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Bisphosphonates and metastatic bone disease

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introduction

Malignant bone disease is a frequent complication of several common solid tumours including breast, lung, prostate and renal cancer. A greater understanding of tropic bone tumour cells, especially the understanding of those properties which lead to their successful growth within the bone microenvironment is the first step to devise innovative approaches.

Bone metastases are generally characterized as osteolytic, leading to bone destruction, or osteosclerotic (osteoblastic), leading to new bone formation. The classification of bone metastases as either osteolytic or osteoblastic is the schematic representation of a complex phenomenon wherein both biological scenarios coexist. Breast, lung and renal cancer metastases are usually osteolytic, on the other hand prostate cancer metastases are usually osteoblastic. The type of metastasis is a reflection of the primary mechanism of interference between tumour cells and the bone remodelling system. Hence, the development of osteolytic and osteoblastic lesions results from a functional interaction between tumour cells and osteoclasts or osteoblasts, respectively. Bone is a dynamic organ composed of cells of various embryonic origins; with regards to bone disease two cell types, osteoclasts and osteoblasts regulate bone modelling that occurs during development and bone remodelling that occurs in the adult. Osteoclasts are derived from precursors in the mononuclear-phagocyte lineage and are responsible for bone resorption [1]. Osteoblasts are derived from the stromal cell lineage and are responsible for laying down new bone matrix. A significant factor regulating bone remodelling is the direct interaction between osteoblasts and osteoclasts. The expression of RANK ligand (RANKL) on the surface of osteoblasts engages the receptor, RANK, on osteoclast precursors, leading to their maturation. Hence, osteoclasts release proteases that resorb bone matrix. In addition, a plethora of systemic and locally acting factors deriving from endocrine, immune, and other systems can impact osteoclast and osteoblast function, including the urokinase-type plasminogen activator (uPA), platelet derived growth factor (PDGF), endotheline-1 (ET-1), tumour necrosis factor (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), paratyroid hormone-related protein (PTHrP), the insulin-like growth factor (IGF) and transphorming growth factor beta (TGF-beta). Such factors can enhance the activity of osteoclasts either indirectly through stimulating the expression of RANKL on osteoblasts, or through direct effects on osteoclast and osteoblast function. On the contrary osteolysis is suppressed by osteoprotegerin (OPG) which inhibits RANKL binding to the RANK receptor. In according to the above described mechanism breast cancer cells without RANKL expression fail to sustain osteoclastic activity [2].

From a clinical point of view, the epiphenomenon of this biological scenario is represented by bone disease and ultimately, for patients, in a significant skeletal morbidity, which can decrease the quality of life and, potentially, survival. Median survival after the development of bone metastases ranges from 6–48 months, depending on tumour type.

The potential complications of bone metastases include pain, hypercalcemia, pathological fractures and spinal cord compression. Based on this background it is easy to understand why the preservation of skeletal health is emerging as an important aspect of patient care in the oncology setting.

The management of skeletal complications is based on a multidisciplinary approach which includes radiotherapy, radiopharmaceuticals, orthopaedic surgery, chemotherapy, hormone therapy and bisphosphonates. The aim of a multidisciplinary approach in the management of bone metastases includes pain relief combined with restoration of skeletal function and improvement patients' quality of life.

bisphosphonates

Bisphosphonates are taken up by the bone at sites of active bone metabolism [3]. They inhibit osteoclast activity and survival hence reducing osteoclast mediated bone resorption. The binding with mineralised bone matrix is promoted by a central structure containing a phosphorus-carbon-phosphorus sequence (P-C-P), while a variable R' chain determines the mechanism of action, the potency and side effects. According to the type of R' chain bisphosphonates can be divided in two groups: first group includes etidronate and clodronate which lack nitrogen in their molecules; in the second group there are the newer nitrogen-containing bisphosphonates, such as zoledronic acid, pamidronate and ibandronate. The first group either forms cytotoxic metabolites in ostoclasts or inhibits protein tyrosine phosphatases. The second group inhibits the mevalonate pathway in osteoclasts. This prevents the post-translational modification of small GTPase signalling proteins such as RAS, which are important for osteoclast function [4].

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Bisphosphonates also cause apoptosis in osteoclasts, and may have direct apoptotic effects in tumour cells. The nitrogen containing bisphosphonates are much more potent than first generation compounds and inhibit bone resorption at micromolar concentrations. The clinical activity in terms of clinical benefits have been evaluated in several large clinical trials, evaluating as primary end point efficacy the time to first skeletal event, fractures, the need of radiotherapy, spinal cord compression, hypercalcemia related to malignancy, the percentage of patients with more than 1 skeletal event. Most trials have used a composite end point, with the aim of capturing data on all clinically relevant events which may influence the morbidity of the pts [5]. These models calculate the cumulative incidence of skeletal complications and provide sensitive and extensive assessment of bisphosphonates in cancer patients with bone metastases.

