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Hematological Toxicity during Breast Cancer Chemotherapy in Pointe-Noire (Congo Brazzaville)

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Abstract

Introduction: The objective of our study was to determine the prevalence of hematological toxicity during breast cancer chemotherapy. **Patients and Methods:** This was a cross-sectional descriptive study that took place in the cancerology and internal medicine department during the period from January 1, 2021 to December 31, 2021, *i.e.* a period of 1 year. Were included in our study: patients with and histological diagnosis, and having received at least two cycles of chemotherapy and having presented hematological toxicity: anemia and/or neutropenia. The variables studied were: Age, level of study, socioeconomic level, stage of extension, type of chemotherapy, type of toxicity: neutropenia and anemia. Bivariate analysis was done between anemia, neutropenia and type of chemotherapy. **Results:** The average age of the patients was 50.35 ± 13.6 years. The extremes were 27 years and 79 years old. The most represented age group was the age group from 37 to 46 years with 18 cases or 33.33%. The most represented level study in our study was the primary level 63%, followed by secondary level 26% and the upper or superior level 11%. Metastatic stage of location was represented in 16.6% of cases, the local stage was represented in 16.7% of cases. The most common chemotherapy used was FAC protocol in 50% of cases, followed by FAC + DOCETAXEL in 47% of cases, AC protocol was used in 3% of cases. The most represented grade of neutropenia was grade 3 in 53% of cases, followed by grade 2 in 27% of cases and grade 1 in 20%. Grade 1 anemia was the most represented in 70% of cases, followed respectively by grade 2 in 27%. The majority of patients had received more than 3 courses of chemotherapy in 83% of cases. Grade 3 neutropenia was observed mostly in the advanced stages, 15 cases at the locoregional stage. Grade 1 anemia was most common in patients who received

more than 3 courses of chemotherapy. The FAC chemotherapy protocol was responsible for more grade 3 anemia in 14 cases. FAC-type chemotherapy was associated with grade 3 and 2 neutropenia in 8 cases and 4 cases, but the results were not significant. FAC + DOCEAXEL type chemotherapy was also responsible for grade 3 and 2 neutropenia in 8 cases and 4 cases P > 5% respectively. **Conclusion:** Hematological toxicity in the context of our limited resources is dominated by anemia and neutropenia. The knowledge of this hematological toxicity is necessary for the limitation of the delay of chemotherapy.

Keywords

Breast Cancer, Chemotherapy, Hematological Toxicity, Congo Brazzaville

1. Introduction

Breast cancer is currently one of the most prevalently diagnosed cancers and the 5th cause of cancer-related deaths with an estimated number of 2.3 million new cases worldwide according to the GLOBOCAN 2020 data [1] Breast cancer is leading cancer and the leading cause of cancer death in women worldwide [1]-[16]. This pathology was diagnosed in women at a frequency of 24.2% and was responsible for nearly 15% of deaths in 2018 [3]. In developing countries, it is the first cancer diagnosed and the leading cause of cancer death in women [2]. In these low income countries, breast cancer is often diagnosed at advanced stages and has a poor prognosis [6]. Breast cancer patients are usually treated in a multimodality approach which includes surgery, radiotherapy, chemotherapy, hormonal treatment and targeted therapy. Adjuvant chemotherapy represents a significant advance in the management of breast cancer. It leads to prolongation of both disease-free and overall survival. Its intent is to eliminate or delay the subsequent appearance of clinically occult micrometastatic diseases which are thought to account for distant treatment failures after local treatment alone [17].

Most chemotherapy regimens used in adjuvant treatment of breast cancer lead to varieties of temporary and reversible side effects. The side effects include myelosuppression (includes neutropenia), mucositis, alopecia, nausea, vomiting, diarrhea, anorexia and localized skin reactions. The chemotherapy toxicities must be considered when assessing the relative risk benefit ratio of adjuvant treatment. In general, the benefit gained in terms of survival exceeds the negative impact of toxicities on a patient's quality of life [18] [19].

Chemotherapy-induced neutropenia is the major dose limiting toxicity of systemic cancer chemotherapy, and it is associated with substantial morbidity, mortality, and costs. Neutropenia may result in febrile neutropenia, chemotherapy dose delay or reduction of the dose of chemotherapy [20].

To our knowledge, no study has been carried out on this subject. It is for this reason that our study aimed to determine the prevalence of hematological toxic-

ity during chemotherapy of breast cancer in Pointe-Noire.

