Neutropenia Associated with the Treatment of Breast Cancer: Integrative Literature Review

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Neutropenia Associada ao Tratamento do Câncer de Mama: Revisão Integrativa da Literatura

Neutropenia Asociada al Tratamiento del Cáncer de Mama: Revisión Integrativa de la Literatura

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Abstract

Introduction: Breast cancer is the most frequent neoplasm among women and chemotherapy drugs are used as an alternative to its treatment. Neutropenia is the most serious chemotherapy-induced hematologic toxicity. **Objective:** To evaluate through bibliographic review the occurrence of neutropenia as hematological toxicity in patients with breast cancer, based on studies that address different chemotherapeutic treatment regimens. **Method:** Integrative literature review. Data from three databases PubMed, Capes and LILACS were collected. The terms used were *neutropenia, breast cancer, chemotherapy e toxicity hematological*. The selected articles were published between 2013 and 2018. A total of 101 articles were initially evaluated and 23 were selected. For data analysis, it were extracted information about the number of patients included in the study, age and occurrence of neutropenia, total number and frequency. **Results:** In total, 19,528 women underwent chemotherapy and were included in the study. Of the 13 chemotherapy drugs reported in the selected studies, the most used regimens were epirubicin, fluorouracil, cyclophosphamide and docetaxel (D-CSF), docetaxel and cyclophosphamide (CT) and docetaxel, cyclophosphamide and doxorubicin (CT). All the therapeutic regimens studied caused neutropenia grade 3 and 4 as hematological toxicity. In nine studies, neutropenia was greater than 50%. **Conclusion:** Neutropenia has a high occurrence, regardless of the chemotherapy treatment utilized to treat breast cancer. The most associated schemes were platinum/taxanes and cyclophosphamide/anthracyclines/taxanes, which are most often used for their high efficacy.

Key words: Breast Neoplasms; Drug-Related Side Effects and Adverse Reactions; Neutropenia; Drug Therapy, Combination.

Resumo

Introdução: O câncer de mama é a neoplasia mais frequente entre as mulheres e como alternativa para o seu tratamento são utilizados medicamentos quimioterápicos. A neutropenia é a toxicidade hematológica mais séria induzida pelo tratamento quimioterápico. **Objetivo:** Avaliar, por revisão bibliográfica, a ocorrência de neutropenia em pacientes com câncer de mama, a partir de estudos que abordam diferentes regimes de tratamento quimioterápicos. **Método:** Revisão integrativa da literatura. Foram coletados dados nas três bases de dados PubMed, Periódicos Capes e LILACS. Os termos utilizados foram *neutropenia, breast cancer, chemotherapy* e *toxicity hematological*. Os artigos selecionados foram publicados entre 2013 a 2018. Um total de 101 artigos inicialmente avaliados e 23 selecionados. Para análise dos dados, foram extraídas as informações sobre o número de pacientes incluídas no estudo, a idade e a ocorrência de neutropenia, número total e frequência. **Resultados:** No total, 19.528 mulheres realizaram tratamento quimioterápico e foram incluídas na pesquisa. Dos 13 medicamentos quimioterápicos relatados nos estudos selecionados, os regimes mais utilizados foram epirrubicina, fluorouracil, ciclofosfamida e docetaxel (FEC-D), docetaxel e ciclofosfamida (TC) e doxorrubicina, ciclofosfamida e docetaxel (AC-T). Todos os regimes terapêuticos estudados causaram neutropenia grau 3 ou 4 como toxicidade hematológica. Em nove estudos, a neutropenia foi superior a 50%. **Conclusão:** A neutropenia apresenta elevada ocorrência, independente do tratamento quimioterápico utilizado para o tratamento do câncer de mama. Os esquemas mais associados foram platina/taxano e ciclofosfamida/antraciclinas/taxanos, que são os mais frequentemente utilizados por sua elevada eficácia.

Palavras-chave: Neoplasias da Mama; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Neutropenia; Quimioterapia Combinada.

