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Bone protection during breast cancer treatment

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Few medical areas have changed as much through the last decades as the treatment of breast cancer (BC). From Halsted's theory of the progression of an initially local disease, with a first loco-regional and then metastatic extension, to the most recent studies in molecular biology that identify the gene personality of each tumor, there have been many advances. Old TNM classification originally designed for solid tumors have been abandoned and all areas related to hormonal dependence and gene expression of each tumor have grown in importance. All this is aimed at better facing a global therapeutic approach.

Almost 20 years ago, an important biological research laboratory provided us with a detailed study of the basal estradiol levels of the patients in the placebo group of the MORE study[1]. An increased risk of breast cancer associated with raised serum estradiol levels was demonstrated, confirming the previous results on the hormonal dependence of this neoplasm. With the introduction of chemotherapy (QMT) in the final decade of the last century, the general mortality of women from breast cancer was reduced in all western countries. At the time, and just a few years later, the implementation of massive early detection programs at the population level facilitated an increase in the diagnosis of tumors in early stages.

Currently, women survive BC for many years more than just twenty years ago, increasing the risk of various chronic diseases, to which little or no attention was previously given by oncology teams. To this we must add that treatments that seek to eliminate hormonal influence such as surgical oophorectomy, GnRH agonists, and QMT with consecutive induction of iatrogenic early ovarian failure, may increase the risk of loss of bone mass and the appearance of osteoporosis (OP) in surviving women.

Breast cancer *per se* does not influence the increased risk of OP. In fact, the prevalence of fractures among patients diagnosed with untreated breast cancer and who do not have bone metastases the frequency is similar to that of the general population[2]. In these women, the bone mineral density (BMD) in the lumbar spine, hip and radius is similar to that of healthy women. These results are observed in both premenopausal and postmenopausal women[3]. Significant changes in the biochemical markers of bone remodeling (BMBR) have not been reported in women with BC, at least before starting anti-tumor treatment[4]. So it does not appear that the prevalence of OP in women with BC is increased at the disease onset. At the same time, once again using the placebo groups of the trials as biological laboratories, it has been described that the proportion of patients with at least one event related to the skeleton is significantly higher in the group with BC than in the cancer patients generally related to bone damage, such as multiple myeloma or even prostate cancer[5].

The constant reduction in mortality from breast cancer, the diagnosis earlier and the increasingly selective but high intensity aggressiveness in the therapeutic approach, put on the table of the clinicians involved a new challenge: to avoid damage in these patients bone as a tribute that too many times, too many women pay to achieve a survival that, let us not forget, we are in a position to improve with an adequate quality of life.

Thus, anti-neoplastic therapy makes the difference in surviving patients with BC, regarding their bone risk. Premenopausal women with BC who receive ovarian irradiation also have accelerated bone loss as a result of cessation of ovarian activity. Regarding systemic treatment, both cytotoxic drugs and anti-hormonal therapies can facilitate the development of osteoporosis. The former, cytotoxic agents, in addition to acting on neoplastic cells, can alter osteoblastic and gonadal activity. The main cause of this disorder is cyclophosphamide, which, along with other drugs (methotrexate, doxorubicin, and fluoracil), is included in classic

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therapeutic regimens, all of which are capable of damaging the cells of the granular layer of the ovary. Gonadal dysfunction, which is present in most women at the end of treatment with this drug, can persist indefinitely depending on the age of the patient and the dose and duration of treatment[6]. Furthermore, regardless of the duration or dose of therapy, when ovarian failure occurs, patients develop a state of estrogenic deficiency and a subsequent increase in bone resorption[6]. This increase in resorption causes a decrease in BMD in the first years after the cessation of menstruation, decreasing vertebral bone density by 21% compared to eumenorrheic women of the same age. QMT effects on gonadal function seem to be responsible for the loss of bone mass that is observed in premenopausal women with BC who undergo QMT and that can exceed 5% per year.

By verifying the influence of QMT on fracture risk, it has been found that it is four times higher for vertebral fracture[7]. The data provided by one of the branches of the WHI (Women's Health Initiative) showed that the risk of presenting a vertebral or wrist clinical fracture is increased by 30% in postmenopausal women who have survived BC, while it does not appear that the incidence of hip fracture increases significantly[8]. Other authors also found inconclusive results for hip fracture[9].

