

ORIGINAL ARTICLE

Is there a role for ibandronate in the treatment of prostate cancer patients with bony metastases?

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Abstract

Purpose. Zoledronic acid is widely accepted as the treatment of choice for a number of cancers which metastasise to bone and is the only bisphosphonate licensed for the treatment of prostate cancer. However, drug related nephrotoxicity, although rare, does pose a significant complication when using zoledronic acid. Prostate cancer patients are generally older than 65 years of age and already exhibit some form of impaired renal function. Thus, for prostate cancer patients who are unable to tolerate zoledronic acid there is a need for an alternative bisphosphonate. One possibility could be ibandronate which is also a potent third generation, nitrogen-containing bisphosphonate and is an attractive choice for some patients due to the fact it is available in both intravenous and oral preparations. **Methods.** This article reviews the current published literature regarding the use of ibandronate in the treatment of metastatic prostate cancer. **Results.** Preliminary data emerging from small Phase II studies suggests ibandronate may provide a therapeutic alternative for the treatment of metastatic prostate cancer when zoledronic acid is deemed unsuitable. **Conclusion.** Further *in vivo* research with ibandronate in prostate cancer is urgently needed in order to elucidate whether this bisphosphonate may play a role in the treatment and palliative management of metastatic prostate cancer.

Worldwide, it is estimated that greater than 1.5 million cancer patients have bone metastases [1] with breast and prostate cancer accounting for more than 80% of the cases [2]. Since their introduction in the mid-1990s, bisphosphonates have been used for their therapeutic benefits in reducing osteoporosis, fractures, spinal cord compression and other conditions of bone fragility in patients with malignant bone disease (MBD). As a result, bisphosphonates have become part of the standard of care when treating MBD.

Bisphosphonates are analogues of the naturally occurring pyrophosphate, a substance that inhibits mineral deposition. The phosphoanhydride linkage (P-O-P) is replaced by a non-hydrolysable P-C-P bond. This P-C-P backbone and two covalently bound side chains (R¹ and R²), give rise to a variety of structures which differ in their pharmacologic properties and potency (Figure 1) [3]. As a result of their side chains, bisphosphonates can be grouped into two classes depending on their mode of action. The first generation are those which lack a nitrogen

containing functional group (clodronate, etidronate) and are metabolised intracellularly into non-hydrolysable ATP analogues [4]. The more recent generation of bisphosphonates contain either a nitrogen-containing aliphatic side chain (pamidronate, alendronate, ibandronate) or a heterocyclic ring (zoledronic acid) [5]. These nitrogen containing bisphosphonates are more potent than their earlier counterparts by several orders of magnitude (Figure 2). They act on the mevalonate pathway by inhibiting the enzyme farnesyl diphosphate synthase [6] and the post-translational prenylation of small GTPases of the Ras and Rho family [7].

Currently four bisphosphonates are used in the clinical setting for treating MBD. These are clodronate, pamidronate, zoledronic acid and ibandronate [8]. For breast cancer patients, oral clodronate, oral or intravenous (i.v.) ibandronate, i.v. pamidronate and i.v. zoledronic acid are recommended in European guidelines [9]. In prostate cancer only zoledronic acid is currently licensed for use [10]. Zoledronic acid has demonstrated the broadest

