Tocogynecology/Mastology

Evidence of the action of bisphosphonates in the prevention of breast cancer

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Chlebowski *et al.*[1] showed the results of the Women's Health Initiative (WHI) regarding the risk of breast cancer in women who used bisphosphonates. Thus, in an observational study with 154,768 patients, 2816 of whom used oral bisphosphonates (90% alendronate and 10% etidronate), they observed that, after 7.8 years of follow-up, the incidence of invasive breast cancer was lower in patients who used bisphosphonates (hazard ratio [HR], 0.68, 95%CI, 0.52-0.88; $p < 0.01$). When they performed segmented analysis of the data, they observed that the effects of the drug was observed both in patients with estrogen receptor (ER)-positive breast cancer, where a reduction of the incidence reached a HR of 0.70 (95%CI, 0.52-0.94; $p < 0.02$), and ER-negative patients, although the results in the last group were not statistically significant, probably due to the low number of women in this group (HR, 0.66, 95%CI, 0.31-1.39; $p < 0.27$). Gad Rennert *et al.*[2], observed that the use of bisphosphonates for at least 1 year before the diagnosis of breast cancer was associated with a significant reduction in the risk of breast cancer (Odds Ratio [OR] 0.61; 95%CI, 0.50-0.76), which remained significant after adjusting them for variables, such as age, ingestion of fruits and vegetables, physical activity, family history of breast cancer, ethnic group, body mass index, use of calcium supplements/hormone replacement therapy, number of pregnancies, breast feeding, and age of first pregnancy (OR, o.72; 95%CI, 0.57-0.90). Besides, ER-positive and well differentiated tumors were observed more often in patients treated with bisphosphonates.

Comments

Bisphosphonates are commonly used for prevention and treatment of osteopenia and osteoporosis, but they also to reduce bone metastasis-related bone fractures. Besides, studies with patients using oral and intravenous bisphosphonates also demonstrated the possibility of reducing locoregional recurrence of breast cancer[3].

Studies have evaluated the influence of the adjuvant use of clodronate on recurrence of breast cancer. In the study with the greatest cohort, placebo-controlled and randomized study, patients who used 1600 mg/day of clodronate showed a significant reduction in bone metastasis and greater overall survival[4].

Gnant *et al.*[5] have demonstrated that the association of zoledronic acid to the endocrine therapy of patients with premenopausal ER-positive breast cancer determine longer disease-free survival when compared to the group of patients who did not use this association. They also observed six cases of contralateral breast cancer in the group of 899 patients who were on zoledronic acid against 10 cases in the group of 904 patients who did not. Thus, they hypothesized that this drug might have chemoprotective properties, since it reduced the incidence of contralateral breast cancer instead of simply suppressing metastasis.

In the conjoined analysis of the ZFAST (Zometa-Femara Adjuvant Synergy Trial) ZOFAST (Zoledronic acid in the Prevention of Cancer Treatment-Induced Bone Loss in Postmenopausal Women Receiving Letrozole as Adjuvant Therapy for Early Breast Cancer) trials, 35% reduction in disease recurrence was observed ($p = 0.04$)[6] in postmenopausal patients with breast cancer treated with 4 mg of intravenous zoledronic acid every six months. In the AZURE trial (Adjuvan Zoledronic acid to RedUce Recurrence), the use of zoledronic acid as a neoadjuvant doubled the remission rate of the disease[7]. Those results suggest that the direct inhibitory effect against breast cancer could be the mechanism involved.

Corroborating the studies of Chlebowski *et al.*[1] and Gad Rennert *et al.*[2], Newcomb *et al.*[8], in the University of Wisconsin, observed, through case-controlled studies with a 3-year follow-up in 2936 breast cancer patients and 2975 patients without the disease, that the use of bisphosphonates was a reducing factor in the risk of breast cancer in non-obese patients, with HR of 0.67 (95%CI, 0.51-0.89, $p = 0.01$).

In vivo studies using animal models with breast cancer-induced bone disease have demonstrated that bisphosphonates have anti-tumor effects through inhibition of osteolysis and reducing bone disease. Besides, preclinical

studies have demonstrated and synergic anti-tumor effect between commonly used chemotherapy agents used in the treatment of breast cancer and bisphosphonates[10].

The mechanisms by which bisphosphonates can reduce the incidence of breast cancer are not known. Based on preclinical studies, it has been hypothesized that this drug can affect angiogenesis by reducing VEGF, therefore inducing apoptosis, besides reducing the proliferation and prevent invasion of the extracellular matrix[9]. Those mechanisms differ from those involved in the action of selective estrogen receptors modulators (SERMs), where protection is seen exclusively in ER-positive breast cancer[11], while with bisphosphonates, protection is seen also in ER-negative breast cancer, corresponding to 30% of breast cancers.

Despite those data justifying a possible chemopreventive action of bisphosphonates in breast cancer, it is premature to use it in the prevention of this disease. Further randomized studies are necessary to test their real efficacy in clinical use.

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