]. These effects can affect the quality of life of cancer survivors, and the health team, including physicians and nurses, must be prepared to assist these patients[7].

Due to the concern with quality of life after cancer treatment, studies that aim to determine the main changes in the female reproductive cycle are important in order to prevent, or at least minimize, any emotional damage in patients with oncological diseases. The aim of this study was to describe the prevalence of climacteric symptoms in young women undergoing cancer treatment and to analyze their relationship with the number of chemotherapeutic cycles.

METHOD

Cross-sectional study carried out between March 2019 and July 2020 with women undergoing cancer treatment, aged between 18 and 45 years, in outpatient clinics of two public hospitals of oncological reference in São Luís, Maranhão, Brazil. The inclusion criteria were: minimum age of 18 years and maximum of 45 years; having menstrual function present in the last six months before chemotherapy; and, having undergone oncological treatment against any type of cancer. Exclusion criteria were: women who had already undergone uterine or ovarian surgery for any indication (except for caesarean section); or women with neurological and/or psychiatric changes that could influence the completion of the form.

The inclusion of patients in the study occurred after chemotherapy cycles, some with completed cycles and others, being able to return to treatment, since definitive discharge only occurs after five years. After applying the inclusion and exclusion criteria, 47 women were approached to complete the structured questionnaire. The questionnaire contained sociodemographic variables and information on menstrual function and climacteric symptoms presented in the last six months after chemotherapy.

For statistical analysis, the sample was stratified into two groups according to the number of chemotherapy cycles. The first group was made up of women with two to five cycles of chemotherapy, and the second group with women with more than five cycles of chemotherapy. This division was based on the data collected from the patients' medical records. About half of the women had undergone up to five cycles and the other half more than five cycles. Therefore, for statistical reasons, both groups were intended to have a similar number of patients.

Categorical variables were described as proportions and assessed by bivariate analysis using the chi-square or Fisher's exact test. The variables that showed statistical significance at $p<0.05$ were included in a binary logistic regression model in order to evaluate the

relationship between the predictor variables and the number of chemotherapy cycles that the participants underwent. The analyses were performed in the IBM SPSS version 24 statistical program, adopting a p-value of 0.05 as the significance level. The Word and Excel 2007 programs were used to analyze the data, and the data were expressed as mean, absolute and relative frequency through charts and tables.

The study was approved by the Research Ethics Committee (CEP) of the University Hospital of the Federal University of Maranhão - HU/UFMA, under opinion no. 3164958.

RESULTS

Table 1 presents the sociodemographic data of 47 women undergoing antineoplastic treatment in hospitals in São Luís, Maranhão. The mean age was 31.71 (±0.97) years. Most of the patients came from the state capital city, 32 (68.1%), had brown skin color 24 (51.1%), a married/stable union marital status 30 (63.8%) and income between one and three minimum wages 40 (85.1%). In addition, 41 (87.2%) participants did not smoke, 20 (42.6%) had menarche before 13 years of age and 34 (72.3%) had no history of abortion. There was no statistical difference in relation to the variables between the groups of women undergoing up to five chemotherapy cycles or more than five chemotherapy cycles (p>0.05).

Table 1. Sociodemographic data of 47 women with cancer treated in hospitals in São Luís, Maranhão, and their relationship with the number of chemotherapy cycles. São Luís, MA, Brazil, 2023

VARIABLE	Number of chemotherapy cycles			
	Total (%)	2-5	>5	p-value
Age (Mean ± SD)	31.71±0.97	33.65±6.92	30.16±5.84	0.08
Origin São Luís Noncapital city	32 (68.1) 5 (31.9)	14 (30) 6 (70)	18 (66.7) 9 (33.3)	0.81
Education Complete/Incomplete Basic Education Complete/Incomplete High School Complete/Incomplete College	10 (21.3) 32 (68.1) 5 (10.6)	4 (20) 12 (60) 4 (20)	6 (22.2) 20 (74.1) 1 (3.7)	0.53
Skin color White Brown Black	16 (34) 24 (51.1) 7 (14.9)	7 (35) 9 (45) 4 (20)	9 (33.3) 15 (55.6) 3 (11.1)	0.62
Marital status Single/Divorced/Widowed Married/Stable union	17(36.2) 30 (63.8)	6 (30) 14 (70)	11 (40.7) 16 (59.3)	0.47

