Hormone therapy/adjuvant chemotherapy induced deleterious effects on the bone mass of breast cancer patients and the intervention of physiotherapy: a literature review

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Summary

In recent years, breast cancer has witnessed some notable improvements regarding early diagnosis and new therapeutical strategies, mainly because of the utilization of new drugs and systemic treatment protocols, which have had a direct impact in the increase of these patients' global survival rate. At the same time, it is an ever-growing concern among oncology professionals to identify and minimize as much as possible the effects of long-term toxicity resulting from cancer therapies. Within this context, physiotherapy fits as a preventive and rehabilitating factor regarding functional and skeletal alterations, deriving not only from the direct action of breast cancer, but also from the treatment to which these patients are submitted. *Objectives:* The aim of this study was to revise the scientific literature on possible adjuvant chemotherapy-induced secondary deleterious effects on the bone mass of patients diagnosed with breast cancer, and also to revise the literature on the intervention of physiotherapy in cases of secondary bone mass loss caused by adjuvant chemotherapy in patients suffering from breast cancer. *Methodology:* The research was carried out by consulting the following medical websites: Medicus Medline Index, Lilacs, Sciello, PubMed (National Library of Medicine), Google Academic and Capes (a Brazilian website for scientific information). The selection gathers articles written in different languages, English in special, published from January 1998 to October 2008. *Results*: 24 studies explicitly mention chemotherapy-induced direct and/or indirect effects upon bone mass. Different authors refer to bone mass loss as one possible secondary deleterious effect resulting from adjuvant chemotherapy applied in breast cancer treatment. Nonetheless, no scientific articles were found on the subject of physiotherapy intervention aimed at patients in this specific condition. *Conclusion:* the results achieved in this revision study point out the possible chemotherapy-induced late deleterious effects on patients diagnosed with breast cancer, as well as the additional risks for the development of further osteoporotic conditions. Hormone therapy and adjuvant chemotherapy treatments may in fact augment and accelerate the loss of bone mass, be it directly, through the action of chemotherapeutical drugs, or indirectly, through the reduction of estrogenic levels and precocious menopause. The scarce material on the rehabilitation of bone mass loss deriving from adjuvant treatments reveals, as it seems, a strong need for new studies on the subject.

Key words: Breast cancer; Physiotherapy; Hormone therapy; Adjuvant chemotherapy; Osteoporosis; Bone mass.

Introduction

Occurrences of malignant neoplasias are a Brazilian and a worldwide spreading phenomenon. At the same time, the treatment of oncological patients itself has witnessed some notable improvements, originating from new approaches and from more accurate cancer prognoses. Among all malignant tumors, breast disease is the second most frequent type of neoplasia all over the world, totaling 22% of new occurrences of women's cancer [1]. Recent reports from the INCA (Instituto Nacional do Câncer) regarding new cases of breast cancer in Brazil, show that occurrences amounted to 49,000 cases in 2008, with an expected risk of 51 cases for every 100,000 women [1]. The global survival rate of women diagnosed with breast cancer has been augmenting considerably in recent years, mainly due to early diagnosis and more efficient therapies aimed at cancer treatment [2]. Nevertheless, patients who have survived breast cancer manifest greater risks of developing chronic-degenerative diseases, such as osteopenia and osteoporosis, induced by the secondary action of antineoplastic drugs (combined in the chemotherapy process) on the bone mass, and by the absence of hormonal reposition schemes during menopause [3]. Osteoporosis is today considered, especially in developed countries, one of the most serious problems to affect the elderly population, chiefly women in the postmenopause period. It is characterized by low bone density and the subsequent degeneration of the microstructure, responsible as it is for increased bone fragility, which may result in the occurrence of fractures. Estimations show that one in every two women may suffer at least one osteoporotic fracture during their lifetime, which makes us more concerned about public health [4]. Moreover, the occurrences of osteoporosis are rising not only among the elderly population, as a result of the natural aging process, but also among those who have overcome cancer in their lives, chiefly breast cancer, as a result of their crescent survival rate, and also the chemotherapy-induced secondary effects which many of them are subjected to [5].