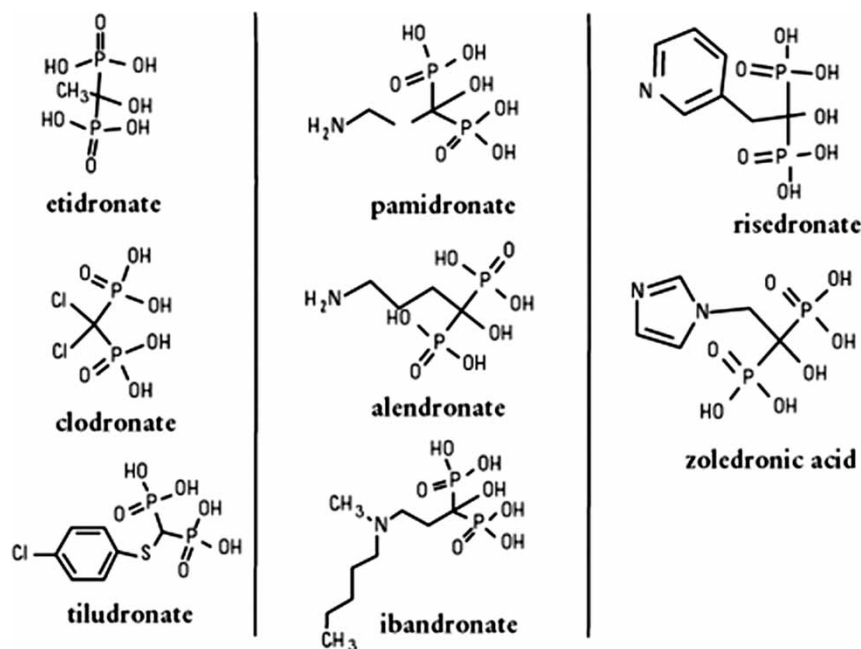


Figure 1. Different chemical structures of bisphosphonates.

clinical activity and is regarded as the most potent bisphosphonate. It is widely accepted as the treatment of choice and is the benchmark for the prevention of skeletal complications arising from bone metastases [11]. In prostate cancer patients with bone metastases, zoledronic acid reduces skeletal related events [10,12,13], prevent bone loss, by increasing bone mineral density and suppress N-telopeptide (NTX) and bone specific alkaline phosphatases, which are biochemical markers of bone resorption [14]. In addition, zoledronic acid can also prevent bone loss in non-metastatic prostate cancer patients receiving androgen deprivation therapy [15]. However, a significant side-effect,

although considered rare, associated with the use of zoledronic acid is renal toxicity [16–18]. Nephrotoxicity is potentially life-threatening [19,20]. In the USA, Chang et al. [21] highlighted 72 cases in which clinicians reported renal failure associated with zoledronic acid therapy to the Food and Drug Administration; 27 patients required dialysis, and 18 died. Other retrospective studies show renal toxicity associated with zoledronic acid [16,18,22, 23]. Prostate cancer patients are generally over 65 years of age and usually have pre-existing renal impairment. Thus, for prostate cancer patients who are unable to tolerate zoledronic acid or it is deemed unsuitable due to pre-existing renal impairment there is a need for an alternative bisphosphonate. One possibility could be ibandronate, another third generation bisphosphonate, which was licensed for use in patients with metastatic breast cancer in the European Union in 2003, and is an attractive choice for some patients due to the fact it is available in both i.v. and oral preparations.

Bisphosphonates efficacy and tolerability have primarily been investigated in patients with bone metastases associated with breast cancer (osteolytic lesions) and ibandronate is no exception. However, bisphosphonates are also efficacious in bone metastases associated with prostate cancer (osteolytic lesions) [13,14,24]. In order to understand the usefulness of ibandronate in the clinical setting and the need to investigate its efficacy and tolerability in prostate cancer, this article summarises the current breast cancer clinical trials, *in vitro* data and then reviews the prostate cancer literature to address the

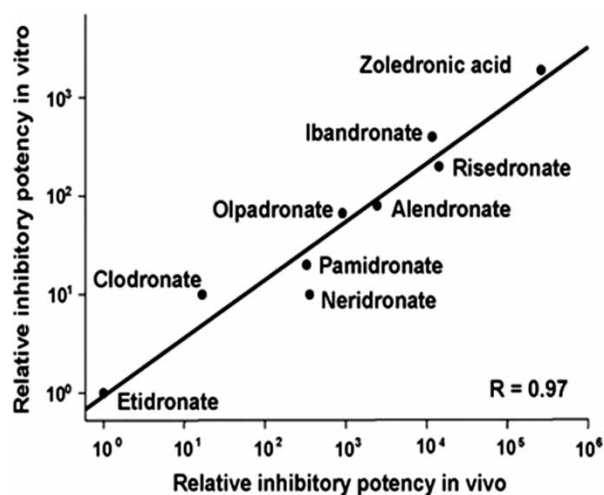


Figure 2. Differences in potency of different classes of bisphosphonates [9].

question: Is there a role for ibandronate in the treatment of prostate cancer patients with bony metastases?