Resumen

Introducción: El cáncer de mama es la neoplasia más frecuente entre las mujeres y como alternativa para su tratamiento se utilizan medicamentos quimioterápicos. La neutropenia es la toxicidad hematológica más grave inducida por el tratamiento quimioterápico. **Objetivo:** Evaluar por revisión bibliográfica la ocurrencia de neutropenia en pacientes con cáncer de mama, a partir de estudios que abordan diferentes regímenes de tratamiento quimioterápicos. **Método:** Revisión Integrativa de la Literatura. Se recolectar datos de tres bases de datos PubMed, Periódicos Capes y LILACS. Los términos utilizados fueron *neutropenia, breast cancer, chemotherapy* e *toxicity hematological*. Los artículos seleccionados fueron publicados entre 2013 y 2018. Un total de 101 artículos inicialmente evaluados y 23 seleccionados. Para el análisis de los datos, extrajimos información sobre el número de pacientes incluidos en el estudio, la edad y la frecuencia y el número total de neutropenia. **Resultados:** Total 19.528 mujeres realizaron tratamiento quimioterápico y fueron incluidas en la investigación. De los 13 medicamentos quimioterápicos reportados en los estudios seleccionados, los regímenes más utilizados fueron epirubicina, fluorouracil, ciclofosfamida y docetaxel (FEC-D), docetaxel y ciclofosfamida (TC) y doxorrubicina, ciclofosfamida y docetaxel (AC-T). Todos los regímenes terapéuticos estudiados causaron neutropenia grado 3 o 4 como toxicidad hematológica. En nueve estudios la neutropenia fue superior al 50%. **Conclusión:** La neutropenia tiene una alta incidencia, independientemente del tratamiento de quimioterapia utilizado para tratar el cáncer de mama. Los esquemas más asociados fueron platino/taxano y ciclofosfamida/antraciclinas/taxanos, que se utilizan con mayor frecuencia por su alta eficacia.

Palablas clave: Neoplasias de la Mama; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Neutropenia; Quimioterapia Combinada.

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INTRODUCTION

Regardless of important advances in research, cancer continues to be a major health concern, because it is one of the principal causes of death in the world, surpassed only by cardiovascular diseases[1]. More than 1.7 million new cases of cancer should be diagnosed in 2019[2], of which 600 thousand cases will be in Brazil[3].

Breast cancer is the most frequent neoplasm among women and its incidence rates and mortality are expected to increase significantly in the upcoming five to ten years[4]. It is an uncommon disease before 35 years old with increasing incidence, mainly after 50 years[3], which is associated to genetic factors, hormone alterations, obesity and tobacco addiction[5].

Breast cancer treatment is complex and depends on the tumor clinical staging, of the characteristics of the neoplasm (triple-negative, positive Human Epidermal growth factor Receptor-type 2 (HER-2), luminal etc.) and of the clinical conditions of the patient. Chemotherapy is the frequently indicated treatment alternative that includes a large spectrum of antineoplastic drugs and can be indicated in metastatic, adjuvant and neoadjuvant contexts.

Neoadjuvant chemotherapy is known as primary or pre-operatory, utilized by patients with breast cancer locally advanced and operable, whose main objective is to reduce the primary tumor and favor the conservation of the breast[6]. Adjuvant chemotherapy is utilized after the surgical procedure, is intended to cure and together with hormone therapy in selected cases, prolongs the patient survival; the main chemotherapeutics utilized for breast cancer are anthracycline and taxanes[7].

Even with the advances from the discovery of increasingly effective chemotherapeutic drugs, the toxicity associated to the treatment is still frequent. This occurs because the mechanism of action of chemotherapeutics does not act exclusively on the tumor cell. Normal cells renewing constantly as bone marrow are affected as well by their action, resulting in toxicity side effects.

Neutropenia-induced chemotherapy is the most serious hematologic toxicity and characterizes by the reduction of the white blood cell in the blood flow with a count below 1,5 $x10^9/L$[1]. This toxicity ranges from 16% to 81% among patients who receive some chemotherapeutic treatment. It is described as one of the main adverse events of antineoplastic chemotherapy and is the toxicity that interferes the most in the continuity of the treatment.

According to Pathak et al.[8], neutropenia, when associated to fever, is a potentially fatal complication, demanding more health care and expenses because of the extensive hospitalization of these patients[8]. The occurrence of neutropenia is associated to the increase of mortality, morbidity, treatment costs, reduction of doses or extension of dosage intervals, directly affecting the oncologic treatment and its efficacy[9].

The evidence of neutropenia is the reduction of white blood cells in the blood count and this test occurs routinely during the chemotherapy treatment. There are five grades that classify neutropenia: grade I - $3x10^9$ cells/L; grade II - 2 to $3x10^9$ cells/L; grade III - 1 to 2 $x10^9$ cells/L; grade IV - $<1x10^9$ cells/L; and grade V, which indicates death of the patient submitted to the treatment[5].