Currently the four most used bisphosphonates in metastatic bone disease are oral clodronate and ibandronate, and intravenous pamidronate, zoledronate and ibandronate. Among these all but one, clodronate, are nitrogen-containing bisphosphonates.

clodronate

Oral clodronate has been approved for osteolytic and bone pain associated with skeletal metastases in patients with breast carcinoma or multiple myeloma. Oral clodronate is administered at a dose ranging from 800 to 2400 mg daily. Only 5% of the orally administered dose is absorbed. It is recommended one hour pre-food fasting period to help absorption, which in combination with the higher doses required (and the large size of the tablets) may reduce patients' compliance. In at least three randomised trials performed in breast cancer patients, oral clodronate showed activity as compared to placebo [6–8]. In the first study oral clodronate significantly reduced the event rate for hypercalcemia, vertebral fractures, vertebral deformity, and the combined event rate for all events. In the remaining trials oral clodronate delayed the time to the first event. Oral clodronate was less effective than the newer bishosphonates at reducing the risk of skeletal related events in breast cancer patients with bone metastases. Two major randomized trials have been performed to date in multiple myeloma. Lahtinen et al. [9] reported the reduction of the development of new osteolytic lesions by 50% in myeloma patients who received oral clodronate for 2 years. In the other study [10], after 1 year of follow-up, both vertebral and non-vertebral fractures as well as the time to first non-vertebral fracture and severe hypercalcemia, were reduced in the clodronate group. At 2 years, the patients who received clodronate had better performance status and less myeloma-related pain than patients treated with placebo [11, 12]. Finally oral clodronate failed to demonstrate superior activity compared to placebo in preventing skeletal complications in prostate cancer patients [13].

pamidronate

Pamidronate has been approved for osteolytic and bone pain associated with skeletal metastases in patients with breast carcinoma and multiple myeloma. An oral formulation is not available and the drug must be infused over 2 h at 60 or 90 mg every 3–4 weeks. Two large randomised placebo-controlled studies demonstrated that pamidronate is efficacious and safe when administered to breast cancer patients with bone metastses [14, 15]. In both the above mentioned studies pamidronate significantly reduced and delayed the onset of skeletal related events (pathological fractures, spinal cord compression, surgery, hypercalcemia, and the need of radiotherapy). In a pooled analysis of the two studies a reduction in pain and analgesic use was observed as compared with placebo [16].

In a double-blind, placebo-controlled patients with multiple myeloma and at least one lytic lesion were randomized to placebo or intravenous pamidronate [17, 18]. The mean number of SREs per year and the median time to the first skeletal event were reduced in the pamidronate group. Pain scores and quality of life were also significantly improved in the pamidronate group. Although there was no difference in terms of survival between the two treatment groups, this study identified a subgroup of patients, who had received more than one previous anti-myeloma regimen, in which pamidronate was associated with prolonged survival [18].

The Cochrane Myeloma Review Group has reported a meta-analysis based on 11 trials and involving 2183 assessable patients. This review concluded that both pamidronate and clodronate reduce the incidence of hypercalcemia, the pain index and the number of vertebral fractures in myeloma patients [19].

zoledronate

Zoledronate recently received broad regulatory approval for the treatment of bone metastases secondary to all solid tumour types and bone lesions from multiple myeloma. Zoledronate was compared with pamidronate in 1648 pts with bone disease from breast cancer or myeloma [20]. The primary endpoint was the proportion of patients with at least 1 skeletal-related event (SRE), defined as pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone. Secondary analyses included time to first SRE, skeletal morbidity rate and multiple-event analysis. After 25 months of follow-up, zoledronic acid reduced the overall proportion of patients with an SRE and reduced the skeletal morbidity rate similar to that of pamidronate. Most notably, multiple events showed that zoledronic acid significantly reduced the development of SREs by an additional 16% compared with pamidronate during the 2 years of treatment.

The efficacy and safety of zoledronic acid in patients with bone metastases secondary to solid tumours other than breast or prostate cancer was demonstrated in a phase III randomised double blind study [21].

Among 773 patients with bone metastases from lung cancer or other solid tumours, the proportion of those with an SRE was reduced in both zoledronic acid groups compared with the placebo group.

Additionally, 4 mg zoledronic acid significantly increased time to first event and significantly reduced the risk of developing skeletal events by multiple event analysis.

ibandronate

Ibandronate has been approved in both IV and oral formulations for the prevention of skeletal events in breast cancer and bone metastases.