Efficacy of ibandronate in *in vitro* and animal models of breast cancer

Like other bisphosphonates, ibandronate inhibits cell growth of breast cancer cells and induce apoptosis [25–28]. Ibandronate is more potent at inducing apoptosis in long term cell cultures than zoledronic acid [26], as well as exerting synergistic effects with radiation to inhibit breast cancer cell growth [29]. *In vivo* evidence from rat models show ibandronate can reduce tumour burden by inhibiting growth of cancer cells [30] and significantly reducing the growth of infiltrating cancer cells at metastatic sites [31].

Efficacy of intravenous and oral ibandronate in breast cancer patients

To date, only one phase III clinical trial has been conducted to assess the efficacy of i.v. ibandronate in reducing the incidence of skeletal complications in breast cancer patients. The trial recruited 466 patients who were randomised to a placebo arm ($n=158$), 2 mg ($n=154$) or 6 mg ($n=154$) ibandronate arm every 3–4 weeks up to 2 years and the primary efficacy parameter was the number of 12 week periods with new bone complications, which was expressed as the skeletal morbidity period rate (SMPR). Patients who received 6 mg ibandronate had a significant reduction in the frequency of 12 week periods with SMPR compared with the placebo group. The mean number of new bone events per patient was also significantly lower in the 6 mg ibandronate group versus placebo (2.65 events versus 3.64, $p=0.032$) and the time to a first new bone event was also significantly longer in the 6 mg ibandronate arm than for patients receiving the placebo (50.6 weeks v 33.1 weeks, $p=0.018$). In addition, patients in the 6mg ibandronate arm showed a significantly improved bone pain score over time compared with the placebo arm [32]. In a pooled analysis of two phase III clinical trials of oral ibandronate, 287 patients were given 50 mg ibandronate/daily while 277 patients received a placebo [33]. Again the primary efficacy parameter was SMPR and for all new bone events SMPR was significantly reduced in the ibandronate group compared to placebo ($p=0.004$). Analyses of new bone events showed the mean number of events and the mean number of measurement periods with events per patient were significantly reduced in the ibandronate group when compared with placebo

($p=0.008$ and 0.015 respectively). Multivariate Poisson's regression analysis revealed a 38% risk reduction for a skeletal event that was significantly lower than the placebo group ($p<0.0001$).

These trials have demonstrated the efficacy of both i.v. and oral ibandronate in reducing skeletal related events in MBD associated with breast cancer. However, does this efficacy and safety translate into the prostate cancer setting?

Efficacy of ibandronate in *in vitro* and animal models of prostate cancer

There is very limited *in vitro* data regarding the efficacy of ibandronate. However, three papers of particular interest show ibandronate inhibits growth and induces apoptosis of the prostate cancer cell line PC-3 [34] and prevents prostate cancer cells adhering to bone [35]. In addition, ibandronate has been shown to accumulate in the prostate of rats following subcutaneous administration causing a decrease in the revascularisation of the prostate gland, when rats were stimulated with testosterone, resulting in a reduction in prostate re-growth [36].

Efficacy of intravenous and oral ibandronate in prostate cancer

Two open, non-randomised trials have assessed the clinical efficacy of ibandronate in the management of symptomatic skeletal metastases due to prostate cancer and other urological cancers. In the first study, 25 patients with painful osseous metastases due to hormone refractory prostate cancer were treated with 6 mg ibandronate every 4 weeks. The primary endpoint was pain reduction using a 10-point visual analogue scale. Twenty-three patients (92%) achieved significant reduction in their pain score (6.5–2.0, $p<0.001$), 9 (39%) of which were completely pain free [37] (Figure 3). The second study was conducted to evaluate the tolerability of high dose ibandronate in metastatic urological cancers. Fifty-three patients with either prostate,

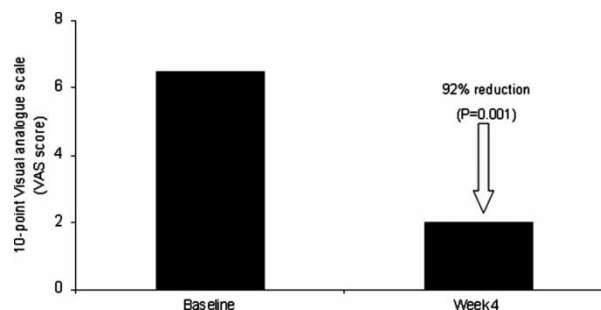


Figure 3. Reduction in bone pain of prostate cancer patients treated with 6 mg ibandronate every 4 weeks [37].

