Bisphosphonates: Beyond Prevention of Bone Metastases

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Bisphosphonates have traditionally been indicated for treatment and control of osteoporosis because they inhibit osteoclast-mediated bone resorption and reduce the release of calcium into the blood stream (1). They are currently being used by millions of people (mostly women) worldwide (2). Accumulating evidence over the past 10 years has demonstrated that the use of third-generation nitrogen-containing bisphosphonates can effectively treat bone metastases in women with breast cancer (3). It has been hypothesized that bisphosphonates can also prevent bone metastases altogether and could therefore be implemented in an adjuvant setup in women with breast cancer (4,5). A recent randomized controlled study failed to demonstrate such an effect using third-generation bisphosphonate (6).

If bisphosphonate use is associated with a generalized reduced risk of malignancy, one would expect to see reduced risk of developing breast cancer or other cancers in regular users of second-generation bisphosphonates, such as osteoporotic women. One would also expect to see reduced risks of developing contralateral breast cancer in women with breast cancer who were further treated with bisphosphonates. Three descriptive studies have thus far shown a strong and similar negative association between the use of common second-generation oral bisphosphonates and the risk of breast cancer (7–9). These findings raised the possibility of confounding by indication. Bisphosphonates are used by osteoporotic women, and osteoporosis is the result of reduced circulating estrogen levels. Estrogen is strongly associated with risk of breast cancer, and women with low estrogen levels are expected to have lower breast cancer rates. Thus, the negative association with bisphosphonate use could actually reflect a negative association with low estrogen levels in the body. However, evidence that the degree of breast cancer risk reduction among bisphosphonate users was not correlated with the degree of bone density loss (7), that risk reduction was seen only after a year of treatment (8), and that postmenopausal bisphosphonates users also demonstrated a reduced risk of colorectal cancer (10,11), all suggest that the association between bisphosphonate use and reduced risk of cancer is real.

Mechanistically, nitrogen-containing bisphosphonates inhibit protein prenylation by blocking the mevalonate pathway. Selective inhibition of farnesyl pyrophosphate synthase by bisphosphonates can lead to diminished posttranslational prenylation of small GTPase proteins (including signaling molecules such as proteins of the Ras and Rho families) that promote tumorigenesis and metastases (12). In a mouse model, use of bisphosphonates was associated with the suppression of Rho and Ras pathways (13).

Further support for a possible role of bisphosphonates in primary prevention of cancer comes from numerous previous reports on the negative association between the use of statins and the risk of cancer in various organs [eg, (14–20)]. Statins, which use the same mevalonate pathway as do bisphosphonates (acting upstream of the farnesylation–geranylination step), have been shown to be associated with cancer risk reduction and with possibly improved survival of patients with cancers in multiple sites (21).

In this issue of the Journal, Monsees et al. (22) describe their findings of reduced risk of contralateral breast cancer in women with breast cancer who were using mostly second-generation bisphosphonates. This important finding adds another piece of necessary evidence to the hypothesis that bisphosphonates actually express a direct antitumor effect. Evidence of a reduction in risk of contralateral breast cancer has for many years served as an indicator of the primary prevention potential of different medications (23). It was first shown with tamoxifen [originally reported in 1992 (24)] and has since been proven in randomized controlled trials to prevent breast cancer. Studies of aromatase inhibitors have also suggested that they reduce the risk of contralateral breast cancer (25,26), and these drugs are currently being considered as possible candidates for primary prevention of breast cancer. With this new evidence (22) now in place for bisphosphonates, only one more piece of information is needed before randomized controlled trials of primary prevention of breast cancer with bisphosphonates can be justified: descriptive studies that show improved survival of breast or other cancers in women using bisphosphonates specifically for osteoporosis control (not for the treatment or prevention of bone metastases). This survival advantage needs to be shown especially for tumor sites that do not commonly produce metastases in the bones.
If bisphosphonates are ever to be used for the purpose of primary cancer prevention by the population at large, they need to be cheap, commonly available, and free of major side effects. It would therefore be of interest to establish that a preventive effect, similar to that suggested for third-generation bisphosphonates, can be achieved with the use of simple second-generation bisphosphonates such as alendronate or risedronate, which are available as generic drugs. Given the current long-term experience with these drugs by many millions of women, it is clear that their side-effect profile is low, with only rare reports of osteonecrosis of the jaw and atypical subtrochanteric and femoral shaft fractures (mostly reported for newer intravenous-administered formulations) (27). It is as yet unclear if these or other side effects should be expected in non-osteoporotic users of bisphosphonates, a question that will only be resolved through randomized controlled trials. Until all of these additional pieces of information are available, this class of drugs remains a strong, but as yet unproven, candidate for effective prevention of malignant processes.

References

Notes
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