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Zoledronic acid (ZOMETA): a Significant Improvement in the Treatment of Bone Metastases

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Bone metastases are frequent complications of breast, lung and prostate cancers, multiplex myeloma, and less frequently of other neoplasms, causing pain, pathological fractures, hypercalcemia, spinal cord compressions.[1] These symptoms have a major impact on the quality of life and should be controlled by appropriate therapy. Bisphosphonates became an essential element in the treatment of bone metastases. These pyrophosphate analogues target and inhibit osteoclast activity,[2] and in the past 15 years were included in many clinical trials.

Newer N-containing bisphosphonates (e.g. zoledronate, pamidronate, ibandronate) inhibit the mevalonate pathway of cholesterol biosynthesis *in vitro*, and interfere with protein prenylation in osteoclasts *in vivo* by inhibiting farnesyl diphosphate synthase. Prenylation is an important posttranslational modification of small guanosine triphosphate-binding proteins (as Ras, Rho, Rac) which have many important regulatory functions.

It was proved that members of bisphosphonate family (as clodronate, pamidronate) could reduce the incidence and severity of skeletal complications (skeletal-related events, SREs).[3,4] Further improvement has been achieved by zoledronic acid which in comparative studies with other bisphosphonates was more convenient to use and was also more effective, further decreasing the skeletal-related events.[5,6] Recently, the effect of zoledronic acid (4 mg, 15 min infusion, every 4 weeks for 1 year) has been studied in 227 Japanese women with bone metastases (mainly osteolytic lesions) from breast cancer.[7] Besides decreasing the pain (median pain score), the study showed a significant 39% reduction in the rate of SREs in patients treated with zoledronic acid compared with placebo.

There are increasing evidences that newer aminobisphosphonates, especially zoledronic acid, have direct antitumor activity.[8] Several clinical trials support that bisphosphonates can increase the survival when used in adjuvant setting. In a randomized, multicenter trial clodronate (1600 mg/day) significantly reduced the risk of bone metastasis, and there was also an improvement in overall survival with long term follow-up.[9] In another study with oral clodronate, overall survival improved in breast cancer patients with micrometastases.[10] The Adjuvant Zoledronic acid to Reduce Recurrence (AZURE) trial is under evaluation, targeting the effect of zoledronic acid on disease-free survival and incidence of bone metastases in patients given standard adjuvant treatment.[11]

Cessation of estrogen production increases the risk of bone loss in postmenopausal women with breast cancer. Therefore it is understandable that aromatase inhibitors can even increase the bone resorption marker levels and accelerate the bone loss. In a recent clinical trial (Z-FAST trial, 6-month study assessment) the lumbar spine and total hip bone marrow density increased in patients (postmenopausal women with early breast cancer) receiving letrozole and upfront zoledronic acid.[12] The evaluation at 12 months reflected the same results.[13]

Many of the above mentioned results created positive echo at the ASCO Annual Meeting (2005). Botteman et al[14] found that zoledronic acid appears to be the most cost effective i.v. bisphosphonate therapy compared to generic pamidronate and ibandronate, or to no therapy. In a phase III trial advanced breast carcinoma patients with at least one confirmed osteolytic or mixed bone lesion received either oral ibandronate (50 mg/day) or i.v. zoledronic acid (4 mg, 15 min infusion, every 4 weeks for 12 weeks).[15] When markers of bone resorption were compared, oral ibandronate seemed to be as effective as i.v. zoledronic acid. The primary endpoint was the change of cross-linked C-terminal telopeptide of type I collagen in serum (S-CTX). Using another marker of bone resorption (urinary N-telopeptide) Lipton et al claimed that in breast cancer and multiple myeloma the normalization of the elevated level of this marker after 3 months of treatment with zoledronic acid

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is a good predictor of favorable outcome measured by skeletal-related events and time to first SRE.[16] Adjuvant pamidronate therapy also showed significantly reduced development of bone metastases in perimenopausal women with primary breast cancer according to a survey on 429 patients with primary operable stage I-III breast cancer.[17]

There are still many open questions in the use of bisphosphonates.[18] How can we identify patients responding or not responding to these therapy? What is the reason of the resistance against bisphosphonates and how can we overcome this problem? Is there any useful effect of bisphosphonates in the management of primary breast cancer when added to standard anticancer therapy? Solving these and other similar problems requires a joint effort and sponsorship of many agencies, including pharmaceutical industry, governmental sources or different foundations.

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