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Bisphosphonates for metastatic bone disease: a therapeutic rationale

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Abstract

Metastatic bone disease is a common clinical occurrence in patients with advanced malignancy. Bisphosphonates target the underlying pathophysiology of skeletal metastases by inhibiting the activity of osteoclasts reducing bone turnover. By effectively reducing skeletal complications and improving patient quality of life, mobility and functioning, bisphosphonates have become a standard of care in this indication. Currently, most patients with metastatic bone disease are managed with intravenous (i.v.) bisphosphonates infused every 3–4 weeks. This requires regular hospital treatment and close patient monitoring for renal adverse events. Although daily oral bisphosphonate therapy is available as an alternative to i.v. dosing, its clinical utility is compromised by unpleasant gastrointestinal side effects and dosing inconvenience. The third-generation bisphosphonate ibandronate has been formulated as an i.v. and an oral therapy for the management of metastatic bone disease. Clinical trial data demonstrated that ibandronate reduces the risk of skeletal complications, relieves bone pain, improves quality of life and is well tolerated in patients with bone metastases from breast cancer. The availability of ibandronate will widen bisphosphonate treatment options for metastatic bone disease.

1. Introduction

Metastatic bone disease is an important clinical problem in advanced cancer, most commonly occurring in patients with breast cancer, multiple myeloma, prostate cancer and lung cancer [1,2]. Skeletal metastases lead to significant morbidity, with clinical features which include bone pain, pathological fractures, spinal cord compression, and hypercalcemia of malignancy [3]. The need for radiotherapy or surgery to treat the symptoms and complications of metastatic bone disease has further detrimental impacts on patient quality of life and mobility. Controlling skeletal metastases and reducing their complications are therefore key therapeutic goals. In recent years, bisphosphonates have become the cornerstone of treatment for metastatic bone disease [4–6]. This paper outlines the rationale for the use of bisphosphonates in this indication.

1.1. Pathophysiology of bone metastasis

In healthy individuals, the ongoing processes of bone remodelling are mediated by osteoclasts (bone resorption) and osteoblasts (new bone formation), and the activity of osteoclasts and osteoblasts is closely coupled. In patients with malignant disease, tumour cells secrete a number of humoral factors that are known to act on bone, kidney and gut, altering normal calcium homeostasis. Growth factors released from tumour cells, such as parathyroid hormone-related protein and transforming growth factor beta, stimulate osteoclast activity to increase bone resorption, leading to a loss of overall bone mass [7–9]. Some patients will go on to develop hypercalcaemia, a severe and potentially life-threatening complication [8–11]. Abnormal changes to the bone surface mean that areas of bone resorption are no longer recognised as sites for new bone formation, resulting in new bone being laid down inappropriately elsewhere [7].

The uncoupling and imbalance of bone resorption and formation result in reduced skeletal integrity and lead to the skeletal complications and symptoms of metastatic bone disease. Patients are at high risk of spontaneous long-bone fractures, and axial skeletal compression fractures. It has been estimated that patients with advanced disease experience a major skeletal event on average every 3–4 months [7]. Functional ability is impaired, and patient quality of life is greatly affected. Bone pain and subsequent mobility problems affect between 45–75% of patients with metastatic bone

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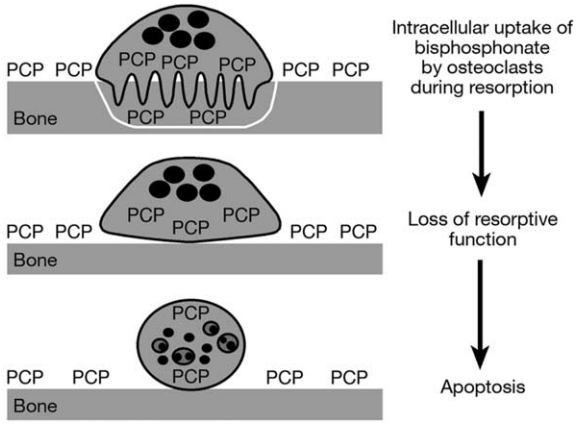

Fig. 1. Mechanism of action of bisphosphonates (reproduced with permission) [9].

disease [1,3], adding to the morbidity burden already experienced from the underlying malignant disease.

1.2. Bisphosphonates: mechanism of action

Since the increased activity of osteoclasts is a key factor in the development of altered bone turnover and skeletal complications, agents that inhibit osteoclast activity have provided treatments for metastatic bone disease and the prophylaxis of skeletal-related events. Bisphosphonates are analogues of pyrophosphate with a stable phosphorus-carbon-phosphorus (PCP) bond, which bind to mineralised bone matrix (and preferentially to active sites of bone remodelling). Once bound, bisphosphonates act directly on the resorption activity of mature osteoclasts, slowing the development of metastases. Proposed mechanisms of osteoclast inhibition include changes to the cytoskeleton, changes in enzyme activity, and the induction of apoptosis (Fig. 1) [12–14].