Income				
<1 minimum wage	3 (6.4)	1 (5)	2 (7.4)	0.32
1 to 3 minimum wages	40 (85.1)	16 (80)	24 (88.9)	
>3 minimum wages	4 (8.5)	3 (15)	1 (3.7)	
Smoking				
Yes	6 (12.8)	3 (85)	3 (11.1)	0.63
No	41 (87.2)	17 (15)	24 (88.9)	
Menarche				
Before 13 years old	20 (42.6)	9 (45)	11 (40.7)	0.71
After 13 years old	27 (57.4)	11 (55)	16 (59.3)	
Abortion				
Yes	13 (27.7)	8 (40)	5 (18.5)	0.18
No	34 (72.3)	12 (60)	22 (81.5)	

Data presented in proportion format. The chi-square or Fisher's exact test was used for the analyses; *p<0.05.
SOURCE: The authors, 2023.

Breast cancer was the most prevalent among the 29 women (61.7%), seven (14.9%) had metastasized, and 14 (29.8%) were using Taxol®-derived drugs. Among the climacteric symptoms, 27 patients (57.4%) reported amenorrhea and a little more than half did not menstruate again after the cycles. Hot flushes were the second most frequent symptom (40.4%) with 19 patients, followed by vaginal dryness, sweating, weight change, loss of libido and dyspareunia being the least frequent (Table 2).

Table 2. Clinical data, treatment and climacteric symptoms of 47 women with cancer treated in hospitals of São Luís, Maranhão. São Luís, MA, Brazil, 2023

VARIABLE	Number of chemotherapy cycles			
	Total (%)	2-5	>5	p-value
Type of cancer				
Cervix	3 (6.4)	1 (5.0)	2 (7.4)	0.82
Breast	29 (61.7)	12 (60)	17 (63)	
Other	15 (31.9)	7 (35)	8 (29.6)	
Metastasis				
Yes	7 (14.9)	1 (5)	6 (22.2)	0.16
No	40 (85.1)	19 (95)	21 (77.8)	
Treatment				
Taxol®-derived drugs	14 (29.8)	2 (10)	12 (44.4)	*0.03
Doxorubicin® and associations	7 (14.9)	3 (15)	4 (14.8)	
Other	26 (55.3)	15 (75)	11 (40.7)	
Amenorrhea				
Yes	27 (57.4)	8 (40)	8 (88.9)	*0.05
No	20 (42.6)	12 (60)	1 (11.1)	
Returned to menstruating after treatment				
Yes	13 (27.65)	4 (20)	9 (33.3)	0.16
No	14 (29.78)	4 (20)	10 (37)	
Did not stop	20 (42.57)	12 (60)	8 (29.7)	

Hot flushes				
Yes	19 (40.4)	5 (25)	19 (70.4)	* 0.03
No	28 (59.6)	15 (75)	8 (29.6)	
Vaginal dryness				
Yes	16 (34)	5 (25)	11 (34)	0.25
No	31 (66)	15 (75)	16 (66)	
Sweating				
Yes	15 (31.9)	5 (25)	10 (37)	0.38
No	32 (68.1)	15 (75)	17 (63)	
Weight changes				
Yes	13 (27.65)	6 (30)	7 (25.9)	0.45
No	34 (72.35)	14 (70)	20 (74.1)	
Loss of libido				0.99
Yes	9 (19.15)	3 (15)	6 (22.3)	
No	38 (80.85)	17 (85)	21 (77.7)	
Dyspareunia				
Yes	2 (4.3)	0 (0)	2 (7.4)	0.21
No	45 (95.7)	20 (100)	25 (92.6)	

Data presented in proportion format. The chi-square or Fisher's exact test was used for the analyses; *$p<0.05$.
SOURCE: The authors, 2023.

The variables amenorrhea, hot flushes and types of treatment were more present in women undergoing more than five chemotherapy cycles ($p<0.05$). They were included in a binary logistic regression model to analyze the relationship between these variables and the number of chemotherapy cycles.

After analysis, it was observed that amenorrhea (2.759-95% CI 0.671-11.44-$p<0.05$) and hot flushes (1.362-95% CI 0.289-6.409-$p<0.05$) were not related to the number of chemotherapy cycles, thus, it is inferred that in this sample population the increase in the number of chemotherapy cycles was not associated with the presence of amenorrhea and hot flushes ($p > 0.05$). On the other hand, drug treatment was a variable that correlated with the number of cycles, i.e., using Doxorubicin® and associations increases by 6.642 (95% CI 1.118-39.467-$p<0.05$) the chance of belonging to the group of participants who undergo more than five cycles of treatment (Table 3).

