Narrative review

Effect of chemotherapy on sexual function in patients with non-metastatic cancer

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Abstract
Non-metastatic breast cancer is defined as breast cancer that has not spread from the primary site. More than 90 % of people that received a breast cancer diagnosis is non-metastasic. Chemotherapy reduces the mortality rate by up to 40 %, but it also causes physical, psychological, sexual and social effects. Therefore, we aimed to identify changes in sexual function caused by chemotherapy in patients with non-metastatic breast cancer. Chemotherapy includes four groups of drugs: anthracyclines, alkylating agents, antimetabolites, and taxanes. These cause local ischemia and depletion of primordial follicles, resulting in early menopause and physiological changes that affect physical, sexual and psychological function. A review of the literature was carried out using indexes or databases such as PubMed, SciELO, Elsevier, as well as the journals The Lancet and Nature. Original and peer-reviewed articles in English and Spanish that were published between 2019 and 2023 were included. One of the best treatment options for non-metastatic breast cancer currently is chemotherapy, but it has been shown to cause early menopause, alterations in sex hormones and alterations in sexual function.

Keywords
Breast Cancer, Chemotherapy, Sexuality, Physiological Sexual Dysfunction.

Resumen
El cáncer de mama no metastásico es aquel que no se ha diseminado desde el sitio primario. Más del 90 % de las personas que reciben un diagnóstico de cáncer de mama son no metastásicos. La quimioterapia reduce la tasa de mortalidad hasta un 40 %, pero también causa efectos físicos, psicológicos, sexuales y sociales. Por lo tanto, el objetivo fue identificar los cambios en la función sexual causados por la quimioterapia en pacientes con cáncer de mama no metastásico. La quimioterapia incluye cuatro grupos de fármacos: antraciclinas, alquilantes, antimetabolitos y taxanos. Estos provocan la isquemia local y el agotamiento de los folículos primordiales, lo que resulta en una menopausia temprana y cambios fisiológicos que afectan la función física, sexual y psicológica. Se llevó a cabo una revisión de la bibliografía utilizando índices o bases de datos como PubMed, SciELO, Elsevier, así como las revistas The Lancet y Nature. Se incluyeron artículos originales y revisados en inglés y español que se publicaron entre 2019 y 2023. Una de las mejores opciones de tratamiento para el cáncer de mama no metastásico actualmente es la quimioterapia, pero se ha demostrado que provoca una menopausia temprana, alteraciones en las hormonas sexuales y alteraciones en la función sexual.

Palabras clave
Cáncer de Mama, Quimioterapia, Sexualidad, Disfunciones Sexuales Fisiológicas.

Introduction

Breast cancer is the most common type of cancer in women worldwide and at present one of the most frequent causes of death.[i] The World Health Organization (WHO) reports that one in 12 women will develop breast cancer at any stage of life. Although chemotherapy treatment can reduce the mortality rate by up to 40 %, the prevalence of physical, psychological, sexual, and social consequences is increased.[ii]

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Efecto de quimioterapia en la función sexual de pacientes con cáncer de mama no metastásico

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More than 90 % of women who are diagnosed with breast cancer for the first time have non-metastatic breast cancer,[iii] which does not spread beyond the milk ducts or lobules of the breast and does not invade normal tissues inside or outside the breast.[iv] The most common noninvasive tumor is ductal carcinoma *in situ*, which is typified by the presence of malignant cells within the breast ducts without rupturing them.[v]

In the early stages, a breast cancer diagnosis is based on breast self-examination, a complete physical examination, and a combination of imaging, including mammography, ultrasound, and MRI, as the gold standard. The mammography and data retrieval system (BI-RADS), which is standardized, establishes categories for guidelines for action and is one of the main benefits of mammography.[vi]

The side effects of treatment in women receiving chemotherapy for this cancer primarily affected sexual function. These effects increase the cognitive, emotional, and behavioral burnout of patients.[vii] In a study of 201 breast cancer patients, Aiying Qi *et al.* found that 83.08 % of patients experienced sexual dysfunction after starting chemotherapy.[viii]

Early and periodic detection can facilitate the development of an optimal and timely treatment plan, avoiding the progression of problems in women under treatment for breast cancer, since sexual function in cancer patients treated with chemotherapy is a topic that health personnel are unaware of for various reasons, such as lack of time, knowledge or experience to address it.[ix]

Currently, as the survival rate from chemotherapy increases in women with breast cancer, the physical, psychological, sexual, and social effects are increased.[x] In a stud of 174 breast cancer patients with chemotherapy, Ospino *et al.* found a five-year relapse-free- survival of 88.8 %, disease-free survival of 63.3 %, and an overall survival of 84.4 %.[xi]

It is important to ensure that women who receive a breast cancer diagnosis are informed about the potential effects of chemotherapy treatment on their mental and sexual health. To ascertain this, a review of the literature, as well as indexes or databases such as PubMed, SciELO, Elsevier, and journals such as The Lancet and Nature, was conducted. Additionally, the official websites of the World Health Organization/Pan American Health Organization (WHO/PAHO) and the Ministry of Health (MINSAL) of El Salvador were consulted. Original and peer-reviewed articles in English and Spanish published between 2019 and 2023 were included. The MeSH descriptors: "breast cancer," "Chemotherapy," "Sexuality," and "Physiological, Sexual Dysfunctions" were used employing the Boolean operator "AND".