renal or bladder cancer and with painful osseous metastases were given ibandronate (6 mg) infused over one hour each day for three consecutive days and this regimen was continued at 4 week intervals. Forty-four patients (83%) reported significant improvement in bone pain starting on day 2. Mean bone pain at the start of the study was 6.8 using a VAS score and on day 3 mean bone pain was scored as 2.5 ($p < 0.001$) [38] and remained below baseline throughout the 20 week study (Figure 4).

At present, there is only one double-blind randomised study that has looked at oral ibandronate in prostate cancer patients [39]. Sixteen prostate cancer patients, along with breast cancer (77), myeloma (3) and 14 other patients, were given 5, 10, 20 and 50 mg ibandronate or placebo. The primary endpoint was calcium excretion (UCCR) as well as bone resorption assessed by measurement of the collagen breakdown products pyridinoline (Pyr) and deoxypyridinoline (Dpd) and the N-terminal (NTX) and C-terminal (crosslaps) portions of the collagen cross linking molecules. A statistically significant dose dependent reduction in UCCR ($p < 0.001$) and biochemical markers of bone resorption ($p < 0.0023$) was observed as well as in relation to baseline values (UCCR = $p < 0.001$, Dpd = $p < 0.0001$). Although patient numbers were low, similar results were seen across all tumour types.

Efficacy of i.v. versus oral ibandronate

The very nature of bisphosphonates means they rapidly bind to bone or are excreted, unchanged, in the urine. Thus, the half-life of bisphosphonates in the circulation is between 0.5 and 2 hours [40]. Pharmacokinetic studies show that oral bisphosphonates are poorly and variably absorbed from the gastrointestinal tract (1–10%) [40]. Oral ibandronate has a linear dose-dependent increase in plasma concentration that is non-saturable [41], while peak plasma concentrations of i.v. ibandronate (6 mg) is 1 μM which rapidly declines to 10% of the maximal

concentration between 3–8 hours after administration [42]. Mystakidou et al. (2008) are the only authors to carry out a comparison of oral versus i.v. ibandronate in a variety of tumours, one of which was prostate cancer. Patients received either 6 mg i.v. ibandronate infused over 15 min every 28 days or 50 mg/day oral ibandronate. After 6 months the size and number of bone metastases were measured by bone scintigraphy and radiography. I.V. and oral ibandronate produced similar responses across all tumour types with 84.6 and 88.5% of patients showing a complete (resolution and recalcification of all osteolytic metastases) or partial (resolution of some but not all existing osteoblastic metastases, or a decrease in the size of measurable osteoblastic metastases or at least partial recalcification of ≥ 1 osteolytic metastases and no new bone metastases) response. The Median percentage decreases in S-CTX levels were -39% and -35% for i.v. and oral ibandronate respectively. This comparable efficacy may be due to the fact that the bioavailability of a 50 mg (daily) oral dose, and the resulting plasma concentration, matches that achieved by monthly administration of 6 mg i.v. [41].

Safety issues of bisphosphonates

Both types of preparations of bisphosphonates are associated with adverse events. However the severity and nature varies depending on the route of administration. Unfortunately, for some patients, i.v. bisphosphonate therapy proves problematic. Patients run the risk of developing infusion related adverse events such as injection site reaction, flu-like symptoms, joint pain and pyrexia lasting 1–2 days, although usually associated with the first infusion [8]. In addition, peripheral venous access is not always possible. In such instances, central venous catheterization is used and complications following this procedure can increase problems for the patient [43]. All these i.v. infusion related effects further adds to the problems already faced by patients with advanced metastatic cancer [33].

