E8. Bone metastases in breast cancer

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Introduction

The skeleton is the most common site of metastatic disease in breast cancer and the most common site of first distant relapse. The clinical consequences of cancer-mediated bone destruction are a source of misery for breast cancer patients. Complications of tumour bone disease include severe and incapacitating pain, requirement for radiotherapy, pathological fractures, requirement for bone surgery, spinal cord compression and hypercalcaemia [1]. Patients with bone metastases only have a much higher rate of skeletal-related events (SREs) than patients with bone and visceral metastases [2]. Taken from data for placebo groups of randomised bisphosphonates trials, the mean skeletal morbidity rate in breast cancer, i.e. the mean number of objective SREs per year, varies between 2.2 and 4.0. Bone destruction due to metastatic infiltration is essentially mediated by the osteoclasts, the formation of which is stimulated by secretory products of tumour origin. The bone cells and the bone matrix release various growth factors and cytokines, in particular insulin-like growth factors (IGFs), which stimulate the proliferation of tumour cells. Transforming growth factor-beta (TGF-β) is also released and activated during bone resorption and will stimulate the secretion of parathyroid hormone-related protein (PTHrP) by breast cancer cells, leading to a further increase in the recruitment of osteoclasts [3]. Bisphosphonates are able to interrupt this vicious circle by acting directly on the osteoclasts and maybe also on tumour cells [4].

The indications for bisphosphonate therapy go from the correction of cancer hypercalcaemia to the prevention of cancer-treatment-induced bone loss.

Tumour-induced hypercalcaemia

Tumour-induced hypercalcaemia (TIH) is an adverse prognostic factor implying a median survival of 3–4.5 months. The newer bisphosphonates, ibandronate and especially zoledronic acid, achieve better results than pamidronate for patients with severe hypercalcaemia. Success rates are generally above 90% [5].

Metastatic bone pain

Bisphosphonates are useful co-analgesics for the treatment of moderate to severe bone pain. Placebo-controlled trials have shown that all bisphosphonates exert analgesic effects. An American Society of Clinical Oncology (ASCO) panel considered it reasonable to start bisphosphonate treatment in women with abnormal bone scan with localised pain and normal plain radiographs, but not if the abnormal bone scan is asymptomatic [6]. The administration of a high 'loading' dose of ibandronate could be especially useful in patients with severe bone pain and this concept is now being tested in controlled trials [7].

Prevention of the complications of tumour bone disease

For patients with metastatic disease demonstrated on plain films, computed tomography (CT) or magnetic resonance imaging (MRI), the ASCO panel recommended to start either pamidronate 90 mg over 2 h or zoledronic acid 4 mg over at least 15 min administered every 3–4 weeks [6]. Placebo-controlled trials have established that, when administered over a prolonged period by the oral route (clodronate and ibandronate) or by the intravenous route (pamidronate, ibandronate and zoledronic acid), bisphosphonates reduce the skeletal morbidity rate by 25–40% in patients who present with breast cancer metastasised to bone. It has been shown in a 2-year controlled comparative trial between pamidronate and zoledronic acid that this latter compound has a superior efficacy by using a multiple event analysis according to the Andersen–Gill model as the likelihood of getting a SRE during therapy is reduced by 20% [8]. Zoledronic acid is also more convenient to administer than pamidronate. However, rare cases of acute tubular necrosis have been reported after the completion of the phase III trials. This has led to the recommendation that serum creatinine, and more recently creatinine clearance, be checked before each zoledronic acid infusion. Zoledronic acid 8 mg was not more effective than the 4 mg dose level, which suggests that we have reached some form of a ceiling effect at least with classical therapeutic schemes. Ibandronate is well tolerated by the oral or

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the intravenous route. In phase III trials, this compound had a renal safety profile similar to placebo [9]. Recent data suggest that the long-term administration of 50 mg of oral ibandronate has a comparable efficacy to monthly 6-mg infusions [10]. A short-term face-to-face trial comparing intravenous zoledronic acid with oral ibandronate has shown a comparable degree of inhibition of bone resorption, and comparative trials between these two potent bisphosphonates have now started using clinical endpoints. Osteonecrosis of the jaw has recently been reported in patients on bisphosphonate therapy, but the pathogenesis of this dramatic complication remains largely unknown [11]. Lastly, the ASCO panel recommends that, once initiated, intravenous bisphosphonates should be continued until "evidence of a substantial decline in a patient's general performance status" [6]. However, the long-term consequences on bone health of a quite prolonged therapy with very potent bisphosphonates are unknown and some experts prefer to adjust therapy to the individual patient and maybe to the levels of biochemical markers of bone resorption.

Prevention of bone metastases

Bisphosphonates have the potential to reduce tumour burden in bone, whether indirectly by decreasing bone turnover or directly by some anti-tumour effects. Available clinical data remain, however, limited. A recent double-blind placebo-controlled trial involving more than 1000 unselected breast cancer patients after surgery has shown that a 2-year treatment with 1600 mg clodronate daily can reduce the incidence of bone metastases by about one-half and also prolong survival [12]. Although of considerable interest, the use of bisphosphonates as an adjuvant treatment for breast cancer should still be regarded as experimental. Quite importantly, it will be essential to select the patients at high risk of developing bone metastases before recommending a general primary preventive use of bisphosphonates in the adjuvant setting.

Prevention of cancer-treatment-induced bone loss

Much effort is now devoted to demonstrate the clinical usefulness of bisphosphonates for the prevention of cancer-treatment-induced bone loss (CTIBL), especially during administration of aromatase inhibitors in the adjuvant setting. As a consequence of CTIBL, patients are indeed at greater risk for fractures [13]. Bisphosphonates are now recommended for all patients who are osteoporotic before starting aromatase inhibitor therapy or who become so during therapy.

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