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The female population is exposed to a greater risk of developing long-term osteoporosis, especially in the post-menopause stage of life, due to the systemic reduction of estrogen levels. Notwithstanding, if subjected to adjuvant chemotherapeutic treatment, patients who have overcome breast aplasia develop an additional factor which favors the pathological evolution, even before menopause. Some of the substances employed in the adjuvant chemotherapeutical schemes induce ovarian failure and the anticipation of menopause [3]. This paper aims at revising the medical literature produced throughout the last decade, in order to identify the possible secondary effects deriving from adjuvant antineoplastic chemotherapy on the bone mass of patients diagnosed with breast cancer. The goal is to discuss the potential risks, regarding this specific population, of future osteoporotic developments, and the consequences implied in this morbidity: the increase of bone fragility and fracture risks. Most of these fractures will result in several skeletal alterations, such as deformities and stature reduction, accompanied by serious – at times chronic – algetic processes, disability, hospital commitments and even death [6].

Method

This study was based on revision of the recent literature concerning chemotherapy-induced deleterious effects on the bone mass of patients with breast cancer. The primary criterion observed was to select the sources of information: Medicus Medline Index, Lilacs, Sciello, PubMed (National Library of Medicine), Google Academic and Capes (a Brazilian website for scientific information). In their respective search-engines, the following keywords were used: physiotherapy, cancer, breast cancer, adjuvant chemotherapy, bone loss, secondary effects, osteopenia, hormone therapy, fatigue, and bone densitometry. The selection encompasses articles written in different languages published from January 1998 to October 2008.

The criteria of inclusion were: female patients diagnosed with breast cancer; patients with breast cancer subjected to adjuvant chemotherapy; women in the pre-, peri-, and postmenopause periods, regardless of their age; physiotherapy and physical activity prescribed to patients with breast cancer who suffered from bone mass diminution; physiotherapy and physical exercise programs for osteoporosis; physiotherapy and/or physical activity for patients suffering from breast cancer and subjected to adjuvant chemotherapy treatments. Patients diagnosed with breast cancer but not subjected to adjuvant chemotherapy treatments were not considered. Thirty articles, all of which follow these criteria, were gathered.

Results

In this literature review we selected 24 studies approaching the proposed subject, with explicit references to direct or indirect chemotherapy-induced effects on the bone mass of patients. Different authors point out, among the possible deleterious effects induced by adjuvant chemotherapy, the diminution of bone mass in patients with breast cancer. Twenty-four of these studies made explicit reference to direct and indirect effects induced by chemotherapy on the bone mass of patients [5, 6, 14-32, 34, 43, 44]. No specific references were identified, however, on the physiotherapeutic rehabilitation of breast cancer patients who experience bone mass diminution. Furthermore, no scientific studies were found that mention physiotherapeutic intervention in patients going through adjuvant chemotherapy and who manifest bone mass diminution.

Discussion

Intending not only to improve the local control of the disease, but also to augment the survival rate of patients with breast cancer, several clinical tests based on neoadjuvant chemotherapy took place as a means of treatment, at times followed by radiotherapy [7].

The main goal of adjuvant chemotherapy is to diminish the chances of local and systemic relapse of the cancer, through the long-range elimination of micrometastasis, since it is a matter of clinically occult microscopic focus of the disease [7, 8].

The understanding of molecular and biological processes concerning breast cancer has produced some major improvements regarding therapeutical intervention strategies, such as the introduction of novel antineoplastic agents and the reformulation of breast cancer-aimed systemic treatment protocols. Such strategies have optimized the interaction among systemic, radiotherapeutic and surgical treatments, increasing the disease-free period as well as the global survival rate [9, 10].

Today, it can be assumed that adjuvant systemic treatment is indicated for each and every patient who conforms to "average and high risks" [9-11]. Table 1 below features the most commonly employed chemotherapy schemes aimed at breast cancer.

Table 1. — *Chemotherapy schemes applicable in breast cancer.*

CMF - cyclophosphamide, methotrexate, 5-fluorouracil (5FU)
FAC/CAF-5FU, doxorubicin (adriamycin), cyclophosphamide
CMF±VP - cyclophosphamide, methotrexate, 5FU, vincristine, prednisone
AC - doxorubicin, cyclophosphamide with or without sequential paclitaxel
AC-CMF - doxorubicin, cyclophosphamide/cyclophosphamide, methotrexate 5FM
AC-T - doxorubicin, cyclophosphamide, paclitaxel (Taxol) or docetaxel

More recently, in the sphere of clinical oncology, hormone therapy came to aid the adjuvant treatment of women suffering from invasive breast cancer, being prescribed exclusively or sequentially in the chemotherapeutic treatment of women (either pre or postmenopausal), "whose tumors manifest the presence of hormonal receptors for estrogen and/or progesterone" [9].

