



How bone metastases can influence the management of breast cancer

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It has long been recognised that metastasis to bone occurs very commonly in patients with breast cancer. This was highlighted as long ago as 1890, when English surgeon Stephen Paget, in carrying out autopsies on several hundred women with breast cancer, reached the conclusion that bone appears to be a preferred site of metastasis for breast cancer, rather than lung or liver (1). He concluded that “*in cancer of the breast the bones suffer in a special way, which cannot be explained by any theory of embolism alone*”. This constituted the “seed and soil” hypothesis in which the “soil” of bone supports the survival and growth of breast cancer “seed”, with the implication that bone has special properties which favour metastasis to that site. This concept continues to be validated by clinical observations and by studies extending to the present day, and has provided the stimulus to much research seeking to identify the properties of the bone microenvironment that equip it so well to provide a favourable environment for tumor growth (2).

Although early reports failed to note increased osteoclasts associated with bone metastases (3), evidence accumulated that breast tumor deposits in bone are surrounded by active osteoclasts (4). With increasing recognition of the high incidence of bone metastasis in breast cancer there is little change from earlier estimates in the literature on the frequency of bone metastases varying from 47% to 85% (5,6). Actual incidence is dependent ultimately on duration of disease and nature of treatments. The ability of the tumour to promote osteoclast formation and activity and hence bone resorption is central to the bone metastasizing capability of that tumour. One of the striking ways in which this property manifests itself clinically is the fact that in

breast cancer, bone metastases are predominantly osteolytic, with occasional sclerotic and mixed deposits. This contrasts with metastases in prostate cancer that are almost always sclerotic. Much valuable information about these processes has come from animal models of tumour osteolysis (7). Such models of breast tumour colonization and growth as skeletal deposits in bones of immune-deficient mice have been helpful in studying this process and the effects of inhibiting bone resorption (8,9).

Metastasis—a combination of invasive and bone-specific properties

In the process of metastasizing to bone, there are many properties of breast cancer cells that can be described as “general”, in that they are required of any cancer cell metastasizing to any organ. These include extravasation of the blood-borne cells and local invasion, angiogenesis, survival from immune cell attack, and then proliferation. Subsequent survival and growth in a particular organ may depend on local products of that organ (growth factors, cytokines), and in the case of bone, the ability to recruit the co-operation of host osteoclasts to resorb bone and make a “niche” that is virtually a homing device for the growing mass of tumor cells. This is a concept that was further promoted following the discovery of parathyroid hormone-related protein (PTHrP) as a tumour product that promotes osteoclast formation and bone resorption when it circulates in excess as in humoral hypercalcemia of malignancy, or when it is produced by cancer cells that reach the marrow, and promotes host osteoclast formation around tumour sites

(7,10). It is that ability of tumours to promote resorption that led to the use of resorption inhibitors in the treatment and prevention of bone metastases, and these drugs provide crucially important approaches to that clinical problem.

Thus the Consensus Statement on the diagnosis and treatment of breast cancer bone metastasis (11) is timely, since it considers both anti-cancer treatment by endocrine and chemotherapy approaches, that target the general invasive properties of tumour, as well as the increasingly promising advances offered by drugs that inhibit osteoclast formation and bone resorption. In that respect, the point is well made in the paper that the management of metastatic bone disease in breast cancer often involves multiple specialists in treatment approaches, all underpinning the general management of the patient.

Issues at diagnostic evaluation of patients with bone metastasis in breast cancer

Of the several alternative imaging methods discussed by Jiang *et al.* (11), the most commonly applied in breast cancer is radionuclide scanning, which should be the imaging method of choice at diagnosis (12). This uses radio-labelled bisphosphonate that is visualised because of the increased local blood flow and bone cell activity that accompanies bone metastasis. Such scanning is valuable also in the diagnosis and assessment of Paget's disease, and positives are obtained in trauma and inflammation. The latter provide for false positive bone scans in cancer, a possibility that must always be kept in mind, with assessment of the radionuclide scan data carried out as part of a detailed clinical evaluation. Whereas these radionuclide scans can be useful at the time of diagnosis they are not of value in assessing progress of treatment of bone metastases in breast cancer. Other scanning modalities could of course be available, including PET scanning and whole-body MRI. Each of these is effective in assessing bone metastases but their expense and lack of general availability limit their use.

The possibility of a tissue diagnosis by biopsy of a metastasis is appealing, but this might only occasionally be indicated. In the common situation where bone metastases, either single or multiple, are identified in patients who can readily be seen to have lesions at other sites, biopsy is not indicated. In the event of metastasis that are clearly identified as occurring only in the skeleton, CT-guided tumor biopsy can provide a valuable approach, especially when radiology following radionuclide scanning remains inconclusive.

Pathogenesis—tumour products that increase bone resorption

The osteolytic nature of breast cancer skeletal deposits relates to the ability of the tumor to produce factors by the host cells that promote RANKL production with resulting increased resorption around the site of tumor location (2,7,10,13). This reflects itself in the increased markers of bone resorption that are observed in these patients in serum and urine. This increase in resorption markers can be useful clinically to some extent in following individual patients' treatment, but is of little use for diagnostic purposes. Indications of response to anti-resorptive treatments can be deduced quickly with measurement of resorption markers, whereas evidence of improvement by any of the organ visualization methods is inevitably much slower. Interestingly, in patients with prostate cancer, predominantly due to sclerotic bone metastases, circulating and excreted resorption markers are high, often even higher than in patients with breast cancer (14). These clinical observations highlight how much we need to learn about the pathogenesis of cancer metastasis to bone. While it might seem logical that whether a metastasis is "lytic" or "sclerotic" depends on the net production by the tumors of bone-resorbing and bone-forming cytokines, the findings of comparably increased osteoclasts and resorption by both types of metastasis (as in breast and prostate) leaves that question open.