In preclinical studies ibandronate was more potent than pamidronate in inhibiting the adhesion and spread of MDA-MB-231 breast cancer cells to mouse trabecular bone [22]. Boissier et al. demonstrated that ibandonate is able to inhibit migration and invasion of breast cells in experimental in vitro models [23]. This inhibition was further decreased by the addition of paclitaxel or docetaxel, suggesting an additive effect between ibandronate and the two cytotoxic drugs [24]. Recent data suggest that ibandronate enhances the growth inhibitory effects of the antiestrogens tamoxifen and fulvestrant in vitro [25]. Furthermore ibandronate is able to inhibit both proliferation and realignment of human umbilical vein endothelial cells. Finally Fromigue et al. demonstrated, in two different cell lines, MCF7 and T47D respectively, that ibandronte is able to counteract the proliferative effect of IGF-1 and IGF-2 [26]. It is important to note that ibandronate was most effective in inhibiting the growth of bone metastases when given prior to or shortly after tumour cell inoculation. The above pre-clinical data have clear clinical implications for future studies in the adjuvant setting in order to clarify the role of ibandronate.

Ibandronate is the only third generation aminobisphosphonate, developed in both i.v. and oral formulations for the managment of metastatic bone disease. The oral formulation, instead of clodronate, is characterized by easy-to-swallow tablets taken once a day. Pharmakokinetic studies have demonstrated that for the oral formulation of ibandronate there is a linear dose-dependent increase in the plasma concentrations. This ensures predictability of response to a given oral dose, thus reducing safety concerns [27]. The peak plasma concentrations are highest when the drug is administered before food intake.

The safety and efficacy of oral ibandronate were evaluated in two pooled phase III studies [28]. In these trials, patients with breast cancer and bone metastases were randomised to receive oral ibandronate 50 mg or placebo once daily for up to 96 weeks. The primary end point was the skeletal morbidity period rate (SMPR), defined as the number of 12-week periods with new skeletal complications.

Oral ibandronate significantly reduced the mean SMPR compared with placebo. There was a significant reduction in the mean number of events requiring radiotherapy and/or surgery. Regression analysis confirmed that oral ibandronate significantly reduced the risk of a skeletal event compared with placebo. Overall these data demonstrated that oral ibandronate 50 mg is an effective, well-tolerated and convenient treatment for the prevention of skeletal complications in metastatic bone disease.

In a third trial 466 patients were randomised to receive placebo or 2 mg or 6 mg i.v. ibandronate every 3–4 weeks for up to 2 years [29]. The primary efficacy parameter was the number of 12-week periods with new bone complications, expressed as SMPR. SMPR was lower in both ibandronate groups compared with the placebo group; the difference was statistically significant for the 6 mg ibandronate group. Based on these above mentioned data recommended doses are 6 mg i.v. every 3–4 weeks and 50 mg oral ibandronate daily. Finally two randomised, double-blind, phase III trials have been designed to compare either i.v. ibandronate (administered over a shorter 15-min infusion time) or oral ibandronate with an i.v. zoledronic acid in 450 patients over 24 weeks.

The safety and convenience of treatment are an important issue when choosing a bisphosphonates. This is due to a 'ceiling effect', which has been reached for the currently used bisphosphonates, at least in terms of their ability to prevent skeletal-related events.

Over the past few years, case reports and randomised trials have shown a non-negligible risk for renal toxicity with some i.v. bisphosphonates.

In phase III studies, i.v. ibandronate had a renal safety profile comparable with that of placebo for 2 years of treatment, and non-controlled extension studies showed that long-term use (up to 4 years) showed no additional renal safety concerns [29].

Several open-label studies seem to suggest that i.v. ibandronate administered on consecutive days can provide rapid relief from severe bone pain. In a trial of 18 patients with severe opioid-resistant bone pain resulting from various primary tumours, 4 mg i.v. ibandronate was administered on 4 consecutive days (total dose, 16 mg), leading to significantly reduced bone-pain scores from baseline within 7 days [30]. The reduction was sustained throughout the 6-week study period. Ibandronate also significantly improved scores for quality of life, patient functioning, and performance status.

renal toxicity and osteonecrosis of the jaw

Most bisphosphonates that reach the circulation are rapidly bound to bone and skeletal uptake depends on bone turnover. The remainder of the bisphosphonates is not metabolized and is eliminated unchanged by the kidneys through the glomerular filtration and active tubular excretion [31]. Although all bisphosphonates induce renal damage, their potential to cause renal failure are different.

It has been suggested that the mechanism of bisphopshonate-induced renal toxicity is the aggregation of precipitated bisphosphonate or calcium complexes in the kidney [32]. However, no corpuscular precipitation was reported during renal histopathological analyses in animals. Therefore, it has been postulated that a more probable mechanism is that bisphosphonates induce renal cell death in a manner similar to what happens in the bone [33].

