Biochemical Markers in the Management of Patients with Metastatic Bone Disease

Patients with cancer usually die not as a result of their primary malignancy but of the metastatic disease process that ultimately develops. One-third of cancer patients will have metastases of their primary tumor to bone (1). The metastatic spread of cancer to bone is common to many different malignancies, particularly breast (73%), prostate (68%), and lung (36%) cancers (2). Bone metastases, in fact, account for the highest proportion of first sites of relapse in breast cancer patients. Metastases to bone cause accelerated bone resorption both from direct effects of the tumor itself and through the activation of osteoclast cells in bone via humoral and growth factors such as cytokines, platelet-derived growth factor, and parathyroid hormone-related protein (3). For most cancer patients, treatment of advanced metastatic disease is usually palliative, with quality of life a primary goal of therapy. Although patients will develop visceral as well as bony metastases, in many cases metastasis is exclusively to bone. There are numerous clinical consequences of metastatic bone disease, including hypercalcemia, bone pain, pathological fractures, and spinal cord compression. In many of these patients, appropriate therapy can resolve the hypercalcemia, improve the bone pain, and ward off the development of pathological fractures that compromise the mobility and quality of life for these patients (4). Patients with breast cancer, for example, have a four- to fivefold higher rate of vertebral fracture than age-matched women (5). Therapeutic decisions to treat metastatic bone disease rely on assessing the presence of bone metastases, which are usually difficult to determine radiologically. In addition, therapy in these patients is quite difficult to gauge because radiological changes are generally slow to occur and difficult to detect even with bone scan measurements.

A high percentage of cancer patients with documented bone scan evidence of metastases show increased urinary excretion of the bone resorption markers pyridinoline and deoxypyridinoline and their associated N-telopeptides (6). Several studies have shown that patients with metastatic bone disease have significantly higher concentrations of markers of bone resorption and formation than age-matched controls (7).

Recently, N-telopeptide, a bone resorption marker, has been shown to be a significant predictor of the presence of bone metastases (8). In these studies, it was noted that a small but significant number of patients without bone scan evidence of metastatic disease also had increased concentrations of the resorption markers. It has been suggested but not yet demonstrated that these patients might have early bone involvement or micrometastases that cannot be detected, even with bone scan or bone survey methods. The major question that arises from these studies is whether the biochemical markers can provide advance warning that bone metastases are evolving in patients with early metastatic disease.

To that end, there is considerable interest in determining the value of bone markers in the early diagnosis of bone metastases. In addition, there is interest in knowing whether biochemical markers can signal metastatic bone disease progression in patients with advanced disease and how these markers might be used to monitor patient response to antiresorptive and/or palliative therapy for bone pain.

In this issue, Berruti et al. (9) offer yet another possible use of the markers in patients with metastatic bone disease, i.e., to assess both tumor burden and extent of true bone pain. In their retrospective study, they show that markers of bone turnover are significantly correlated with the extent of disease or tumor burden by demonstrating a relationship between marker concentration (serum bone alkaline phosphatase, the C-terminal telopeptide of type I collagen, and urine deoxypyridinoline) and the number of skeletal sites involved (skull, spine, femur, ribs, pelvis, and others). The more skeletal involvement of the disease, the higher the marker concentration. They also showed that the resorption marker concentration (C-terminal telopeptide of type I collagen and deoxypyridinoline), but not the formation marker (bone alkaline phosphatase), is correlated with severity of bone pain and suggest that the resorption markers might be of use to assess the extent of bone pain in cancer patients.

Other reports (10) have also shown that resorption and formation markers correlate with the number of lesions and/or the number of skeletal segments involved, but we still do not know whether the marker concentration is a prognostic factor to decreased survival or a marker of increased probability for developing skeleton-related events (fracture, hypercalcemia, bone pain). A recent abstract (11) presented at the American Society of Clinical Oncology meetings supported the findings of Berruti et al. (9) and showed that bone marker concentrations (N-telopeptides and bone alkaline phosphatase) were correlated to the extent of bone metastases in cancer patients but did not correlate with the presence of extraskeletal metastases (11).

We do not yet know whether normalizing the bone marker concentration with antiresorptive agents such as bisphosphonates in metastatic cancer patients will lead to a lower probability of pathological fractures in the future. We do know from clinical studies that relief of bone pain with bisphosphonate therapy occurs in a high proportion of advanced cancer patients treated. What is needed are prospective studies in patients who have had surgery for cancer (breast, prostate) to see whether the bone markers increase before the bone scan turns positive. Longitudinal studies looking for the development of metastatic disease, however, will take several years to carry out. Patients with metastatic disease present, on average, ~4 years after the time of primary disease presentation; therefore, the results from these prospective studies will take some time to generate. There is also a need for prospective
studies in cancer patients with advanced disease to see whether the markers are able to discern true progression from stable disease. The information gained from these studies would set the stage for therapeutic interventions and/or changes in therapy that might extend beyond palliative care and actually affect survival if the progression is detected much earlier with the markers.

Until then, therapeutic decisions have to be made relying on the best assessment of bone metastasis response to treatment. Currently, that assessment involves the bone scan and bone survey, which have their inherent limitations in bone response interpretation. If the markers ultimately provide an earlier indication of bone metastases presence or progression, they will become powerful tools in the hands of oncologists managing cancer patients at high risk for developing metastases to bone.

References


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