2. Patients and Methods

This was a cross-sectional descriptive study that took place in the cancerology and internal medicine department during the period from January 1, 2021 to December 31, 2021, *i.e.* a period of 1 year. The following were included in our study: patients with a histological diagnosis of cancer and an extension assessment made of a thoraco-abdominal CT scan and/or a chest X-ray and an abdominal ultrasound, all patients who had hematological toxicity (anemia and/or neutropenia) discovered by complete blood count; patients who have received at least two courses of chemotherapy for breast cancer in a neoadjuvant or adjuvant setting.

The type of chemotherapy used was anthracyclines, antimetabolites and taxanes alone or in combination: The Treatments (alone or in combination) used were: surgery (radical mastectomy or conserving breast surgery), chemotherapy and radiation therapy, hormone therapy, targeted therapy. Chemotherapy was neoadjuvant or adjuvant based on anthracyclines (FAC protocol = 5 fluorouracil, dose 500 mg/m^2, doxorubicin 50 mg/m^2 cyclophosphamide 500 mg/m^2) and taxanes (docetaxel protocol dose 100 mg/m^2). AC (doxorubicin 60 mg/m^2 Cyclophospphamid 600 mg/m^2).

The data was collected from the records of patients hospitalized in the department for breast cancer during the study period using a previously established survey form.

The variables studied were:

- Socio-demographic: age, level of study, socio-economical level;
- Clinques: extension stage;
- Type of chemotherapy;
- Type of toxicity: neutropenia and anemia.

A bivariate analysis was performed between type of chemotherapy and type of toxicity. The stage of extension was grouped in local (stage 0 and I), locoregional or advanced (stage II and III) and metastatic for stage IV.

Chemotherapy-induced neutropenia was classified into 4 grades based on neutrophil count (Grade 1 < 2000/mm 3, Grade 2 < 1500/mm^3, Grade 3 < 1000/mm^3, and Grade 4 < 500/mm^3). The risk of developing an infection is high below 500 PNN/mm^3, it is greater below 100/mm.

Chemotherapy-induced anemia was classified into 4 grades depending on the hemoglobin level. 1) Grade 1: hemoglobin between 10 and 12 g/dL; 2) Grade 2: hemoglobin between 8 and 10 g/dL; 3) Grade 3: hemoglobin < 8 g/dL; 4) Grade 4: vital prognosis, emergency intervention.

The collection of data was made from a previously written survey sheet, containing the different variables studied. Data entry was done using the Excel version 2016 software. Qualitative variables were represented in terms of number and percentage. Quantitative variables were represented effective and on aver-

age. The statistical analysis and the data processing were carried out by the Excel 2007 software and the graphpad prism version 7 software. The statistical test used was the chi square test.

3. Results

The average age of the patients was 50.35 ± 13.6 years. The extremes were 27 years and 79 years old. The most represented age group was the age group from 37 to 46 years with 18 cases or 33.33% (Table 1). The most represented level study in our study was the primary level 63%, followed by secondary level 26% and the upper or superior level 11% (Figure 1). Economic level was most represented by low level in 54% of cases, followed by middle level in 30 % of cases and high level in 16% of cases (Figure 2). The most of patients arrived in hospital lately in 66.7%. Metastatic stage of location was represented in 16.6% of cases, the local stage was represented in 16.7% of cases (Table 2). The most common chemotherapy used was FAC protocol in 50% of cases, followed by FAC + TAXOTERE in 47% of cases, AC protocol was used in 3% of cases (Table 3). The grade of neutropenia most represented was grade 3 in 53% of cans, followed by grade 2 in 27% of cases and grade 1 in 20% (Table 4). 87% of patients had received more than 3 courses of chemotherapy (Figure 3). Grade 1 anemia was the

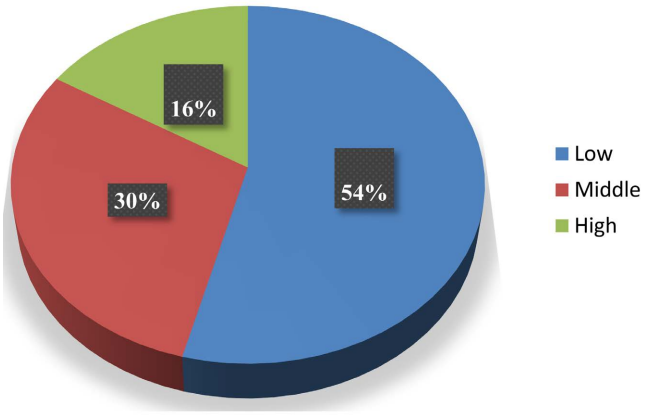

Figure 1. Distribution of patients according socio economical level.