The propensity of breast cancers to metastasize and flourish in bone, as well as their lytic nature that suggests excessive bone resorption, has resulted in much interest in the tumor products which could possibly explain these specific bone effects. Much interest has been focused on PTHrP, that is expressed by 60% of primary breast cancers (15), and was found to be enriched in metastases to bone compared with other sites (10), leading to the suggestion that the ability of breast cells to promote RANKL production and osteoclast formation (13) might be a crucial property in achieving this outcome. Although this might be so, it is a property that is shared with other factors produced by breast cancers, including cytokines IL-1, IL-6 (16), IL-8 (17). Understanding more fully the significance of these tumour products in the pathogenesis of bone metastasis will be of much interest, and particularly whether use can be made of that understanding in developing new approaches to treatment and prevention of metastases. Nevertheless the promise and current success of bisphosphonates is such that any new treatment based on these pathways would need to be effective and safe as well as novel, and would need to

show superiority to the existing antiresorptives.

Clinical outcomes with bone resorption inhibitors in prevention and treatment of bone metastases

The application of inhibitors of bone resorption to the prevention and treatment of bone metastases began with the introduction of bisphosphonates. Bisphosphonates are analogues of pyrophosphate that display similar physicochemical activity but which resist enzymatic hydrolysis and are therefore not broken down metabolically. This is because the two phosphates in the molecule connected by a P-C-P structure which is extremely stable chemically when compared with the P-O-P structure of pyrophosphate. A number of bisphosphonates have been developed since the earlier discovery. A great number of variations are possible, either by changing the two lateral chains on the carbon atom, or by modifying the phosphate groups. The first generation of bisphosphonates, etidronate and clodronate, impair osteoclast activity by accumulating intracellularly as non-hydrolyzable ATP compounds. Clodronate was the first to be studied clinically and appeared to be beneficial in breast cancer bone metastasis (18). The subsequent development of nitrogen-containing bisphosphonates revealed a new action, blocking osteoclast function by impairing the mevalonic acid pathway, thus inhibiting the prenylation of small GTPase signaling proteins. This class of bisphosphonate began with alendronate, introduced in the mid-1990's for the treatment of osteoporosis. Other examples of this class, pamidronate, ibandronate and zoledronate, have been investigated extensively in metastatic disease, beginning with a placebo-controlled study of pamidronate that reduced skeletal complications significantly in patients with lytic bone metastases in breast cancer (19). These findings were amply confirmed with other bisphosphonates (20). Although there are publications indicating that bisphosphonates can exert direct anti-tumor effects, such data has usually been obtained using very high concentrations of drug *in vitro*. Clinical trial data suggesting direct anti-tumor effects of bisphosphonates have been both positive (21) and negative (22).

A recurring question throughout all these studies was whether reduction of skeletal complications might interfere with disease progression and importantly, improve survival. In the early studies with bisphosphonates, although skeletal events were commonly reduced, there appeared to be no effects on survival, as for example with

the first generation bisphosphonate, clodronate (18). This question was addressed directly in the AZURE study—does addition of zoledronate to standard breast cancer endocrine and chemotherapy influence disease outcome? Neither the 2011 (23) nor the 2014 (24) evaluations of the AZURE study showed any benefit of added zoledronate on disease-free survival. A most informative and influential outcome came from pre-planned analysis of a sub-group of patients treated for 10 years in that study. It revealed that there was a disease-free survival benefit conferred by zoledronate addition to treatment for postmenopausal, but not for premenopausal patients (25). A similar outcome was reached in a meta-analysis of randomized clinical trials in almost 20,000 women of adjuvant zoledronate or ibandronate. This showed that the bisphosphonates reduced bone metastases and deaths from breast cancer, but only in menopausal women, either natural or induced (26). This resulted in the view that only women with low levels of reproductive hormones are likely to benefit from bisphosphonate treatment. Importantly, this and other data led to clinical oncology practice guidelines being adopted in USA and Europe recommending the use of zoledronate in the treatment of early breast cancer in postmenopausal women (27).

A few years later an alternative and very efficient way of inhibiting bone resorption was developed. This was denosumab, a monoclonal antibody against RANKL, that acts by binding RANK, the crucial physiological regulator of osteoclast formation, and preventing it from signaling to promote osteoclast formation. As was the case with the bisphosphonates, denosumab reduced skeletal complications of cancer whatever the primary tumor, whether breast or prostate, or the skeletal lesions of multiple myeloma, which are essentially all lytic (28,29). In a randomised comparator study, denosumab was found to be significantly more effective than zoledronate in delaying skeletal-related events in metastatic breast cancer (28), and the reduction in bone resorption markers was significantly greater in denosumab than in zoledronate treated patients. There were no differences in overall survival between the groups. Similarly, in a recent randomised controlled study of 4,500 women with breast cancer, treated with denosumab, metastasis-free survival was the same in control and treatment groups (30).

Thus although survival is not affected by denosumab, it appears as an alternative, powerful inhibitor of bone resorption, to be added to the bisphosphonates. There are side effects of some note that need to be considered with

each of these drugs. Although osteonecrosis of the jaw was first noted as an uncommon but troublesome complication of bisphosphonate treatment, it occurs uncommonly also with denosumab treatment (31). A further point to be kept in mind in the case of denosumab, is that cessation after effective treatment can result in a rebound increase in bone turnover (32), that might not be favourable in the setting of bone metastasis.

Thus advances in availability of bone targeted treatments has brought about major changes in the clinical approach to management of patients with breast cancer. Their use as adjuvant therapy needs to be considered carefully in all patients. The benefits that can accrue from this are increasingly apparent, and they can be applied without impairing the efficacies of standard endocrine and chemotherapy programs.

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