Both single and intermittent dosing led to similar incidences of proximal tubular degeneration and single-cell necrosis. Intermittent doses of zoledronate, however, induced a higher incidence and severity of renal damage than a single dose. Even if the precise reasons are not yet fully understood, available clinical data indicate that they may be influenced by pharmacokinetic properties such as renal tissue half-life or protein binding and intracellular potency. Zoledronate is not recommended in patients with bone metastases and severe renal impairment. Factors such as dehydration and the use of other nephrotoxic drugs that predispose patients to renal

deterioration should be identified and managed if possible. The recommended dose of ibandronate for metastatic bone disease is 6 mg infused over 1 hour every 3–4 weeks. There is no need for adjustement in patients with mild or moderate renal impairment (creatinine clearance ≥30 ml/min). In addition, ibandronate can be used in patients with severe renal impairment. In these patients the dose must be reduced to 2 mg infused over 1 hour every 3–4 weeks to maintain the same drug exposure achieved with 6 mg standard dose. There are no dose restrictions for ibandronate in patients who are also receiving cancer therapies with nephrotoxic side effects [34]. Infusion times less than 2 h with pamidronate or less than 15 min for zoledronate should be avoided [35]. Unexplained renal dysfunction requires the discontinuation of pamidronate or zolendronate until these renal problems have been resolved. Unexplained renal dysfunction is defined as an increase of ≥0.5 mg/dl in serum creatinine or an absolute value of more than 1.4 mg/dl among patients with normal baseline serum creatinine levels. These patients should be reassessed every 3–4 weeks and bisphosphonate should be reinstated with caution when the renal function returns to baseline.

osteonecrosis of the jaw

In 2004, the International Myeloma Foundation conducted a web-based survey to assess the risk factors for osteonecrosis [34]. With censoring the survey at 36 months, osteonecrosis of the jaw developed in 10% of 211 patients receiving zoledronic acid, as compared to 4% of 413 patients receiving pamidronate ($P = 0.002$). The estimation of osteonecrosis, suspicious findings, or both did not differ between patients with myeloma and those with breast cancer.

Recently, Hoff et al. reviewed spontaneous reports, data from controlled clinical trials and data from MDACC, concluding that the incidence of osteonecrosis could be estimated of 0.034%.

A recent publication reviewed 18 cases of cancer patients with osteonecrosis of the jaw, describing history of the lesions, radiographic appearance and treatment [36]. In most patients, the lesions initially occurred after dental extraction, while in other cases accidental trauma by the patient to the involved area was identified. Some patients, however, could not recall a possible causative event.

All of those patients developed lesions while actively receiving bisphosphonates in addition to cancer therapy. Pain and oral discomfort were often the first symptom. The most common clinical finding was an area of ulcerated mucosa and exposed devitalised bone. The exposed bone had a yellow-white discoloration and the surrounding soft tissue areas were often inflammed due to secondary mucosal infection and painful. Probing of the bone was asymptomatic, and bleeding did not occur. Pain appears to have resulted from either secondary infection of surrounding tissues or from trauma to opposing soft tissue areas. The most common site of osteonecrosis was the posterior/lingual mandible, in the area of mylohyoid ridge. Bone necrosis was typically progressive.

Depending on the stage of development of the necrosis, radiographic evaluation did not add substantive value to the clinical database.

Histopathology demonstrated areas of chronic inflammation represented by a mixed cellular infiltration and capillaries. Bone osteoclasts or vascularization were not prominent and the diagnosis was consistent with necrosis.

Authors have sought those patients who reached the hospital because of treatment for intraoral bone necrosis that occurred spontaneously after dental extraction or oral trauma. All these patients presented with a history of a primary malignancy, including myeloma, breast carcinoma or prostate cancer and were all being treated with iv pamidronate or zoledronate to control skeletal complications.

Finally recent data seem to suggest that the length of exposure to bisphosphonates could be the most important risk factor for this complication, while previous dental procedures may be a precipitating factor [37].

conclusions

Bisphosphonates play an important role in the multidisciplinary management of metastatic bone disease and represent the standard care for the prevention and treatment of skeletal-related complications from metastatic bone disease. It is important to note that bisphosphonates, by reducing the reabsorption of bone, are able to reduce pain in osteolytic bone metastases. Albeit they are not strictly analgesic drugs and as a consequence are usually used in combination with a pharmacological approach according to the WHO analgesic ladder. The ongoing trials for the prevention of bone metastases and treatment-related bone loss in cancer pts suggest that we can open a new window in this exiting and intriguing area.

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