This research aims to identify the alterations caused by chemotherapy in the sexuality of patients with non-metastatic breast cancer and to promote early detection and a multidisciplinary approach.

Discussion

Overview and Chemotherapy schemes in non-metastatic breast cancer

Breast cancer is the most common type of cancer in women worldwide and is considered a heterogeneous disease with multiple causes. The Pan American Health Organization (PAHO) indicates it represents 22.7 % of female cancers worldwide. In the Americas, more than 462 000 women are diagnosed with breast cancer each year, and almost 100 000 died as result of this disease.[xii] By 2021, a total of 3509 new cases of breast cancer were registered in El Salvador.[xiii]

Breast cancer is a condition characterized by the rapid multiplication of cells due to changes in the mechanisms of cell division and cell death, leading to the development of tumors or abnormal masses.[xiv] The presence of highly penetrant dominant hereditary genes such as BRCA1 and BRCA2 is present in this disease, and one-third of patients have mutations of these tumor suppressor genes, which are related to alterations in DNA repair.[xv] Although more common in women, this condition can also manifest in less than 1 % of men, making diagnosis difficult due to lack of awareness.[xvi]

Breast cancer is divided into three main subtypes according to the presence or absence of molecular markers for human epidermal growth factor receptor 2 (ERBB2/HER2 neu), estrogen, or progesterone. [xvii] They are classified as follows: hormone receptor-positive/HER2 negative (70 % of patients), HER2 positive (15 %-20 %), and triple-negative (tumors lacking all three molecular markers) 15 %.[xviii]

Eighty percent of non-metastatic breast tumors are ductal carcinoma *in situ*.[xix] There has been an increase in diagnosis by annual mammography screening in recent years,[xx] which results in early detection of 20 % of ductal carcinoma *in situ*[xxi]; leading to an overall survival of 95.1 % at five years and a disease-free survival of 97.6 % at five years due to timely diagnosis and treatment.[xxii]

The mammography report is standardized by the use of the BI-RADS system and mammograms. Seven categories are estab-

lished that determine guidelines for action. BI-RADS 0 suggests a complementary study, BI-RADS 1 suggests a normal study; BI-RADS 2 suggests a benign finding, and category 3, probably benign findings; BI-RADS 5 suggests findings highly suggestive of malignancy, and BI-RADS 6 suggests a malignant finding already proven by histological study.[xxiii]

After mastectomy, adjuvant chemotherapy is often used in non-metastatic breast cancer to eliminate any remaining cancer cells, reducing the likelihood of recurrence.[xxiv] Adjuvant chemotherapy is a set of drugs taken in regular doses that may last from three to six months or longer than six months.[xxv]

Anthracyclines (doxorubicin and epirubicin), alkylating agents (cyclophosphamide), antimetabolites (methotrexate and 5-fluorouracil), and taxanes are the first-line drug groups used in chemotherapy for non-metastatic breast cancer. The most popular drug combinations include AC (doxorubicin and cyclophosphamide) with or without docetaxel, TC (docetaxel and cyclophosphamide), and CMF (cyclophosphamide, methotrexate and 5-fluorouracil).[xxvi]

Low specificity is a characteristic of the mechanisms of action of the drugs used in chemotherapy for breast cancer, which means that they affect both tumor cells and healthy cells with a high turnover rate.[xxvii] The most studied pharmacological group of anthracyclines has a mechanism of action that inhibits DNA synthesis and transcription by intercalating between molecules. This inhibits topoisomerase II, which produces a DNA cleavage complex that increases double-strand breaks and causes cardiomyocyte deaths.[xxviii]

Alkylating agents are one of the antineoplastic pharmacological groups that inhibit cell replication by preventing DNA transcription.[xxix] Antimetabolites stop DNA synthesis by inhibiting the enzyme thymidylate synthase, which is responsible for converting uracil to thymine in the S phase.[xxx] Taxanes act by assembling microtubules, which prevent their depolymerization and disrupt cell mitosis.[xxxi]

Physiological changes caused by chemotherapy

Women with breast cancer frequently describe problems with sexual dysfunction, especially during the first year after diagnosis.[xxxii] Up to 60 % of the population suffers from sexual dysfunction as a result of chemotherapy. Chemotherapy has been described to cause early menopause and painful dermatitis in the genital region, which decreases sexual desire. Symptoms of early menopause include dyspareunia, decreased libido, and vaginal dryness, among others.[xxxiii]

