Bone Targeted Therapy in Breast Cancer – an Old Concept but Still Much to Do

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Several studies showed that at the time of diagnosis tumor cells can be detected in the bone marrow of patients with primary non-metastatic breast cancer. These patients were not only at higher risk for bone metastases but also for distant relapse at other sites. It was hypothesized that the bone marrow may be a sanctuary for dormant tumor cells which may become active and proliferate some years later. In fact, preclinical data showed that osteoclast-mediated bone resorption releases growth factors which may stimulate tumor cells. Moreover if breast cancer recurs, bone is most frequently the distant site of relapse. Approximately 80% of patients with metastatic breast cancer will develop bone metastases and 50–70% of these patients will eventually develop skeletal related complications. Endocrine treatment with gonadotropin-releasing hormone (GnRH) analogues and aromatase inhibitors can be detrimental to bone health, putting women at increased risk of treatment-induced bone loss that eventually leads to osteopenia or osteoporosis.

Thus there are many good reasons to use bone targeted therapy either with bisphosphonates or the recently introduced rank-ligand inhibitor denosumab in women with breast cancer in order to reduce bone turnover and cytokine release which may induce tumor cell proliferation. A landmark trial 20 years ago proved that the bisphosphonate pamidronate (given every 4 weeks for 2 years) significantly reduced the rate of skeletal related events compared to placebo treatment in patients with bone metastases. Unfortunately, since then not much research has been done in this field to optimize the treatment and the recommendation to use bone targeted therapy (every 4 weeks) until substantial decline of the patient's performance status, even beyond 2 years is not based on convincing evidence. In addition there is still no evidence ad-

ressing the consequences after one or more adverse skeletal events such as modifying bisphosphonate treatment or switching to denosumab. Only recently a study showed that a 3 month interval of zoledronic acid was non inferior when compared to monthly intervals after some time of monthly induction bisphosphonate pretreatment. The development of bone targeted therapy in the metastatic setting is an example that proof-of-principle studies are important for the registration of a drug but can only be the beginning of a process to optimally integrate a new drug into our clinical practice.

Another area of controversy is the use of bone targeted therapy as adjuvant treatment to prevent metastases. For more than a decade several trials have been conducted and we still cannot clearly prove that adjuvant bisphosphonates in addition to standard therapy will improve outcome. Retrospective analyses suggest that the benefit is confined to clearly postmenopausal patients. However, prospective data in this particular population are missing and the use of bisphosphonates in this setting cannot be considered standard of care.

Regarding treatment induced bone loss the picture is much clearer. Several studies unanimously show that both bisphosphonates and denosumab can prevent treatment induced bone loss. Bone modifying agents are generally well tolerated; still there are side effects which need to be considered when treating patients with these drugs in order to maximize utility for patients. All these topics are comprehensively reviewed and critically discussed by the authors of the 4 review articles in this edition of BREAST CARE.

Bone targeted therapy is long known and an important part of breast cancer management. But even after almost 20 years there remain many open questions which need to be addressed in further trials.