Reply to the article “Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases” by J.-J. Body et al. (Ann Oncol 2007; 18: 1165–1171)

We read with great interest the paper by Body et al. [1] about the effects of oral ibandronate and i.v. zoledronic acid on bone turnover markers. The study population included patients receiving aromatase inhibitors, tamoxifen and cytotoxic therapy. Levels of serum cross-linked C-terminal telopeptide of type I collagen (S-CTX, urinary CTX (U-CTX), serum bone alkaline phosphatase, serum amino-terminal procollagen propeptide of type I collagen (PINP) and serum osteocalcin (OC) were measured. Both bisphosphonates significantly reduced bone turnover markers.

It is well known that bone is the most common site of metastases in breast cancer. Steroidal hormones are mainly responsible for the balance between bone production and resorption in women. In healthy postmenopausal women, decrease in estrogen levels result in increased bone turnover and bone loss. The effects of aromatase inhibitors and tamoxifen on bone are different. It is obvious that tamoxifen treatment inhibits osteoclastic activity, resulting in a decrease in bone loss. Likewise, it inhibits osteoclastic bone activity in ovariectomized rats. In a study by Marttunen et al. [2], the effects of tamoxifen treatment on bone modeling were evaluated by bone resorption markers and bone formation markers. After 6 months of therapy, urinary N-telopeptide levels were significantly decreased by 33%. In addition, levels of serum amino-terminal (PINP) and carboxy-terminal propeptide of type I collagen and OC levels were found to be significantly lower in patients following 6 months of tamoxifen therapy. Similarly, Yoneda et al. [3] found decreased bone turnover with tamoxifen treatment. The study by Banerjee et al. [4] supports these studies, although they found an insignificant drop in serum CTX levels after 3 months of tamoxifen therapy, which is probably insignificant due to the short duration of therapy. Aromatase inhibitor anastrazole, however, increased CTX levels in contrast to tamoxifen. In the ATAC trial, it was pointed out that tamoxifen caused decreased bone turnover and bone loss [5]. On the other hand, anastrozole treatment resulted in an increase in both bone formation and bone resorption.

Although the study by Body et al. was comparing percent changes in bone turnover markers with ibandronate and zoledronic acid, the effects of hormonal treatments were not taken into consideration. Moreover, there is not enough data about the effects of cytotoxic drugs and biologic agents, such as trastuzumab, on bone metabolism. Although, it was stated that the arms are well balanced, there were 25% more patients treated with tamoxifen in the ibandronate arm. We cannot predict the effect of this imbalance since we were not able to find any subset analysis in the study according to concomitant antitumor treatment received by the patients. There was also no comment in the discussion on the possible confounding effects of these medications. Selection of a mixed study population treated on various modalities might have confounded the results. More accurate results could have been obtained with the use of a more homogenous patient population.

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