Bisphosphonates for care and cure

Jean-Jacques Body

CHU Brugmann, Department of Medicine, Université Libre de Bruxelles, Brussels, Belgium

The skeleton is the most common site of metastatic disease in breast or prostate cancer and the most common site of first distant relapse. Complications of metastatic bone disease (skeletal-related events, SREs) include severe and incapacitating pain, need for radiotherapy, pathologic fractures, need for bone surgery, spinal cord compression and hypercalcaemia. Across all tumour types, patients with breast cancer have the highest incidence of skeletal complications. Taken from data in placebo groups of randomised bisphosphonate 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. The mean skeletal morbidity rate per year is around 1.5 in patients with prostate cancer metastatic to bone [1,2]. Bone destruction due to metastatic infiltration is essentially mediated by the osteoclasts. The dissemination of breast cancer cells to the bone marrow instigates a vicious self-sustaining cycle of destruction, whereby individual tumour cells release growth factors that stimulate production of Receptor Activator for Nuclear Factor kappa B Ligand (RANKL) from stromal cells and osteoblasts, leading to the activation of osteoclasts. These activated osteoclasts resorb bone matrix liberating potent growth factors that promote tumour cell colonisation, inhibit apoptosis, and drive proliferation [3]. Bisphosphonates are potent inhibitors of osteoclasts, thereby interrupting this self-perpetuating cycle.

Bisphosphonates are the standard of care for tumour-induced hypercalcaemia (TIH) with success rates generally above 90%. They are also useful co-analgesics for the treatment of moderate to severe bone pain. Bisphosphonate therapy has become the current standard of care for metastatic bone cancer as they decrease the risk of SREs by 25–50% and slow the rate of development of SREs. 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 significantly reduce the skeletal morbidity rate 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 [4]. Zoledronic acid is the only bisphosphonate with demonstrated efficacy in all tumour types, notably hormone-refractory prostate cancer. However, rare cases of acute tubular necrosis have been reported after the completion of phase III trials. This has led to the recommendation that creatinine clearance be checked before each infusion. Osteonecrosis of the jaw is a complication of prolonged bisphosphonate therapy. The frequency of this dramatic complication can be reduced by excellent oral hygiene and appropriate dental care before and during therapy. Zoledronic acid 8 mg has not been 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. Much hope is placed in denosumab, a specific and potent inhibitor of RANKL, to improve the results currently obtained with potent bisphosphonates [5]. For patients with metastatic disease demonstrated on plain films, CT or MRI, an ASCO panel recommended to start either pamidronate or zoledronic acid and to administer them until marked deterioration of the patient's general performance status [6]. An international expert panel more recently advised that, to maximise the benefit of treatment, clinicians should consider the start of bisphosphonate therapy as soon as bone metastases are diagnosed by radiographic techniques, even if they are asymptomatic. Benefit of bisphosphonate therapy has been shown for a treatment duration of up to 2 years. Since the risk of SREs is going to continue, the expert panel – in the absence of supporting data – recommended that the decision to continue therapy beyond 2 years should always be based on an individual risk assessment [7].

Preclinical and emerging clinical data indicate that bisphosphonates have the potential to prevent the development of skeletal metastases in patients with cancer. Several *in vitro* and animal studies have shown that they can exert direct anti-tumour effects (e.g. [8]). There is also reason to believe that nitrogen-containing

bisphosphonates may exert their anti-tumour effects outside of the bone milieu. The combination of zoledronic acid with chemotherapeutic agents produces synergistic anti-tumour activity in a primary breast cancer murine model [9]. These findings were further supported by preliminary data from the AZURE trial demonstrating that the addition of zoledronic acid to neoadjuvant chemotherapy resulted in smaller residual tumour size and a higher proportion of patients achieving a pathological complete response when compared with chemotherapy alone (data not shown). Recently, zoledronic acid decreased the incidence of metastatic disease in premenopausal patients receiving adjuvant treatment with goserelin plus either tamoxifen or an aromatase inhibitor [10]. The addition of zoledronic acid resulted in a statistically significant 36% reduction in the risk of a disease free survival (DFS) event with also a trend towards an improvement in survival. Although only 137 DFS events had occurred at the time of reporting, zoledronic acid appeared to reduce all categories of breast-cancer related DFS events, namely distant osseous and non-osseous recurrences, loco-regional recurrences, and contralateral primary breast cancers. Subgroup analysis suggested that the observed benefit from the addition of zoledronic acid may have been driven by the anastrozole cohort, lending support to the hypothesis that bisphosphonates may eliminate the fertile breeding ground induced by aromatase inhibitors that increase bone turnover. Preliminary data from another trial (Z-FAST) also suggest a decreased recurrence rate in patients starting zoledronic acid immediately after beginning aromatase inhibitor therapy. It is, nevertheless, too early to claim that early use of bisphosphonates decreases recurrence rate in and outside bone and should largely be prescribed in the adjuvant setting. Reserving final judgment until the results of other adjuvant trials are available is adequate [11]. Further work is also required to more reliably identify the patients at high risk for bone metastases who could benefit from bisphosphonates or other potentially useful bone-targeted therapy in the adjuvant setting.

Conflict of interest statement

None declared.

References

1 Plunkett TA, Smith P, Rubens RD. Risk of complications from bone metastases in breast cancer. implications for management. *Eur J Cancer* 2000;**36**:476–82.

2 Body JJ. Treatment and prevention of bone metastases and myeloma bone disease. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington DC: The American Society for Bone and Mineral Research; 2008. p. 397–404.

3 Roodman GD: Mechanisms of bone metastasis. *N Engl J Med* 2004;**350**:1655–64.

4 Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;**98**:1735–44.

5 Coleman RE, Guise TA, Lipton A, et al. Advancing treatment for metastatic bone cancer: Consensus recommendations from the Second Cambridge Conference. *Clin Cancer Res* 2008;**14**: 6387–95.

6 Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;**21**:4042–57.

7 Aapro M, Abrahamsson PA, Body JJ et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. *Ann Oncol* 2008;**19**:420–32.

8 Daubine F, Le Gall C, Gasser J, Green J, Clezardin P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst* 2007;**99**:322–30.

9 Ottewell PD, Monkkonen H, Jones M, et al. Antitumor effects of doxorubicin followed by zoledronic acid in a mouse model of breast cancer. *J Natl Cancer Inst* 2008;**100**:1167–78.

10 Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;**360**:679–91.

11 Bedard P, Body JJ, Piccart M. Sowing the soil for cure? The recently published results of the ABCSG-12 trial open a new chapter in the evolving adjuvant bisphosphonate story in early breast cancer. *J Clin Oncol* [in press].