The goal of this kind of therapy is to saturate the estrogen receptors located in the cancerous cell, preventing – through multiple events – cell duplication induced by the action of estradiol. Such pharmacons are called *selective estrogen receptor modulators* (SERMs). SERMs induce

estrogenic agonism on specific tissues (such as the bone and liver) while acting antagonistically on breast and uterine tissues.

Among the most commonly adopted pharmacons are tamoxifen, raloxifene and aromatase inhibitors [12]. Tamoxifen's performance is equivalent to 70% of estrogen's action in terms of bone mass increase. According to Murrad [10], "tamoxifen is a non-steroid antiestrogenic featuring agonistic and antagonistic properties that prevent the linkage between estradiol and estrogen receptors, being considered the standard pharmacon in hormone therapy". Furthermore, it can be prescribed to women either in the pre- or postmenopause period for a 5-year term.

Ovarian ablation (surgical, radiotherapeutical, or chemical oophorectomy accompanied by LH-Rh antagonistic substances, such as gosereline or leuprolide) has also been prescribed, isolatedly or associated to tamoxifen, to women in the premenopause period, having achieved some notable improvements on their survival rate [10].

As for women in the post-menopause phase, it has been used for endocrinal therapy purposes, either tamoxifen or aromatase inhibitors, such as letrozole (Femara), anastrosol (Arimidex) and exemestane. Aromatase inhibitors prevent the conversion of testosterone and androstenedione (adrenal androgens) into estradiol and estrone on these patients' tissue level. However, they should not be utilized in women who manifest ongoing ovarian function, since they do not block the estrogen and the progesterone produced by the ovaries [7, 13].

Recently achieved improvements concerning early diagnosis and new possibilities on cancer treatment have had a direct impact on the patient survival rate. Consequentially, it has become an ever-growing concern among oncology professionals to identify and minimize long-term toxicity effects induced by antineoplastic therapies. Cancer-treatment-induced bone loss (CTIBL) is a well-known late effect that manifests itself in a large number of breast cancer patients. Antineoplastic therapies, such as chemotherapy, radiotherapy, hormone therapy and surgical castration, may cause direct or indirect bone damage, inducing additional bone mass loss and, at times, anticipating and intensifying osteopenia and osteoporosis conditions. The primary causes of CTIBL are chemotherapy-induced, radiotherapy-induced, hormone-therapy-induced (SERMs and aromatase inhibitors) and surgical-castration-induced (oophorectomy) hypogonadism. Other factors directly or indirectly linked to decreased bone mass are physical inactivity and inadequate ingestion of calcium and vitamin D5 [14-21]. Thus, one can assume that bone loss occurs more rapidly and more acutely in women going through chemotherapy than healthy women of the same age. That is to say, adjuvant chemotherapeutic treatment is an additional risk factor for osteoporosis that should not be underestimated, considering that it adds to the genetic and constitutional ones, such as race and low body mass rate, estrogenic deficit and lifestyle, to name a few. Different studies assert that chemotherapy-induced effects on the gonadal hormones are the most common causes of bone mass loss in women suffering from breast cancer in the premenopause period, since the treatment schemes that include cyclophosphamide (FAC, CMF, AC) and/or taxanes damage the ovaries, drastically diminishing estrogen levels and thus inducing precocious menopause [19, 22-24].

Ramaswamy and Shapiro [23] confirm that various antineoplastic drugs applied to breast cancer treatment have a straight impact on bone loss, independent of their effects on gonadal hormones. Among those are methotrexate, cyclophosphamide, ifosfamide and doxorubicin. From the tests conducted on animals, it has been ascertained that methotrexate increases bone resorption and decreases its formation, leading to intense bone loss. This particular drug reduces the production of osteoblasts through the inhibiting mechanism of DNA synthesis, just as it seems to debilitate the bone's mineralizing matrix. Cyclosphosphamide and its metabolites prevent both bone formation and resorption, while keeping osteoblast and osteoclast cells from dividing, thus leading to their shortening on the bone's surface. According to these authors and others, *in vitro* studies have verified that doxorubicin inhibits both the proliferation and the differentiation of osteoblasts, selectively reducing bone formation rates while interfering in the action mechanisms between PTH and the osteoblastic receptors [19, 23, 25].

