Osteooncology – Specific Aspects in Breast Cancer Patients

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Affecting a greater number of patients than any other metastatic location, tumor metastasis to bone has a substantial impact on cancer patients' morbidity and mortality, including those with breast and some other solid tumors which are particularly prone to such skeletal disease. Bone metastasis occurs in approximately 70% of women with advanced breast malignancies, bone health thus gaining in relevance as a most critical issue in breast cancer management. While systemic treatment for breast cancer will act to decrease circulating levels of estrogen at any age – further accelerating the natural decline of bone – many women who develop breast disease are postmenopausal and thus already predisposed to osteoporosis.

Studies in the bone microenvironment and its role in metastasis have recently revealed its complex role in tumor growth. Accelerated or cancer treatment-induced bone loss (CTIBL) is a common clinical feature that has been shown to lead to a critical increase in fractures, chronic pain, loss of mobility and other complications. Fortunately, both pre-clinical and clinical research in the potential of adjuvant bone-targeted agents in preventing metastasis and avoiding CTIBL have so far yielded promising results. The potential role of bone-targeted agents is underscored by emerging data from large clinical trials suggesting that additional anticancer benefits can be accomplished due to a positive impact on the bone marrow microenvironment.

The five scholars contributing to this issue's focus on osteooncology have reviewed a genuinely massive body of evidence for preserving bone health in breast care with bisphosphonates and other traditional therapies, as well as newer agents, including antibody treatments. As today's current standard of treatment applied to lower the number and the frequency of bone-related events, both oral and intravenous antiresorptive bisphosphonates have shown encouraging activity in preventing CTIBL in women receiving systemic treatment, be it chemotherapy or endocrine therapy.

In his guidelines for osteoprotection in connection with aromatase inhibitor (AI) treatment, Peyman Hadji [1] scrutinizes recent literature pertaining to AI-associated bone loss and discusses approaches that may have the potential to continue therapy in breast cancer patients in an attempt to derive superior clinical benefits. With a focus on the postmenopausal setting, adjuvant bisphosphonate therapy by Michael Gnant [2] in turn demonstrates how zoledronic acid can effectively prevent CTIBL in women receiving AIs or other estradiol-reducing hormonal treatments. Bisphosphonates have been evidenced to potently inhibit bone resorption, acting by inducing osteoclast apoptosis and thereby preventing CTIBL from the onset. Ongoing clinical trials will further establish whether bisphosphonates are functionally able to halt the development of bone metastasis in women with high-risk breast disease.

As discussed by Ingo Diel in his overview on bisphosphonates in breast cancer patients [3], bone metastasis is known as the most frequent origin of cancer-related pain. In addition to their potential for improving overall quality of life, bisphosphonates, used consistently, serve to reduce bone pain and other typical complications, such as fractures, hypercalcemia, spinal cord compression and instability. Furthermore, recent clinical trials in the adjuvant setting have indicated that there may be additional benefits from bisphosphonate therapy, including advantageous effects on disease recurrence and survival when combined with standard endocrine treatment.

While bisphosphonates today are considered the standard of care in women with breast malignancies and skeletal metastasis, not all such patients are fully spared bone-associated events despite their treatment. As explained by Heinrich Resch and Rupert Bartsch, the proteins regulating bone resorption include receptor activator of nuclear factor kappa-B (RANK) and its ligand RANKL which induces osteoclast activation. Resch, in his paper on new-generation drugs [4], summarizes current evidence according to which the anti-resorptive antibody denosumab inhibits the interaction of

RANKL with its receptor RANK, thereby suppressing osteoclast differentiation.

Reviewing RANK ligand inhibition, Bartsch and co-workers [5] finally emphasize that denosumab is well tolerated and that its clinical activity is seen to be similar to bisphosphonates in metastatic disease. Ongoing clinical investigations have shown that denosumab acts to reduce markers of bone turnover, suggesting a level of efficacy equal to bisphosphonates in lowering the rate of bone-associated events. Overall, with a favorable risk-benefit profile, this antiresorptive antibody has shown to be a possible and promising alternative to bisphosphonate therapy.

The management of bone loss and symptomatic bone metastasis by application of bisphosphonate or antibody therapy remains a key issue in current care for breast cancer patients. While the role of bone-targeted treatment in oncology is likely to expand, an improving understanding of the biomolecular pathways that govern CTIBL continues to identify novel targets for drug development. Investigations in osteooncology will further analyze the effects of bone-targeted treatments and immune cell interactions within the bone microenvironment. Without doubt, future research will then also help generate biomarkers to identify patients most likely to benefit from such therapies and define the optimum type, dose and schedule of adjuvant bone-targeted therapy in breast cancer.

References

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