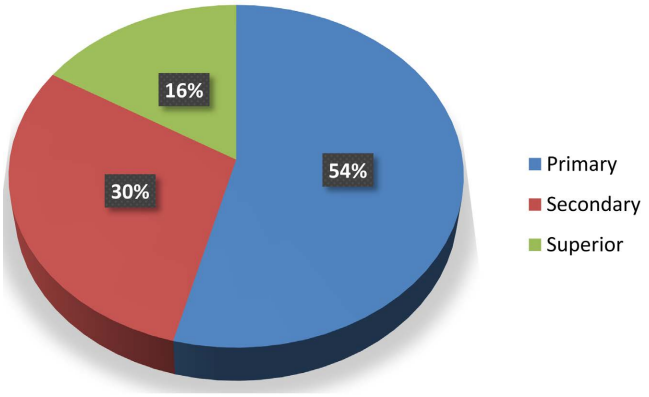

Figure 2. Distribution of patients according to study level.

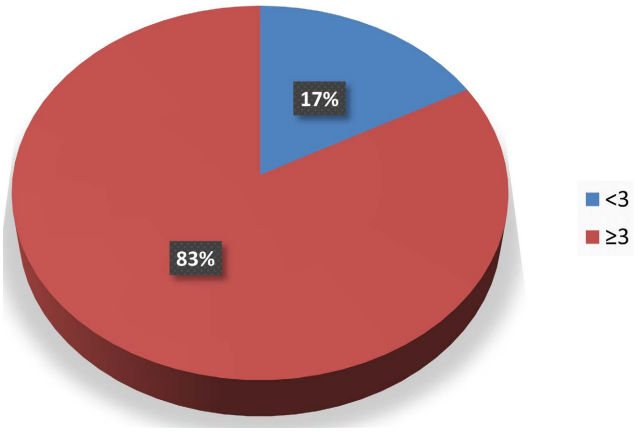

Figure 3. Distribution of patient according to number of cycle of chemotherapy.

Table 1. Distribution of patients according to Goups of age.

Age Groups	Numbers	Percentage
27 - 36	4	13
37 - 46	10	33
47 - 56	8	27
57 - 66	5	17
67 - 76	2	7
77 - 86	1	3
Total	**30**	**100**

Table 2. Distribution of patients according to stage of extension.

Stage of Extension	Number	Percentage
Local	5	16.7
Locoreginal	20	66.7
Metastatic	5	16.6
Total	**30**	**100**

Table 3. Distribution of patients according to type of chemotherapy.

Type de chimiothérapie	Effectif	Pourcentage
FAC	15	50
FAC + TAXOTERE	14	47
AC	1	3
TOTAL	30	100

most represented in 70% of cases, followed respectively by grade 2 in 27% and grade 3 in 3% cases Table 5. The majority of patients had received more than 3 courses of chemotherapy in 83% of cases. 17% had received less than 3 courses.

Grade 1 anemia was most represented in patients who received more than 3 courses of chemotherapy (Table 6). The protocol for FAC chemotherapy was responsible for more grade 1 anemia in 14 cases (Table 7). FAC chemotherapy was associated with grade 3 and 2 neutropenia in 8 cases and 4 cases. Chemotherapy of the fac + docetaxel type was also responsible for grade 3 and 2 neutropenia in respectively 8 cases and 4 cases (Table 8).

Table 4. Distribution of patients according to neutropenia.

Neutropenia	Number	Percentage
Grade 1	6	20
Grade 2	8	27
Grade 3	16	53
Total	**30**	**100**

La neutropenie de grade 1, 2, 3 était representéé respectivement dans 53%, 27%, 20%.

Table 5. Distribution of patients according to Anemia.

Anemia	Number	Percentage
Grade 1	21	70
Grade 2	8	27
Grade 3	1	3
Total	**30**	**100**

Table 6. Distribution of patient according to anemia and number of cycle.

	Anemia			
Number of cycles	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
<3	5	0	0	5
3≥	16	1	8	25
Total	**21**	**1**	**8**	**30**

P > 5% No significant results.

Table 7. Distribution of patient according to type of chemotherapy and anemia.

	Type of Chemotherapy			
Anemia	**AC**	**FAC**	**FAC + TAXOTERE**	**Total**
Grade1	0	12	9	21
Grade2	0	3	5	8
Grade3	1	0	0	1
Total	**1**	**15**	**14**	**30**

P > 5% Non significant results.