The frequency of CTIBL on patients with breast cancer is yet to be understood, since the extension in which the bone loss occurs depends directly on the type and on the combination of the antineoplastic drugs employed, as well as on the ovarian function rate. According to many authors, women who prematurely experience chemotherapy-induced menopause display, in the following 12 months after treatment, considerable bone loss in the vertebral column (4% to 6%), the femur head and the hip (2%). Furthermore, these women keep on losing bone mass up to four or five years after the treatment has terminated. If the ovarian function is not reactivated, this may certainly be extended to over five years [17, 26, 43, 44].

Exposing similar ideas, Adler [27] and Greenspan *et al*. [28] attest that osteoporotic fractures are indeed the potential late effect induced by adjuvant chemotherapy on bone tissue. According to recent studies, breast cancer survivors who have undergone chemotherapy would be more exposed to future osteoporosis developments and even fracture risks, especially the vertebral column and the hip [27, 28]. Other works report that the employment of tamoxifen could increase bone loss in women with breast cancer during their *premenopause* period. The very treatment that frequently precedes chemotherapy may have both an intensifying effect on bone mass loss and an opposite action, reducing the loss and increasing bone density over approximately 2.4% in one year (for women in the *postmenopause* period), thus depending on the menopausal status of the patient [27, 29-31].

Hirbe [32] and others [26, 33] suggest that tamoxifen can reduce bone loss up to 50% in patients precociously in menopause as a result of chemotherapy treatment.

The studies of Maxwell and Vialle [17] and Gralow and Bone [34] suggest that patients undergoing hormone therapy with tamoxifen display additional risks of CTIBL. The reason is that the effects induced by this particular drug, during both the pre and postmenopausal periods, are opposite: in postmenopause it preserves the bone mineral density, increasing it between 0.6 and 1.2% approximately in one year. As for women in premenopause, the bone mineral density decreases approximately 1.4% [17, 34].

According to Ramaswamy and Shapiro [23] (an important reference in most articles selected on the theme), aromatase inhibitor-based therapies, such as anastrosol and letrozol, may also induce intense bone mass loss. Therefore, the caretaking of these patients should include early preventive action chiefly regarding everyday life style, physical exercise, calcium consumption and specific medications (biphosphonate, raloxifene, calcitonin), among others [23].

Different authors refer to the various benefits derived from the intervention of physiotherapy for treating osteoporosis in menopaused women. According to Nogueira *et al*. [35], physical exercise can help women with osteoporosis during menopause to relieve pain, increase bone mass and muscular resistance, improve their articulation mobility as well as their posture. Furthermore, physiotherapy is designed to orient and educate these women, and also to prevent immobility. However, it should not be neglected that, in the case of women subjected to cancer treatment, chemotherapy in particular, states of inactivity, fatigue and pain are frequently increased, which makes both the evaluation and safety margins of these patients' rehabilitation very important. After all, more accurate parameters applicable in the physical exercise of oncological patients, regarding intensity, frequency, strength and resistance-training, are yet to be established.

The possibilities of caretaking and preventing osteoporosis within specific populations, such as the cancer-diagnosed, should include the adaptation of protocols, parameters and safety margins aimed at improving the rehabilitation of elderly people and the treatment of chronic diseases, for example. In these cases, high intensity and impact exercises should be avoided after cancer treatments, since they could eventually induce stress augmentation and imunosuppresant effects. Low and moderate intensity exercises should be chosen instead. The goals and modalities of physiotherapeutic procedures should be based on a detailed evaluation of these patients, including: the kind and the condition of the tumor, the treatment protocol (surgical approach, chemotherapy, number of cycles and kinds of chemotherapeutic drugs, and radiotherapy), a report on physical activity or inactivity, favorite physical activities, basal aptitude, co-morbidities, and also the personal answers given during treatment (nausea, extreme fatigue, cardiotoxicity, neuropenia, peripheral sensorial neuropathy, among others).