Table 3. Binary logistic regression of participants with cancer, stratified by number of chemotherapy cycles. São Luís, MA, Brazil, 2023

	CHEMOTHERAPY CYCLES			
Variables	**Odds ratio**	**CI (95%)**	**Wald**	**p-value**
Amenorrhea				
Yes	2.759	0.671-11.44	1.981	0.11
No	Ref.			
Hot flushes				
Yes	1.362	0.289-6.409	0.153	0.63
No	Ref.			

Treatment				
Taxol®-derived drugs	Ref.			
Doxorubicin® and associations	6.642	1.118-39.467	4.337	**0.03**
Other	1.591	0.257-9.838	0.250	0.62

Binary Logistic Regression Model. CI: Confidence Interval; Ref - reference.
SOURCE: The authors, 2023.

Table 4 shows the analysis of the association between the types of chemotherapy and the presence of amenorrhea and other climacteric symptoms. Among the participants with amenorrhea, there was a preponderance of the use of microtubule inhibitor chemotherapy (n = 6; 22.2%), as well as in women with climacteric changes there was also a predominance of use of this class of drugs (n = 5; 34.6%). However, there was no association between both amenorrhea and climacteric symptoms variables with chemotherapy classes (p>0.05).

Table 4. Chemotherapy use in participants with cancer divided by presence of amenorrhea and climacteric changes. São Luís, MA, Brazil, 2022

	Amenorrhea			Climacteric changes		
	No n (%)	Yes n (%)	p-value	No n (%)	Yes n (%)	p-value
	20 (42.5)	27 (57.5)	0.08	21 (44.7)	26 (55.3)	0.11
Chemotherapy						
Alkylating agents	1 (5)	1 (3.7)		2 (9.5)	0 (0)	
Folic acid analogs	0 (0)	1 (3.7)		1 (4.8)	0 (0)	
Antimetabolite + Platinum	0 (0)	1 (3.7)		0 (0)	1 (4.8)	
Anthracyclines	7 (35)	2 (7.4)		5 (23.8)	4 (15.4)	
Anthracyclines/alkylating agents	4 (20)	0 (0)		3 (14.3)	1 (4.8)	
Cannabinoid	1 (5)	0 (0)		0 (0)	1 (4.8)	
Platinum derivatives	1 (5)	5 (18.5)		2 (9.5)	4 (15.4)	
Platinum derivatives/folic acid analogs	0 (0)	1 (3.7)		1 (4.8)	0 (0)	
Platinum derivatives/microtubule inhibitors	0 (0)	1 (3.7)		0 (0)	1 (3.8)	
Microtubule inhibitors	2 (10)	6 (22.2)		3 (14.3)	5 (19.2)	

SOURCE: The authors, 2023.

DISCUSSION

The potential loss of fertility caused by a cancer diagnosis, or its treatment is one of the greatest impacts on long-term quality of life in young patients of reproductive age (14 to 45 years)[6]. With advances in treatments and increased survival, health professionals should be aware of the long-term effects of chemotherapies that include possible sterility.

A systematic review evaluated the emotional consequence and impact on the reproductive quality of life of cancer patients with a mean age ranging from 27.8 to 39.9 years, and identified that more than half of the patients did not know about their fertile potential and did not remember if the health professional had informed about the possible risk to fertility[8].

There are resources for fertility preservation in female patients, among them egg preservation[7-8]. However, this is an expensive procedure and is not offered everywhere in Brazil, especially in the Unified Health System (SUS). The patients in this study were mostly middle- and low-income, earning a maximum of three minimum wages, and therefore unable to afford egg freezing. We did not have access to information on whether this possibility had been considered by the clinical staff of the hospital where the research took place.

In addition to the emotional issue, due to the possible loss of fertility, female cancer patients still experience physical effects associated with hormonal suppression that include symptoms of early menopause, or climacteric, the main ones being loss of libido, vaginal dryness, weight gain, dyspareunia, hot flushes, sweating and amenorrhea[3,7].

Amenorrhea was the most commonly reported climacteric symptom among patients in the present study ($p < 0.05$), with the majority not having returned menstrual cycles. A similar result was found by researchers from São Paulo who reported that 84% of patients treated for breast cancer suffered amenorrhea, with many of them never returning to menstruate[3].