Because it is a frequent and important event for the treatment outcome, some strategies can be done to control neutropenia in clinical practice. They consist in the reduction of the dose of chemotherapeutics, postponement of new cycles and use of stimulating factors of colonies. However, these strategies can interfere in the final quality of the therapy, reducing its efficacy, mainly in the cases of reduction of the dose and deferment of new cycles[10].

Due to the high risk of severe infections, low count of neutrophils directly affects the quality of life of oncologic patients who are oriented to follow strict rules during the treatment as avoiding crowds and eating raw or ill-washed food[5].

The present study has the objective of discussing the occurrence of neutropenia in the principal chemotherapeutic treatments utilized in patients with breast cancer through bibliographic review of the literature.

METHOD

Integrative review. Data collected in databases PubMed, journals from Coordination for the Improvement of Higher Education Personnel (CAPES) and Health Information from Latin American and the Caribbean Countries (LILACS). The terms used in the search were *neutropenia, breast cancer, chemotherapy* and *toxicity hematological*. The articles selected were published between 2013 and 2018.

The articles that considered only genetic polymorphisms, as neutropenia can be influenced by this cause, and failed to address the keywords of the study in the title or abstract were excluded. The selection of the articles is shown in Plan 1.

The number of the patients included in the study, age, occurrence of neutropenia, total number and frequency were extracted from the articles to analyze the data.

RESULTS

Of the 101 articles read, 23 were selected to form the database of the study. All the articles selected described cases of breast cancer among which there were the characteristics HER-2 positive or negative and positive

Plan 1. Selection of articles

Period	Published from 2013		
Descriptors	Neutropenia, breast cancer, chemotherapy e toxicity hematological		
Database	PubMed	Periódicos CAPES	LILACS
Articles encountered	18	149	4
Articles evaluated	17	80	4
Articles selected	6	16	1
Total	23 articles		

Source: Adapted from Kalil Filho et al.[17].

or negative receptors of estrogen and progesterone, chemotherapeutic drugs utilized in the treatment and grades of neutropenia (Table 1).

Totally, 19,548 patients were included in the studies with ages between 18 and 92 years old who used chemotherapeutic medications for breast cancer treatment in neoadjuvant and adjuvant regimens. The 11 medications studied were nab-paclitaxel/paclitaxel, gemcitabine, eribulin, carboplatin, docetaxel, trastuzumab, doxorubicin, cyclophosphamide, epirubicin, fluorouracil and tipifarnib. The most described treatment regimen in the studies was epirubicin, fluorouracil, cyclophosphamide and docetaxel (FEC-D), with ten studies, followed by regimens docetaxel and cyclophosphamide (TC) and doxorubicin, cyclophosphamide and docetaxel (AC-T), described in five studies each. Of the participants, 17.6% had conditions of neutropenia grade 3 and 4 and occasionally this condition was associated to fever, escalating with hospitalization, dose reduction or delay of the chemotherapy cycle.

Table 1. Relation among the participants of each study, cases of neutropenia and chemotherapy utilized

Author/year	Participants (n)	Neutropenia (n)	Neutropenia (%)	Chemotherapeutics evaluated
Ghani et al., 2014	1	1	100	Carboplatin, docetaxel and trastuzumab
Tezuka et al., 2017	6	5	83	Nab-paclitaxel, carboplatin and trastuzumab
Yoshitomi et al., 2016	9	2	22	Nab-paclitaxel and gemcitabine
Yam et al., 2018	30	24	80	Gemcitabine
Takashima et al., 2016	35	22	63	Eribulin
Sugitani et al., 2017	50	18	36	Carboplatin, docetaxel and trastuzumab
Gozzo et al., 2011	72	43	60	Docetaxel, cyclophosphamide and epirubicin
Park et al., 2017	74	49	66	AC-T
Bajpai et al., 2017	133	53	40	AC-T
Chiarotto et al., 2013	154	51	33	AC-T, TC and FEC-D
Li et al., 2018	175	103	59	Carboplatin, doxorubicin, FEC-D
Chow et al., 2017	227	116	51	TC
Assi et al., 2014	251	55	22	FEC-D
Lote et al., 2016	325	62	19	Nab-paclitaxel, docetaxel and FEC-D
Redana et al., 2016	325	62	19	FEC-D
Mullard et al., 2014	342	102	30	FEC-D
Ma et al., 2016	410	330	80	AC-T, TC, FEC-D
Xie et al., 2018	569	284	50	Epirubicin, cyclophosphamide and docetaxel
Schraa et al., 2017	622	143	23	AC-T, TC, FEC-D and Trastuzumab
Faqeer et al., 2017	876	130	15	Docetaxel
Schröder et al., 2016	3.755	1.344	36	FEC-D and FEC-D
Goyal et al., 2018	11.107	450	4	Nab-paclitaxel, AC-T, TC and FEC-D

Captions: FEC-D: epirubicin, fluorouracil, cyclophosphamide and docetaxel; TC: docetaxel and cyclophosphamide; AC-T: doxorubicin, cyclophosphamide and docetaxel.