Different generations of bisphosphonates are reported to have slightly differing mechanisms of action. Older, non-nitrogen containing bisphosphonates such as clodronate are thought to be incorporated into non-hydrolysable analogues of ATP, while the newer, nitrogen-containing bisphosphonates such as pamidronate, zoledronic acid and ibandronate inhibit the mevalonate pathway [15–16]. *In vitro* and *in vivo* studies also suggest that newer generation bisphosphonates are more effective inhibitors of bone resorption than older agents [17]. It is less clear whether or not this translates to improved clinical efficacy.

Pre-clinical studies suggest that bisphosphonates may also have direct antitumour effects, and could therefore have a future role as adjuvant therapy in patients at risk of developing metastatic bone disease. Reported antitumour effects include the induction of apoptosis, and the inhibition of cell growth, invasive behaviour and angiogenic factors [14,16,18].

1.3. Current bisphosphonate treatment of metastatic bone disease

In recent years, bisphosphonates have become a standard of care for the management of metastatic breast cancer [19–28]. The dosing regimens of available bisphosphonates are shown in Table 1.

Currently, most patients with metastatic bone disease are managed with i.v. bisphosphonates infused every 3–4 weeks [6]. Although effective against skeletal complications, i.v. agents have their disadvantages. Hospital visits for infusions are often lengthy, which is inconvenient for the patient and costly to administer. Despite being indicated for 15-min infusion in the product labelling, average hospital visit duration for infusions has been estimated at over 1 h for zoledronic acid [29]. In the same study, the average duration of a clinic visit for pamidronate infusion was almost 3 h [29]. Zoledronic acid and pamidronate may cause renal toxicity in rare cases [30–32], and close renal function monitoring is required. Elevated serum creatinine levels (defined by increases of 0.5 mg/dL if baseline <1.4 mg/dL or 1.0 mg/dL if baseline $\geqslant 1.4$ mg/dL; or an increase of twice the baseline value) were reported in 8–9% of patients receiving zoledronic acid or pamidronate in a clinical trial [26]. Discontinuation of treatment may be necessary in some patients, due to renal impairment [33]. Infusion-related reactions may also occur (typically on the first infusion, but occasionally during subsequent infusions).

The burden of i.v. therapy on the patient and on hospital resources could be reduced by use of oral bisphosphonate therapy, administered on an outpatient basis. Although oral clodronate, an older-generation bisphosphonate, is available for the treatment of metastatic bone disease, its use is associated with unpleasant gastrointestinal (GI) side effects [34,35]. Patients may also find the recommended dosing regimen difficult to

Table 1
Bisphosphonates for metastatic bone disease—available treatment regimens

Bisphosphonate	Intravenous regimen	Oral regimen
Clodronate	900 mg infused over 2–4 h every 3–4 weeks (rarely used)	1040–2400 mg daily
Pamidronate	45 mg, 60 mg or 90 mg; infused over >2 h every 3–4 weeks	Not available as an oral formulation
Zoledronic acid	4 mg infused over 15 min every 3–4 weeks	Not available as an oral formulation

adhere to (typically multiple daily doses, with a 1-h pre-food fast). Poor compliance may further compromise the effectiveness of treatment.

1.4. Ibandronate: a new bisphosphonate for metastatic bone disease

Ibandronate is a third-generation, aminobisphosphonate which has been used in the treatment of hypercalcaemia of malignancy in several European countries since 1996. Ibandronate has been developed as an i.v. dose (6 mg infused over 1 h every 3–4 weeks) and an oral formulation (50 mg/day taken as a single tablet before breakfast). Phase III studies have evaluated the efficacy and safety of ibandronate in patients with bone metastases from breast cancer and the results are presented in this supplement [36–39]. They demonstrate that both formulations of ibandronate reduce the skeletal complications and symptoms of metastatic bone disease, and are well-tolerated [40–44]. Oral ibandronate is suitable for long-term, at-home maintenance therapy, which offers improved convenience when compared with regular hospital visits for infusions.

2. Summary

Bisphosphonates have an important role to play in the management of metastatic bone disease. Although currently available bisphosphonates are effective against skeletal complications, their clinical utility is reduced by renal and GI tolerability issues and inconvenient treatment regimens. Ibandronate has the potential to optimise metastatic bone disease management by offering a highly effective treatment with a superior renal safety profile the convenience of an at-home oral dosing option.

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