Amenorrhea can be explained by the gonadotoxic action of chemotherapeutic agents that affect ovarian follicles, reducing their reserve and inducing amenorrhea, which is irreversible in some cases[8-9]. Studies report that many young women develop amenorrhea during chemotherapy, but in some cases, especially if the age is below 40 years, menstrual cycles and fertility may recover months to years after the end of therapy[3,7,10].

Hot flushes were the second most common climacteric symptom among patients in this study, with a significant difference ($p < 0.05$) in the first statistical evaluation. In a study conducted in São Paulo with young women treated for breast cancer, hot flushes were also the second most reported symptom among women ($p < 0.05$)[3].

Sweating was a symptom present among the participants in this study, but without statistical significance. Dyspareunia, vaginal dryness, weight change and loss of libido were also present among women, but there was no association with the number of chemotherapy cycles.

Breast cancer was the most prevalent tumor type among our patients. A study conducted in the United States of America evaluated the most common types of tumors among individuals aged 15 to 39 years[6]. In the group of women aged 30-39 years, breast cancer was the most common tumor type.

Two Brazilian studies, from the South and Southeast regions of Brazil, aimed to evaluate the prevalence of amenorrhea and climacteric symptoms among women of childbearing age undergoing chemotherapy treatment[3,7]. In the study conducted in the Southeast region, of the 50 patients undergoing different types of tumors, the mean age was 35.8 years and breast cancer was also the most prevalent tumor, with 66% of cases[3].

In fact, female breast cancer is the most incident in the world, with 2.3 million (11.7%) new cases[11]. In Brazil, without considering non-melanoma skin tumors, female breast cancer is also the most incident, as well as in all regions of the country with an estimate for the triennium from 2023 to 2025 of 74,000 (10.5%) new cases[12].

Regarding the chemotherapeutic agents used, women who used Doxorubicin® with associations were submitted to more than five cycles of treatment. Agents such as

5-fluorouracil®, Methotrexate®, Vincristine®, Bleomycin®, Dactinomycin®, Etoposide® and Doxorubicin® are attributed to less severe tumors, which may regress to some degree over time[2]. This may explain the lack of association between climacteric symptoms and chemotherapy classes in this study.

Research has reported that the effects of chemotherapy drugs on the female reproductive system depend not only on the agent in question, but also on the cumulative dose[2]. Despite this, in the multivariate analysis, no relationship was observed between the presence of climacteric symptoms and the number of chemotherapy cycles.

Women of childbearing age undergoing chemotherapy and with a high chance of ovarian function impairment should be advised by their oncologist about fertility preservation methods before cancer treatment. However, because it is a delicate time, with many demands to be resolved in a short period, this conduct is not often followed. In addition, patients and physicians also experience difficulty in obtaining up-to-date information and access to fertility preservation procedures[6,13].

Oncofertility (the area of fertility preservation in patients undergoing cancer treatment) demonstrates advances and perspectives, but there is still a lack of research to address this issue that presents serious challenges to the scientific and medical community. The uncertain prognosis and the poor quality of doctor-patient communication can lead to lack of information to these patients.

Oncologists, haematologists, mastologists, reproductive medicine specialists, embryologists and psychologists need to work together in a multidisciplinary way to provide a humanized and efficient service to patients. Many individual characteristics, especially the patient's age, histological type of tumor, stage of disease, chemotherapy regimens and treatment prognosis should be discussed with the patient, who should receive adequate psychological care and objective information about the real chances of obtaining future pregnancy with the established techniques and the limitations of experimental techniques.

It is always important to have a high sample number for a statistical scope, therefore, a limiting factor of the study was the number of patients (47) which, despite this, can be considered good for the period that unfortunately caught the beginning of the COVID-19 pandemic, when we were prevented from accessing patients.

CONCLUSION

Breast cancer was the most prevalent tumor, and the predominant climacteric symptoms were amenorrhea and hot flushes. Doxorubicin® was the class of antineoplastic most used by patients who had undergone more than five chemotherapy cycles. Despite this, there was no association between the types of chemotherapy and the presence of amenorrhea and other climacteric symptoms.

The importance of this study stands out in triggering further research on the management of climacteric symptoms in young women undergoing chemotherapy, since women surviving such a serious disease should have good quality of life and a prospect of having children with the preservation of their fertility.

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