Currently, AC-T treatment regimen is the most utilized in breast cancer treatment. It was described in five articles, but in one of these articles, it was associated to other treatment and neutropenia listed was not separated by medication[11]. In one of the studies, 53 of the 133 patients evaluated had neutropenia during the treatment, reaching 39.8% while in other study, the frequency of neutropenia was higher, occurring in 66.2% of the patients[12,13].

Three studies evaluated the regimen of chemotherapy with epirubicin, cyclophosphamide and docetaxel; the first study evaluated 569 patients and 49.9% of neutropenia; the second, 72 patients and 43 cases (59.7%) of neutropenia and the third study included 410 patients and neutropenia as hematologic toxicity occurred in 330 patients, reaching the rate of neutropenia of 62.45%[1,5,14].

Three studies evaluated the regimen FEC-D and included 918 patients in total, of which only 157 had neutropenia as toxicity, covering 23.8% of the patients[10,15,16].

The treatment TC formed by the drugs docetaxel and cyclophosphamide was evaluated in five studies and in four of them, it was evaluated together with other regimens and only in the study of Chow et al.[17] was evaluated separately. In this study, 227 women with breast cancer received chemotherapy with regimen TC, of which 116 participants had neutropenia as hematologic toxicity during the treatment[17].

The chemotherapeutic regimen formed by carboplatin, docetaxel and trastuzumab was mentioned in four articles that included patients with positivity for HER-2. In the first study, 50 patients received chemotherapeutic treatment and 18 presented hematologic toxicity as neutropenia[18]. In another study, it was described a case report where a 45 years old woman with HER-2 positive breast cancer was treated with this regimen and had severe and recurrent neutropenia during her treatment[19].

Three articles reported the utilization of gemcitabine in combination with nab-paclitaxel, tipifarnib and to the FEC-D regimen and presented elevated neutropenia rates of until 80%[20]. The study that compared the treatment FEC-D with or without gemcitabine showed that the arm of gemcitabine, despite higher frequency of neutropenia, its incidence of febrile neutropenia was lower[21].

Nab-pacilitaxel/paclitaxel was described in five studies, always in association to other chemotherapeutics. In two of them was used together with the regimen FEC, presenting neutropenia in only 4.47% of the cases. However, when associated to carboplatin and trastuzumab, 83% of the patients had neutropenia[22-24].

Notwithstanding being included in several treatment regimens, normally associated to other medications, only one article evaluated the toxicity isolated after the administration of docetaxel. In this study, the use of docetaxel (taxotere®, sanofi) was compared to two generic formulas (docetaxel ebewe and docetaxel hospira). In total, 130 participants presented neutropenia as hematologic toxicity, of which, 30 received docetaxel ebewe, 47, docetaxel hospira and 53, docetaxel sanofi. Of the participants with neutropenia, 98 received doses of 100 mg/m^2 and 32 doses of 75 mg/m^2 of docetaxel. Eighty-seven (87) participants had episode of febrile neutropenia after the administration of chemotherapy and the occurrence was higher in patients who used docetaxel ebewe (73%, 22 participants of total 30 of this group). The participants who received the generic formulas had higher rates of neutropenia[25]. Only one study evaluated the chemotherapeutic eribulin and presented myelotoxicity with neutropenia grade 3 or 4 over 50%[26]. Some studies evaluated other different combinations of chemotherapeutic medications, but neutropenia was not evaluated as an isolated factor for each medication. The study of Li et al.[27] provided the first epidemiologic evidence that the increased risks of neutropenia grade 4 and febrile are associated to change of the circadian rhythm of patients with breast cancer in adjuvant treatment[27].

DISCUSSION

Neutropenia was a very frequent toxic event regardless of the medication used or tumor characteristics ranging from 15% to 100% and, of the 23 articles evaluated, in nine of them, neutropenia reached more than 50% of the study population. This is because all chemotherapeutic medications act in cytotoxic manner on the cells in rapid multiplication and this is a characteristic of neutrophils.