Renal safety

As mentioned above, a significant disadvantage with some i.v. bisphosphonates is the risk of renal impairment. Although this risk is considered rare, it has been reported in 2.6–25% of patients in phase III trials [44]. Renal damage is associated with high doses and short infusion times [8]. Zoledronic acid is administered as a 4mg/15 minute infusion every 3–4 weeks and renal deterioration is the most significant toxicity associated with its use. Serum creatinine monitoring is required before each dose and is

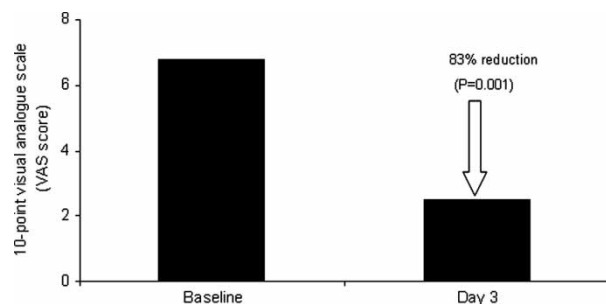


Figure 4. Reduction in bone pain in patients with metastatic urological cancers receiving 6 mg ibandronate over 1 hr each day for 3 days. VAS score remained below baseline throughout the 20 week study [38].

contraindicated when renal failure is present. The potential for renal toxicity, therefore, does mean that the usefulness of zoledronic acid is limited in patients with pre-existing renal dysfunction.

***In vivo* model assessing renal safety of intravenous bisphosphonates**

In an *in vivo* assay to investigate renal damage caused by i.v. administered zoledronic acid and ibandronate, rats were administered the bisphosphonates as a single injection or once every three weeks for 6 months. Intermittent i.v. injections (1 mg/kg) of zoledronic acid induced renal degeneration and single cell necrosis but was not seen in ibandronate treated rats using the same concentration [45]. One explanation for the differences in nephrotoxicity maybe explained due to the dose dependent accumulation and retention of bisphosphonates in the kidney [46] and the half lives of the respective drugs. Zoledronic acid has a half life (in soft tissues) of around 150–200 days [47] while ibandronate has a half life of only 24 days [48].

Renal safety of zoledronic acid in prostate cancer patients

To date, there has only been one placebo-controlled study of men with advanced prostate cancer, receiving 4 mg zoledronic acid via 15 minute infusion. The trial recruited 643 patients who were randomised to a placebo (n=208), 4 mg (n=214) or 8/4 mg (n=221) arm. Thirty-one percent of the placebo arm (n=65), 38% of the 4 mg (n=81) and 28% of the 8/4 mg (n=62) arm completed the 15 month study. Kaplan-Meier estimates of time to first renal function deterioration were determined. Patients who received zoledronic acid had a relative risk ratio of 1.07 (95% CI=0.46 to 2.47; p=0.882), compared with patients who received placebo [12], demonstrating that the zoledronic acid treatment arm had a comparable safety profile to the placebo group.

In a separate study of 221 patients with hormone sensitive prostate cancer, patients received zoledronic acid as a 4 mg via a 15-minute infusion every 3 weeks for 1 year. The study revealed mean maximal change in serum creatinine (SCr) level from baseline was 0.3 mg/dl (where notable SCr increases is defined as an increase ≥ 0.5 mg/dl for patients with normal baseline SCr levels <1.4 mg/dl, an increase ≥ 1.0 mg/dl for patients with abnormal baseline SCr levels or ≥ 2 times the baseline value) [49]. However, notably increased SCr levels were reported in 47 patients (21.2%) and for 21 (44.6%) of these patients, treatment was discontinued.

A retrospective, observational analysis assessing the risk of renal impairment in 122 [50] patients with HRPC has also been reported. Renal impairment was assessed using the same parameters as those of Polascik et al. 2005 [49]. A risk factor analysis was conducted using the Andersen-Gill extension to the Cox proportional hazards model. Renal impairment was observed in 23.8% of patients. The risk increased with extended duration of zoledronic acid treatment (36.8%) among patients who received zoledronic acid for 2 years (not statistically significant) and in patients who had prior treatment with pamidronate compared to those who had not (45.5% vs. 19% respectively). Furthermore, 20.8% of the patients who discontinued zoledronic acid did so as a result of renal complications. Although the authors conceded that reducing the dose for patients with mild or moderate renal complications may reduce the incidence of renal impairment, they report results of renal toxicity and drug discontinuation at approved doses of i.v. zoledronic acid.