The true workhorse in the past two decades has been the use of universal anti-hormonal therapies in patients with positive hormone receptor (HR) BC. The aromatase enzyme is known to be responsible for the peripheral conversion of androstendione and testosterone to oestrone and estradiol. It is present in the breast, fat, muscle and brain tumor tissue. The biological action of aromatase inhibitors (AI) is to block aromatase, inhibiting the cytochrome P450 isoenzyme, responsible for the peripheral conversion of androgens to estrogens. Estrogens maintain bone mass, and AI treatment involves rapid bone loss due to estrogen deficiency. Given that the main source of estrogens in postmenopause is extraovarian, the suppression of circulating estrogens is profound in these patients, approximately 95-98%. Thus, their indication is limited to postmenopausal patients. Third generation aromatase inhibitors are divided into two groups: steroidal or type I inactivators and non-steroidal or type II inhibitors. Exemestane, a steroid inhibitor and an andrendrendione analog, irreversibly binds the aromatase enzyme, while letrozole and anastrozole, type II inhibitors, reversibly bind the enzyme. Various *in vivo* animal studies suggest that exemestane (steroid) may be less detrimental to bone health than non-steroidal inhibitors, perhaps because it is structurally related to androstendione and has an affinity for the androgenic receptor. Its main metabolite in humans and rats, 17-hydroxyexamestane, is also androgenic and strongly binds to the receptor. By contrast, non-steroids have no proven androgenic effects[10].

All clinical trials have shown that its use always improves the disease-free survival period, and at the same time reduces the risk of contralateral BC (the existence of a BC being the main risk factor for the development of a second BC in the same woman).

However, AIs are able to significantly reduce the BMD of treated patients. In a sub-study of the five-year Arimidex trial, tamoxifen (TAM), alone or in combination (ATAC), postmenopausal women with MC and anastrozole therapy were found to have increased bone loss in the lumbar spine (LS) and total hip (TH), 6 and 7.2%, respectively, compared to those assigned to TAM (increase of 2.8 and 0.74%, respectively)[11]. In a substudy (206 patients) of the Intergroup Exemestane Study (IES), in which postmenopausal women who had taken TAM for two or three years were randomly assigned to switch to exemestane or to continue TAM, it was found that those who switched to exemestane experienced a greater decrease in BMD in LS (2.7%) and hip (1.4%) after six months, compared to those who remained with TAM (without changes in any of the places)[12]. Bone loss slowed in the remaining 18 months of the study, decreasing an additional 1 and 0.8% in LS and TH, respectively, in subjects assigned to exemestane.

In premenopausal women, in whom the main source of estrogen is the ovaries, AIs alone are not effective. However, in combination with gonadotropin-releasing hormone (GnRH) agonists, goserelin, AIs cause more bone loss than TAM. In the Austrian trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)[13], premenopausal women were randomly assigned to TAM plus goserelin versus anastrozole plus goserelin. Half of each group received zoledronic acid (ZOL). Significant bone loss occurred in the subset of patients who did not receive ZOL (reductions of 17.3 and 11.6% in patients who received anastrozole-goserelin and TAM-goserelin, respectively).

Regarding BMBRs, in several of the previously described assays, both bone resorption (urinary n-telopeptide and serum C-telopeptide [CTX]) and training (serum bone-specific alkaline phosphatase [BALP], N-terminal propeptide 1 procollagen [P1NP]) increased significantly with AI treatment[11-13].

Whatever the case, the most important bone damage in BC patients on AI treatment is the increased relative risk (RR) of fractures. These reportedly appear in patients of age ranges much earlier than that observed in the general population, as early as age 50, involving even hip fractures[14]. Compared to TAM, all AIs significantly increased the RR of fractures: anastrazole 43% higher than TAM in one study[15] and 100% in another[16]; letrozole 48% in one study[17], 15% in another[18]; exemestane 45%[19].

In this issue, the first results of a large cohort in our country of patients with BC treated with AI are published, and these extremes of bone risk are verified[20]. In this cohort of almost 1,000 patients followed consecutively for up to five years and one after the end of their therapy, the authors observed that the main risk factor detected for incident fracture in patients treated with AI is the diagnosis of osteopenia or osteoporosis. In their hands, the FRAX® calculation and the determination of β-CTX levels were useful in identifying high-risk patients.

Indeed, a complete evaluation of mineral metabolism (with measurement of BMD, RX of CL and of the thoracic spine, as well as MBRO and quantification of 25 OH vitamin D, at least) must be unequivocally part of the diagnostic study of any BC in a pre-patient or postmenopausal. The bone risk inherent in anti-neoplastic therapies used as part of health care after initial surgery, either QMT or with various anti-hormonal therapies, particularly with AI, is frequently updated in very notable loss of BMD in all locations with increased RR of fractures at ages sometimes up to ten to twenty years earlier than would be expected from the usual development of osteoporosis.

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