Bisphosphonates and early breast cancer

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“I am sure that today I would not say it, there is nothing better to change the opinion that a solid hope”


Bisphosphonates (BP) have been used for some time as a treatment for bone metastasis in different types of cancer and subsequently this indication has been extended to the prevention of osteoporosis and related fractures in patients with adjuvant endocrine therapy in breast cancer. It has been observed that patients receiving treatment with BP had a better prognosis than those who did not receive it, so it was began the formal study at pathophysiological and clinical level of these drugs effects as part of the treatment of breast cancer. This phenomenon of incidental discovery of a new indication for a drug, due to the beneficial side-effect, is not uncommon and has been described with numerous drugs. One of the best examples of serendipity is tamoxifen, initially formulated as a contraceptive and currently remains as the most important endocrine therapy in the treatment of breast cancer. With the BP, it seems to be happening something similar.

The BP are a group of analogues of bone pyrophosphates, which inhibit bone resorption by osteoclasts, which are the cells responsible for destroying the bone tissue, acting as a counterpart of the osteoblasts that synthesize it, thus forming a balance that maintains adequate bone mass through bone turnover. The BP prevent bone resorption by inducing the osteoclast apoptosis by inhibiting the production of ATP in its interior in the case of the simple BP, such as clodronate, or through the dysfunction of the osteoclast in the case of the nitrogen-containing BP such as alendronate, ibandronate and zoledronate. In addition to the decrease of bone resorption, there have been described antitumor actions of the BP, as the inhibition of the tumor proliferation, induction of apoptosis of tumor cells, inhibition of adhesion and tumor invasion, anti-angiogenesis, synergism with anti-neoplastics drugs and increase in immunological surveillance. It is for this reason that in recent decades it has been evaluated the benefit of these drugs especially in breast cancer, in conjunction with the endocrine adjuvant therapy, specifically aromatase inhibitors, for the prevention of secondary osteoporosis induced by hypoestrogenism.

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It is recognized as a primary event in breast cancer metastases, the existence of niches of malignant cells in the bone marrow that migrated from the primary tumor and that can remain dormant for many years until an event stimulates its growth generating clinical or paraclinical apparent bone metastasis\(^2\). It is estimated that the BP could act at that level, preventing the development of bone metastases, according to evidence from several studies.

To clarify what is the role of the BP on the prognosis of early breast cancer, the Group Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) conducted a meta-analysis of individual data from 18,766 patients with and without treatment with BP who participated in 26 clinical trials. In this series the recurrence was assessed both distant as locoregional and the incidence of a second primary in the contralateral breast, as well as also the mortality from breast cancer \(^3\).

Firstly, recurrence rates were lower in patients treated with BP, difference that did not reach statistical significance (RR: 0.94; 2p = 0.08). Likewise reported a discrete reduction of distance recurrence, which was statistically significant (10-year risk 20.4% with BP vs. 21.8% non BP; 2p = 0.03). This decrease of distant recurrence is given mainly by reduction of bone metastases (10-year risk 7.8% with BP vs 10% without BP; 2p = 0.004). There was no effect of the BP in the prevention of local recurrence or in the contralateral breast, however, breast cancer mortality was significantly lower, although borderline, in patients with adjuvant therapy with BP (10-year risk 16.6% with BP vs 18.4% non BP; 2p = 0.04), as well as any other cause mortality (10-year risk 20.8% with BP vs 22.3% non BP; 2p = 0.06).

The interesting thing about this study is the analysis performed in the subgroups of women under 45 years old and 55 years and older, because it allows to define those who benefit more from the use of these drugs. In younger patients, there is no effect of the BP on bone recurrence (RR: 1; 2p = 0.97), however, in older patients, it shows a significant difference with the use of BP, both in bone recurrence (RR: 0.72; 2p = 0.002), as in any distant recurrence (RR: 0.82; 2p = 0.0003). These results were not influenced by the histological type of tumor, the presence or not of estrogen receptors, positive or negative axillary nodes, or used BP type and regime. However, the benefit was observed in the first four years of treatment and not after that time. When it was analyzed the recurrence and mortality at year 10, comparing subgroups of pre-menopausal and post-menopausal patients, regardless of age, it was observed a significant effect of the BP in postmenopausal women. This finding highlighted the overall recurrence (RR: 0.86; 2p = 0.002), distant (RR: 0.82; 2p = 0.0003) and bone recurrence (RR: 0.72; 2p = 0.0002). Similarly, there was a decrease in the risk of breast cancer mortality by a 3.3% (RR: 0.82; 10-year risk 14.7% with BP vs 18% non BP, 2p = 0.002). In the light of these results, it seems that the hormonal status really influences the beneficial effect of the BP over the course of the disease, i.e., in patients with hypoestrogenism the BP improve significantly the early breast cancer prognosis.

Studies in animals that simulate pre and post-menopausal state models, showed that the growth of malignant cells in the bone marrow is mediated by osteoclasts only in post-menopausal, as zoledronic acid prevented the cell growth in ovariectomized mice and not in mice with preserved ovarian function\(^2\). It was also noted that the hypoestrogenism increases the levels of RANKL, a
molecule that mediates the osteoblast-osteoclast interaction, stimulating the formation and activity of the osteoclasts, making them more vulnerable to inhibition by the BP. The presence of estrogen leads to apoptosis of osteoclasts, reducing the population of this target cell. This would explain convincingly why BP are more effective in the presence of hypoestrogenism.

Another aspect that is important to take into account is related to the secondary effects that could have the BP in patients with early breast cancer. It has been shown that treatment with BP is safe since the adverse events, such as osteonecrosis of the jaw or renal complications in patients with kidney disease are uncommon and are usually associated with higher doses\(^1\). Accordingly, the benefits far outweigh the BP potential negative side effects, so there are few cases in which its use would be contraindicated.

Ultimately, the use of BP in the patients with natural or induced menopause with early breast cancer should be recommended as part of adjuvant treatment on a routine basis, especially for its effect on survival and improvement of bone health\(^1\). To promote the use of BP, in parallel with other measures such as exercise and a healthy diet, will result in a longer life and of better quality.

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References