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Chemo-Induced Cardiotoxicity in Patients Treated for Breast Cancer at Brazzaville University Hospital

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Abstract

Summary: Chemotherapy remains indispensable in the management of breast cancer, acting by inhibition of tumor cell proliferation or by non-selective cell destruction; hence the multiple side effects observed, including cardiac toxicity.

Patients and Methods: This was a cross-sectional analytical study involving patients with histologically confirmed breast cancer, treated with anthracycline- and/or taxane-based chemotherapy for at least three months, without pre-existing cardiac disease.

Results: The sex ratio favoured women. The mean age of patients was 50.63 ± 10.1 years, with extremes of 28 and 80 years. The incidence of chemo-induced cardiotoxicity was 37.06%, all grades combined. Factors associated with the occurrence of chemo-induced cardiotoxicity were age (p=0.013), arterial hypertension (p=0.0001), histopronostic grade SBR II (p= 0.042) and initial metastatic stage (p=0.017).

Conclusion: the frequency of chemo-induced cardiotoxicity is high, and its grades are progressive, irrespective of the cumulative dose of anthracyclines. This cardiotoxicity is accompanied by myocardial structural abnormalities in the form of dilated cardiomyopathy, and it is presented clinically as global heart failure.

Keywords: chemotherapy; cardiotoxicity; cancer; breast; CHU-Brazzaville

Introduction

Breast cancer is a major public health problem, given its ever-increasing incidence and mortality rate. [1].

Today, its management is well codified and more personalized, thanks to major scientific advances that have led to the development of several therapeutic modalities, including hormone therapy, targeted therapies and immunotherapy [2]. Despite the advent of these new therapies, chemotherapy remains indispensable for patient management.

Chemotherapy is a cytotoxic or cytostatic-based treatment developed since 1940. It acts by inhibiting tumor cell proliferation or by non-selective cell destruction of both cancerous and normal cells; hence the multiple side effects observed [3]. One of the most serious side effects is cardiac toxicity, known as chemo-induced cardiotoxicity.

According to the European Society of Cardiology, chemo-induced cardiotoxicity corresponds to left ventricular dysfunction characterized by a reduction in left ventricular ejection fraction (LVEF) of less than 50% or a fall of 10% compared with baseline LVEF or a fall of 15% in *Global longitudinal strain* compared with baseline, with or without signs of heart failure. [4; 5]. These manifestations can range from subclinical myocardial dysfunction to irreversible, life-threatening heart failure [6].

In order to improve the management of patients treated with chemotherapy for breast cancer, we conducted this study.

Patients and Methods

This was a cross-sectional analytic study with retrospective data collection, carried out in the cancerology department of the Brazzaville University Hospital from January 1st 2017 to December 31th 2021. Sampling was exhaustive.

This study included patients with histologically confirmed breast cancer who had been treated with anthracycline- and/or taxane-based chemotherapy for at least three months with good compliance. Patients with pre-existing heart disease were not included.

The variables studied were sociodemographic, notably age and gender; clinical, namely hypertension, diabetes, dyslipidemia, alcohol consumption, smoking, HIV status and initial staging; Para clinical, notably histological type, molecular profile, LVEF (initial, during treatment and one year after); and therapeutic (chemotherapy molecules).

Grades of cardiac toxicity have been defined as follows [7] :

-Grade 1: LVEF between 50 - 59%;

-Grade 2: LVEF between 40 - 49%;

-Grade 3: LVEF between 20 - 39%;

-Grade 4: LVEF less than 20%.

Data were analyzed using Epi-info version 7.2.5.0 and Excel from Microsoft 2010. Categorical variables were expressed as headcount and percentage. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range. To study factors associated with the occurrence of chemo-induced cardiotoxicity, a simple logistic regression analysis was performed; odds ratios (OR) with their 95% confidence intervals were calculated and assessed according to the Wald test. Variables deemed significant were then used in a multivariate logistic regression model to eliminate confounding factors. The significance threshold was set at 5%.

Results

During the study period, 116 cases meeting the inclusion criteria were identified.

The study population comprised 114 women and 2 men, giving a sex ratio of 0.017. The mean age of the patients was 50.63 ± 10.1 years, with extremes of 28 and 80 years.

Forty-six patients experienced chemo-induced cardiotoxicity, representing a frequency of 37.06% across all grades.

Table I shows the cardiovascular risk factors for patients with chemo-induced cardiotoxicity.

Table II summarizes the patients clinical presentation.

Table III shows the distribution of patients with cardiotoxicity according to prognostic and predictive criteria.

Table IV shows the grades of cardiotoxicity and structural abnormalities after 04 courses of chemotherapy under the AC60 protocol.

Table V gives the grades of cardiotoxicities and structural abnormalities after 04 courses of AC60 + 4 courses of Docetaxel.

Figure 1 illustrates the grades of cardiotoxicity and structural abnormalities one year after the start of chemotherapy.