Table 8. Distribution of patient according to type of Chemotherapy and neutropenia.

	Neutropenia			
Type of Chemotherapy	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
AC	1	0	0	1
FAC	3	4	8	15
FAC + TAXOTERE	2	4	8	14
Total	**6**	**8**	**16**	**30**

P > 5% No significant results.

4. Discussion

Apart from the limitations of our study in relation to the size of the sample, our study made it possible to identify the characteristics of hematological toxicity during chemotherapy of breast cancers.

The mean age of the patients in our study was 50.35 ± 13.6 years, the extremes were 27 years and 79 years. Breast cancer affects women at a relatively young age. The average age was relatively young, this average age of the patients in our study was found by most authors in Africa with averages of 47.5 ± 12.36; 47.97 respectively described by Ngowa J. *et al.* [21], Cameroon and Mensah *et al.* Ghana [22]. On the other hand, in developed countries in the USA, for example, the average age of breast cancer patients was 61 years with the extremes of 55 years and 64 years [23]. In Saudi Arabia the average age found was also relatively young 47.16 ± 12.15 [24]. The age group most represented in our study was 37 to 46 years of age, followed by the age group 47 to 56, the younger age groups. These age groups were close to the age groups of the majority of African countries [21] [22]. In the US, the most affected age group was 54 at age 65 [23]. The age groups of patients in both developed and US countries are quite high age groups, unlike age groups in African countries, especially those in developmental pathways. This could be explained on the one hand by the composition of the African population which is a young population and on the other hand by the probable increase in the incidence of breast cancer in this age group but also by the development diagnostic and therapeutic techniques. In fact, the population of developed countries is aging and age is a risk factor for breast cancer. The level of study in our study was primary in our study in 63% of cases, followed by the secondary level 23% of cases. In developing countries, patients had a primary level of education or were illiterate [25]. In developed countries, particularly in the US, the highest level of education is the highest level [26] [27].

The level of study in our study was primary in our study in 63% of cases, followed by the secondary level 23% of cases. In developing countries, patients had a primary level of education or were illiterate [25]. In developed countries, particularly in the US, the highest level of education is the highest level [26] [27].

The majority of patients were seen in advanced stages II and III (locoregional) with a percentage of 57% and metastatic or 23% of cases, the local stages ac-

counted for 10% of cases in our study. Several studies in the developing countries have similar results to those of our study [21] [25]. This could be explained on the one hand by a primary level of study in our study thus generating a weak knowledge of the cancer pathology and the clinical signs of beginning; on the other hand, the socioeconomic level may be considered as a barrier to consultation since access to a health center and cancer treatment remains very expensive [28] [29].

4.1. Type of Chemotherapy

The chemotherapy protocols used in our study were protocols based on anthracyclines (FAC and AC) but also based on taxanes. These treatments were used in a neoadjuvant or adjuvant setting.

The benefit of adjuvant chemotherapy was well established by the 1980s. A meta-analysis including 40 adjuvant chemotherapy trials in over 13,000 breast cancer patients showed multiagent chemotherapy reduced the annual odds of death by about one quarter in the initial 5 years after treatment for women under 50 [30]. Although many of these early data supported the use of the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF), advanced breast cancer studies in the 1980s suggested greater activity of anthracycline-containing regimens based on higher response rates and response durations [31]. Subsequently, multiple randomized trials compared adjuvant anthracycline-based chemotherapy regimens with CMF and suggested a disease free Survival and overall survival benefit with adjuvant anthracyclines [32] [33] [34]. Anthracycline and taxanes. One study established the anthracycline-and taxane chemotherapy protocol as a standard for adjuvant treatment. Notably, the absolute benefit is relatively small, indicating only a small subset of patients with invasive breast cancer derive benefit from adjuvant anthracyclines when compared with other adjuvant chemotherapy regimens [35]. Other authors have used anyhracyclines in 54% of cases [36].

87% of the patients had received more than 3 cures in our study, indeed this could be explained by the fact that they were reaching the advanced stages.