Myelosuppression, mostly neutropenia, is described as the most feared adverse event during treatment, because it increases the probability of morbidity and mortality of users of chemotherapeutic regimens. When associated to fever, it is denominated chemotherapy-induced febrile neutropenia, a condition that aggravates severely the patient status, because significantly increases the risk of death, needing hospitalization and additional use of antibiotics and can compromise the treatment since in these cases there are dose reductions of chemotherapeutic utilized and delays in administering new cycles[15]. Consequently, in addition to increasing costs, the hematologic toxicity affects directly the efficacy of the treatment and the quality of life of the patient. Goyal et al.[23] describe that febrile neutropenia occurs in 3% to 24% of the breast cancer patients in initial stage who receive chemotherapy[23].

All the treatments used in the studies generated some degree of neutropenia, varying the frequency of the affection. The chemotherapeutic regimens most frequently associated to neutropenia were combinations of platinum and taxane (carboplatin and docetaxel; carboplatin, docetaxel and trastuzumab; carboplatin and nab-paclitaxel), followed by the protocol with cyclophosphamide, anthracycline and taxanes (AC-T; epirubicin, cyclophosphamide and docetaxel). The chemotherapeutic regimen with cyclophosphamide, anthracycline and taxanes has been the most effective treatment[13], as well as with the administration of the regimen AC-T has the advantage of overcoming the resistance to the medications, an ability acquired by some tumor types, reducing the levels of recurrence and improving survival[28].

The regimen AC-T is associated to the reduction of the risk of recurrence and mortality better than other chemotherapy regimens. However, this treatment has a significant rate of hematologic toxicity, which limits its utilization[13].

Faqeer et al.[25] conducted a retrospective study about the utilization of generic formulas of docetaxel and demonstrated an incidence of neutropenia significantly higher in patients who received generic formulas[25].

This study reflects the discussion about the generic formula used to reduce health costs that must demonstrate equivalence and bioequivalence for the licensed product on mandatory bases, but allows differences in the characteristics of the product and inactive ingredients. Vial et al.[29] evaluated 31 generic formulas of docetaxel available at the market compared to docetaxel sanofi and showed that 90% of the generic formulas of docetaxel contained insufficient active ingredients and high level of impurities that could affect the efficacy and the safety of the patient[29].

The studies that evaluated gemcitabine in the chemotherapy treatment of breast cancer showed elevated rates of myelosuppression without additional benefit of efficacy and, because of this, this chemotherapeutic is not a favorable therapeutic option in this context[20,21,30].

Chiarotto et al.[31] evaluated the neutrophils count in the day before the beginning of the chemotherapy and demonstrated there were no significant difference in the frequency of chemotherapy-induced febrile neutropenia when the cycle of chemotherapy was applied with neutrophils count <1,5x10^9/L (interval of 0.1 to 1.4x10^9/L) and that this risk remained present even when chemotherapy was applied with neutrophils count over 1.5x10^9/L. Despite the study limitations, the suggestion is that the day before the application of chemotherapy alone is not used to trigger the decision taking about dosages and other factors that could influence the risk of the patient to have an infection should be evaluated[31].

In addition, the strategy of management and prevention of neutropenia is the use of granulocyte colony-stimulating factor – G-CSF that has the function of stimulating the production of neutrophils and reduce effectively the febrile neutropenia. However, this strategy is recommended by the *American Society of Clinical Oncology (*Asco) only in patients with high risk of developing febrile neutropenia. The objective of its use is to diminish the incidence of myelosuppression and duration of neutropenia, being effective in reducing the days of hospitalization and the number of infections confirmed by culture.

CONCLUSION

The studies showed that neutropenia has a high rate of occurrence in patients under chemotherapy treatment for breast cancer, regardless of the drug used. The most associated regimens with neutropenia were the combinations of platinum/taxane and cyclophosphamide/anthracycline/taxanes, that are the most frequent utilized due to its high efficacy.

Chemotherapy-induced neutropenia represents a complication of great relevance because it affects the quality of life of the patient and may lead to dose reductions, delays of the cycles of chemotherapy, and eventually reducing the efficacy of the treatment. The efforts of the healthcare professionals, therefore, should be focused to develop strategies to reduce its occurrence and complications.

CONTRIBUTIONS

Fernanda Mocellin Conte participated of the conception, design, gathering, analysis and interpretation of study data, wording and final approval of the version for publication. Valéria Sgnaolin participated of the design, interpretation of the study data, wording, critical review and final approval of the version for publication. Vanessa Sgnaolin participated of the conception and design of the study, analysis and interpretation of study data, wording, critical review and final approval for publication.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflicts of interest to declare.

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