Table VI shows the factors associated with chemo-induced cardiotoxicity.

Multivariate analysis of factors associated with cardiotoxicity is shown in Table VII.

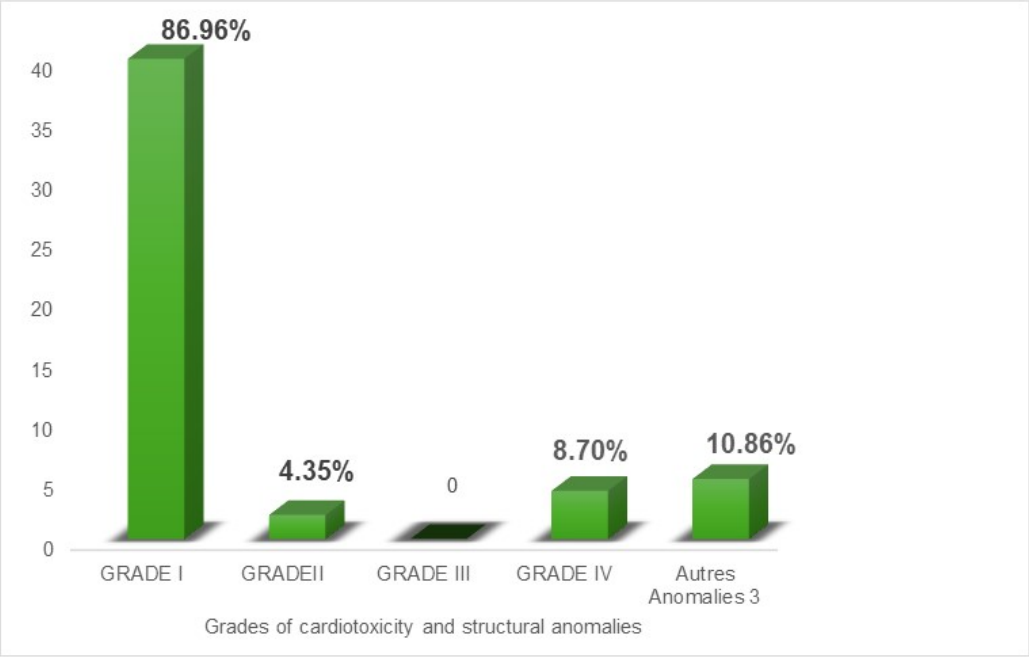

Figure 1: Grades of cardiotoxicity and structural abnormalities one year after the start of chemotherapy

Table I: Cardiovascular risk factors in patients with chemotherapy-induced cardiotoxicity

	CARDIOTOXICITY (n=46)	
	Workforce	Percent
AVERAGE AGE	53.41 ± 10.41	
HTA		
Yes	24	52.17
No	22	47.83
DIABETE		
Yes	03	6.52
No	43	93.48
OBESITY		
Yes	06	13.04
No	40	86.96
TOBACCO		
Yes	02	4.35
No	44	95.65
ALCOHOL		
Yes	03	6.52
No	43	93.48
HIV		
Yes	02	4.35
No	44	95.65
DYSLIPIDEMIA		
Yes	01	1.43
No	45	98.57

Table II: Distribution according to clinical presentation

	CARDIOTOXICITY (n = 46)	
	Workforce	Percent
HTA Yes No	26 20	53,49 46,51
Dyspnea Yes No	02 44	4.65 95.33
Tachycardia Yes No	02 44	4.65 95.33
Respiratory distress Yes No	02 44	4.65 95.33

Signs of OAP No Yes	02 44	4.65 95.33
Signs of congestive heart failure Yes No	02 44	4.65 95.33

Table III: Distribution of patients with cardiotoxicity according to SBR grade

	CARDIOTOXICITY (n = 46)	
	Workforce	Percent
SBR I II III	7 34 5	15,22 73,91 10,87
Molecular profile Luminal B Luminal A Triple Negative HER2 positive Not available	18 11 12 02 03	39.13 23.91 26.09 4.35 6.52
Initial staging Metastatic Non-metastatic	24 22	52,17 47.83
Cumulative dose of Doxorubicin Outdated Not exceeded	01 45	1,37 98.63

Table IV: Grades of cardiotoxicity and structural abnormalities after 04 courses of Doxorubicin

Cardiotoxicity grade	n = 46	
	Workforce	Percentage
Grade I	06	5.17
Grade II	-	-
Grade III	-	-
Grade IV	-	-
Structural anomaly	-	-

Table V: Grades of cardiotoxicity after 04 courses of AC 60 and 04 courses of Docetaxel and structural abnormalities

Grade of cardiotoxicity	n = 46	
	Workforce	Percentage
Grade I	32	27.58
Grade II	02	1.72
Grade III	00	00
Grade IV	03	2.58
Structural anomalies(Dilated cardiomyopathies)	05	4.31

Table VI: Factors associated with the occurrence of cardiotoxicity in univariate analysis.