4.2. Type of Toxicity (Anemia and Neutropenia)

4.2.1. Neutropenia

In our study, the most represented grade of neutropenia was grade 3 and 4. Different studies in different parts of the globe also revealed that neutropenia is the main dose-limiting toxicity in patients on chemotherapy [37] [38] [39] [40]. The highest frequencies of hematologica l toxicities were recorded at 4th cycles of chemotherapy, including overall grade leucopenia, neutropenia, anemia and thrombocytopenia. The most frequent grade 3 hematological toxicities were reported during cycles 3 and 4 [41]. Studies, involving five treatment comparisons, reported neutropenia (grade 3/4). Administration of taxanes first reduced the risk of grade 3/4 neutropenia when compared with anthracyclines first (4 studies with 5 treatment comparisons; 279 attendees; high-certainty evidence; analysis

2.1). There were 23 events in 142 participants in the taxane [42]

4.2.2. Anemia

Even though chemotherapy is considered to be effective, its usage very often leads to several side effects including hair loss, nausea/vomiting, diarrhea, mouth sores, fatigue, increased susceptibility to infections, bone marrow supression, combined with leucopenia, anaemia, easier bruising gold bleeding; other less frequent side effects include cardiomyopathy, neuropathy, hand-foot syndrome, impaired mental functions. In younger women, disruptions of the menstrual cycle and fertility issues might also appear. Special form of chemotherapy is electrochemotherapy which can be used in patients with breast cancer that has spread to the skin, however, it is still quite uncommon and not available in most clinics [43].

4.2.3. Neutropenia Number of Cycle

In our study, hematological toxicity was more marked in patients who had received more than 3 courses of chemotherapy in 25 cases. Toxicity was present as a function of the number of cures but this result was statistically insignificant. This could be explained by the small size of our sample. The highest frequencies of hematological toxicities were recorded at 4th cycle of chemotherapy, including overall grade leucopenia, neutropenia, anemia and thrombocytopenia. The most frequent grade 3 hematological toxicities were reported during cycles 3 and 4 [41].

This result was also observed in the literature by Ahmed *et al.* who found among 58 patients who presented with neutropenia: 20 patients developed first neutropenic event in third chemotherapy cycle (34.5%), 19 patients developed first neutropenic event in second cycle (32.8%), 9 patients developed first neutropenic event during forth cycle (15.5%), 7 patients developed first neutropenic event during fifth cycle (12.1%) and 3 patients developed neutropenic event during sixth cycle (5.1%) [44].

4.2.4. Neutropenia and Taxanes

Taxane toxicity: grade 2 and 3 neutropenia

In our study, grade 2 and 3 neutropenia was frequent in 14 cases, *i.e.* more than half, around 49%. All toxicity mentioned below were only calculated grade 3 - 4. The data on anemia and thrombocytopenia were reported in seven studies. Neutropenia was reported for all trials. Most of these data were homogeneous except for the neutropenia analysis the number of patients experiencing grade 3 - 4 hematologic toxicity was greater in the Gemcitabine Taxanes-based arm. The odds ratio for single studies with anemia analysis ranged from 0.31 to 4.18 [36] [37] [38] [39] [40] [45].

4.2.5. Anemia and Taxanes

In our study, taxanes were responsible for the anemia in 14 cases, *i.e.* 47%. According to the work of Chaumart *et al.* Among 378 patients, anemia was ob-

served in 64% of cases. The occurrence of anemia was significantly related to 6 risk factors: exposure to taxanes, high dose of anthracyclin (epirubicin 100 mg/m^2) [46].

4.2.6. Anemia and Anthracyclins

In our study, the sequential FAC and FAC + DOCETAXEL protocols were the most responsible for anemia in respectively 15 cases and 14 cases, *i.e.* in more than half of the cases. This trend has been observed in several studies in the literature. Indeed Brufman *et al.* has pointed out that the type of chemotherapy is strongly related to the occurrence of anemia. Concomitant taxane schedules (TAC) induced significantly more hematological toxicity than sequential taxane schedules [47].

In addition, a high dose of anthracyclin appears to be significantly related to more myelo-toxicity than low doses. Brufmann *et al.* observed similar findings with epirubicin dose intensity (100 mg/m^2 versus 50 mg/m^2) in metastatic breast cancer [48].

In trials comparing FEC 50 vs FAC 50, epirubicin was linked to lower rates of toxicity, with fewer severe anemia [49].

5. Conclusions

The chemotherapy of breast cancers in our context with limited resources is of the anthracyclines (AC, FAC) and taxanes (docetaxel) type. These chemotherapies are responsible for hematological toxicities such as grade 1, 2 and 3 anemia; neutropenia is represented by grades 2 and 3.

Hence, the utilization of G-CSF should be enhanced to decrease the incidence of neutropenia. Pretreatment blood cell counts can be used to identify patients at increased risk of significant myelosuppression at the start of chemotherapy.

Conflicts of Interest

There were no conflicts of interest during this study.

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