Chemotherapy causes lesions due to vascular damage and cortical fibrosis of the ovaries, resulting in local ischemia and depletion of primordial follicles,[xxxiv] affecting sex hormones, which reduces estrogen levels. It has been shown that anatomical areas such as the vulva, vestibule, labia majora and labia minora, and vagina have a high concentration of estrogen receptors that diminished levels of this hormone may cause a decrease in vaginal lubrication and dyspareunia.[xxxv]

Cobo Cuenca A *et al.* found significant differences with a p value < 0.001 in the presence of sexual dysfunction both before (32.1 %) and after (91.2 %) the initiation of chemotherapy as a treatment for breast cancer. Penetration pain (50.6 %), lubrication (50.6 %), sexual desire (44.6 %), and dysfunctional arousal (44.6 %) were the main causes of sexual dysfunction.[xxxvi] Treatment has worsened sexual relations among 61.1 % of women with breast cancer.[xxxvii]

Decreased testosterone is one of the main regulators of central arousal, leading to a directly proportional relationship between the concentration of this hormone and sexual desire.[xxxviii] In addition, sex hormones contribute to neurological functions therefore, a low level of these hormones increases the risk of anxiety, depression, and neurocognitive dysfunctions, which are common in patients with non-metastatic breast cancer treated with chemotherapy.[xxxix]

In a study of 110 patients, Widiani MO *et al.* found a significant positive correlation between chemotherapy side effect variants and sexual desire, with a p value = 0.003 and R = 0.518[xl]. It demonstrated that chemotherapy has an impact on skeletal muscle, one of the symptoms is cachexia, which exerts negative impact on their body image and is one of the most influential factors for sexual desire.[xli]

Chemotherapy and psychological aspects associated with sexual function

Women's sexual function is affected by the decrease in estrogen and progesterone levels caused by chemotherapy. The change in physical appearance, post-treatment infertility, communication problems between partners, and physical changes such as fatigue, which predisposes to episodes of anxiety and depression, are some of the main concerns or affectations of these patients.[xlii]

Breast cancer patients experience depression and anxiety after diagnosis as they come to understand the significance of the disease. Perez M. *et al.* found 97 % depression and 85 % anxiety.[xliii] Before the first cycle of chemotherapy anxiety increases and leads to a decrease in the ability to tolerate side effects, which increases symptoms such as nausea, vomiting, fatigue, and general physical deterioration, reducing the quality of life.[xliv]

Amado E. *et al.* found a significant relationship between sexual dysfunction and depressive disorders in women with breast cancer after chemotherapy treatment. Sexual dysfunction was found to be common in 61 % of the women, depression in 33 %, and anxiety in 69 %.[xlv] After chemotherapy treatment,[xlvi] an increase in physical affectations such as anxiety symptoms has been associated with varying prevalence from 12 % to 60 % and depression between 8 % to 66 %.

According to Hernández-Blanquisett *et al.*, both the diagnosis and chemotherapy cause changes in physical, mental, and sexual health with hypoactive sexual desire in 83 % of patients.[xlvii] In a study that included 154 patients with breast cancer who received chemotherapy, the degree of emotional distress was found to be severe in 9.1 %, moderate in 29.9, and mild in 61 %.[xlviii]

Chemotherapy treatment reduces physical activity, and increases fatigue, need for more sleep, sexual dysfunction, persistent pain, and quality of life.[xlix] As emotional distress increases, physical and social functioning and quality of life decrease. In a study involving 41 women with non-metastatic breast cancer receiving chemotherapy and administered the EORTC QLQ C-30 and QLQ-BR23 scales, sexual functioning, sexual pleasure, concern for the future, and body image were shown to be the most affected areas.[l]

Conclusion

Chemotherapy causes multiple physiological, physical, psychological, sexual, and social alterations as it affects both cancerous and non-cancerous cells. The scientific community is in constant study to evaluate the onset and severity of these complications suffered by patients after chemotherapy and to identify the symptomatology associated with the treatments to address them early and prevent complications.

Due to its various causes, including the cancer itself, different treatments, and patient idiosyncrasies, sexual dysfunction is a frequent problem. Chemotherapy has demonstrated local ovarian ischemia, leading to early menopause, and altered sex hormone concentrations, resulting in dyspareunia, decreased libido, and vaginal dryness. Breast cancer diagnoses and the reduction of sex hormones caused by chemotherapy increase the risk of psychological disturbances, such as depression and anxiety, which reduce quality of life and sexual function during treatment. The diagnosis and treatment of breast cancer have a psychological effect on patients' lives, affecting their sexual and physical activity. Therefore, it is crucial to use a multifactorial approach from the time of diagnosis to prevent the onset of physical, mental, and sexual disorders.

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