Variables	Cardiotoxicity		OR IC = 95%	p-value
	Yes (n=46)	No (n=70)		
Average age	53.41 ± 10.41	48.81± 9.60	1.05 1.01 ; 1.09	0.0138
Hypertension				
No	24	12	1	-
Yes	22	58	5.30 2.27 ; 12.37	0.0001
SBR grade				
I	7	3	1	-
II	34	63	0.20 0.04 ; 0.83	0.0268
III	5	04	0.53 0.08; 3.53	0.5167
Initial metastatic stage				
Yes	22	49	1	-
No	24	21	0.37 0.17 ; 0.81	0.0138

OR= odds ratio

Table VII: Factors associated with the occurrence of cardiotoxicity in multivariate analysis.

	Cardiotoxicity		ORa IC = 95 %	p-value
	Yes (n=46)	No (n=70)		
Hypertension				
No	24	12	1	-
Yes	22	58	6.07 2.49 ; 14.81	0.0001
SBR grade				
1	7	3	1	-
2	34	63	0.13 0.03 ; 0.60	0.0090
3	5	04	0.26 0.03 ; 2.02	0.1980

ORa= adjusted odds ratio

Discussion

The average age of the population was 53, with a predominance of women. These results are in line with data reported by the Global observatory cancer 2020 [8].

Among cardiovascular risk factors, hypertension, obesity and diabetes were predominant. Hypertension, diabetes, obesity and dyslipidemia are responsible for the resurgence of cardiovascular disease, the world's leading cause of mortality. Their association with breast cancer exacerbates chemotherapy-induced cardiovascular complications, thereby increasing patient morbidity and mortality.

The incidence of cardiotoxicity in patients was 37.07% across all grades. Structural abnormalities such as dilated cardiomyopathy were present in 4.31% of cases. This high frequency could be explained by the fact that almost half of our study population had cardiovascular risk factors; indeed, the existence of such factors has been shown to increase the effect of chemotherapy on the heart muscle. Gripp et al. in Brazil and Qui et al. reported a similar frequency at 40%. [5, 9]. However, Mary O et al. and Slamon et al.

found a lower frequency of chemo-induced cardiotoxicity of 16% and 27% respectively [10, 11].

Grades of cardiotoxicity and myocardial structural abnormalities were variable during patient follow-up. After 04 courses of anthracycline-based chemotherapy, consisting of Doxorubicin 60mg/m² and Cyclophosphamide 600mg/m², grade I cardiotoxicity accounted for 5.17%, and no structural abnormalities were observed. Cardiac evaluation after 4 courses of the second taxane-based chemotherapy sequence (Docetaxel 100mg/m²), notably at 6 months, showed an increase in the frequency of grade I and grade IV cardiotoxicity to 27.58% and 2.58% respectively, as well as the appearance of structural abnormalities such as dilated cardiomyopathy (4.31%).

One year after the start of chemotherapy, grade I cardiotoxicity was the most significant (86.96%), followed by grade IV (8.7%) and grade II (4.35%). Myocardial structural abnormalities such as dilated cardiomyopathy were constant.

Although chemo-induced cardiotoxicity may be acute in some cases, in most it is progressive and asymptomatic. The accumulation of anthracycline doses during treatment and the association with taxanes, which are cardiotoxic molecules, are factors that potentiate the occurrence of cardiotoxicity. The appearance of a myocardial structural abnormality implies discontinuation of chemotherapy and immediate cardiological management, hence the importance of early diagnosis [12; 13].

Factors associated with the occurrence of chemo-induced cardiotoxicity were age (p=0.013), arterial hypertension (p=0.0001), histopronostic grade SBR II (p= 0.042) and initial metastatic stage (p=0.017). Our data are similar to those of Jones et al, who found age, cardiovascular risk factors and cumulative Adriblastine dose greater than 450mg/m² to be factors associated with the occurrence of chemo-induced cardiotoxicity. [14]. Jerusalem et al identified age, hypertension and diabetes as factors associated with the occurrence of cardiotoxicity [15].

Conclusion

Chemo-induced cardiotoxicity is a major and dreaded complication, increasing the morbidity and mortality of patients undergoing treatment with Doxorubicin and Docetaxel for breast cancer. Its frequency is high and its grades progressive, irrespective of the cumulative dose of anthracyclines. It is accompanied by myocardial structural abnormalities such as dilated cardiomyopathy and presents clinically as congestive heart failure. Management is multidisciplinary, involving oncologists and cardiologists. Reference cardiac biochemical markers such as troponins can make early detection, at a preclinical stage, I. This effective, inexpensive and rapid approach is recommended. It should be implemented in our context for efficient collaboration between cardiologists and oncologists, but also enable the development of a new specialty (cardio-oncology) for optimal management of patients followed for cancer in general and breast cancer in particular.

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