LeMura and Duvullard [36], and Spínola *et al*. [37], have revised the specialized literature searching for the influences of physical exercise and/or activity on cancer. They compiled the main recommendations made by Courneya *et al*. [38], and by the *American College of Sports Medicine* concerning the prescription of aerobic exercises for cancer survivors. They also gathered some suggestive data, taken from Schwartz and cohorts [39], attesting that the practice of physical exercises may significantly reduce fatigue levels as well as maintain functional ability of women with breast cancer who have undergone chemotherapy treatment.

Spínola *et al*. [37] have revised the recent literature for the influences of physical exercise and/or activity on cancer, and they have gathered some meaningful data from different authors, confirming that the practice of physical exercises may significantly reduce fatigue levels and maintain the functional ability of women with breast cancer.

This literature review has not found any specific reference about physiotherapeutical intervention on patients with breast cancer suffering from bone mass loss. Neither were there any scientific articles with specific references to physiotherapeutical rehabilitation applying to breast cancer patients who present adjuvant chemotherapy-induced bone mass loss.

Even though there are several articles referring to the role of physiotherapy regarding osteoporosis treatment for women going through their pre or postmenopause period, and regardless of the vast literature concerning breast cancer-oriented physiotherapy, no studies were found that correlate the intervention of physiotherapy aiming at decreaed bone mass loss in patients with breast cancer subjected to adjuvant chemotherapy.

Albeit many studies, such as Navega's and cohorts, [40] point out the benefits implied in physiotherapy as a means to prevent and to minimize osteoporosis-induced deleterious effects, none of these authors have specifically correlated them to adjuvant chemotherapy-induced late effects on breast cancer patients. This attests to the need for new researches that are able to more deeply explore the theme proposed herein, since these women accumulate additional risks of osteoporosis, and given the scarcity of specific cancer-oriented protocols and lines of direction [35, 40].

The physiotherapist should know the cancer patients well, and also the specific aspects involved in their disease and its treatment, so that they are able to promote preventive and rehabilitating actions to improve these women's quality of life and to prevent future morbidities and hospital commitments.

Physiotherapy and the breast cancer patient

It is common sense among specialists today that breast cancer induces a considerable decline in the majority of these patients' quality of life – a setting that favors critique functional losses (cardiovascular and lung, weakness and muscle atrophy), fatigue, sleep and weight alterations, not to mention its role in the diminution of physical activity and exercises. According to LeMura and Duvillard [36], it is not clear yet as to what extent this

decreased physical function is a direct consequence induced by cancer and the treatment, or if it is a result of the secondary inactivity induced by the latter. Even if the side-effects are more intense during the treatment, the late or chronic effects may manifest themselves months and even years after the therapies were ceased [36].

The main goal of physiotherapy on breast cancer patients is to prevent and rehabilitate the complications induced by this disease and eventually originated by the treatments themselves – chiefly the surgical approach, chemotherapy and radiotherapy.

The most common complications are pain and edema, especially in the surgical incision and adjacent areas, scar adherence, retractions and fibrosis, decreased movement amplitude, fatigue, shortening of muscles, lymphatic disorders such as lymphedema, and also sensitivity, posture, self-image and respiratory alterations. After the administration of chemotherapeutic agents, vascular alterations on the superior limbs may occur as well [36, 41, 42].

Conclusion

It can be verified, based on the results achieved in this literature review, that there are several scientific articles approaching the theme herein proposed. Different authors have shown the possible chemotherapy-induced late deleterious effects on the bone mass of breast cancer patients, and the additional risks of future osteoporotic developments, since chemotherapeutic and therapeutic hormone (SERMs) treatments may indeed increase and accelerate bone mass loss, either directly through the action of some specific drugs, or indirectly through the decrease of estrogen levels and precocious menopause. Considering the lack of literature on physiotherapeutic intervention in breast cancer patients who suffer from chemotherapy-induced secondary bone loss, the effort made herein was to contribute to future study advances in this direction. The collected data reinforce our view that new studies are needed to establish specific rehabilitation protocols and exercises, so that they can reach maximum efficacy and maximum safety in the treatment of osteoporosis within special populations, such as cancer patients.

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