The placebo-controlled study conducted by Saad et al. [12] shows zoledronic acid to be well tolerated and safe for use in prostate cancer patients, while the studies conducted by Polascik et al. [49] and Oh et al. [50] would appear to contradict this. The latter two studies, however, were not placebo-controlled. There are many reasons for renal deterioration in cancer patients (progressive disease, nephrotoxic chemotherapy agents, post-renal obstruction, lysis syndrome, uric acid and sepsis [51]) and so due to a lack of adequate controls it cannot be concluded that the zoledronic acid treatment caused or contributed to the renal deterioration observed in the latter studies. Nevertheless all three studies were conducted in patients whose serum creatinine levels were defined as normal. Given that some prostate cancer patients have pre-existing renal complications, it would appear that further investigation into the safety of zoledronic acid is required to fully elucidate the extent to which it may play a role in renal dysfunction/deterioration.

Renal safety of ibandronate in prostate cancer patients

Unlike zoledronic acid, data on the renal toxicity of ibandronate is limited to the very few studies investigating its efficacy in HRPC. Although the aforementioned studies were not carried out using placebo-controlled groups, no renal adverse events were reported. What is interesting is that the two phase II trials using loading-dose ibandronate (6 mg given on three consecutive days) showed no renal adverse effects even in patients with pre-existing renal impairment [37,38] which could make it a

suitable alternative option in prostate cancer patients when zoledronic acid is deemed unsuitable.

Other disadvantages of i.v. bisphosphonates

Osteonecrosis of the jaw (ONJ) is clinically diagnosed by exposed bone in the mouth with pain and poor healing of the wound and tends to occur with long-term exposure to bisphosphonates [52], although a cause and effect has not been established [53]. Zoledronic acid counts for 43% of all cases published, while intravenous ibandronate accounts for 2% (oral ibandronate accounts for 0.5%) [54]. However, these figures appear to reflect the fact that the majority of patients (myeloma, breast and prostate cancer) have been treated with zoledronic acid and to date, the true incidence is not yet known [20]. Another disadvantage of i.v. administration is the requirement of regular hospital visits, which can place additional burden on both patients and the hospital. In spite of the rapid infusion time of zoledronic acid (15 minutes), the actual administration time is far greater due to set-up requirements, pre-infusion of saline, drug preparation and safety follow-up [43]. A time-and-motion study [55] has been carried out to assess medical resources used when administering either oral ibandronate or i.v. zoledronic acid. With zoledronic acid administration, average clinic time was shown to be 1 hr 25 minutes longer per patient than with ibandronate treatment. Average clinician time was greater with zoledronic acid treatment (47 minutes compared to 32 minutes for ibandronate treatment) as well as average nurse time (19 minutes versus 3 minutes) [Table I]. Additionally, it was reported that for some patients requiring infusions, an overnight stay was needed due to transportation issues.

Disadvantages of oral bisphosphonates

The main disadvantages with oral bisphosphonates are the poor bioavailability (<5%) and gastrointestinal toxicity such as nausea, vomiting, reflux oesophagitis and diarrhoea. Due to these adverse side effects, patient compliance is an issue. However, data on non-compliance in patients with metastatic bone disease, is lacking and the only available information in the literature comes from clinical trials using oral clodronate [56]. Clodronate, previously the only licensed oral bisphosphonate available, is a low potency first generation drug that requires high doses to achieve clinical efficacy. The large tablet size of clodronate, which makes it difficult for many patients to swallow, compounds the issue of non-compliance. Non-compliance reduces clinical efficacy and increase morbidity, burden of disease and

Table I. Mean clinic time assessing the burden of oral ibandronate and i.v. zoledronic acid in Western Europe [55].

Mean time (min)	Oral ibandronate (n = 15)	Iv zoledronic acid (n = 13)
Clinician	18	15
Nurse	30	67
Laboratory technician	13	34
Pharmacist	28	37
Other technical staff	11	28
Duration of infusion	0	17
Preparation time before infusion	0	71
Time between iv chemotherapy and bisphosphonate infusion	0	16
Duration of Week 8 visit	97	182

health care costs [56]. Oral ibandronate is a potent third generation bisphosphonate. The dose of ibandronate, therefore, used to achieve an effect is much lower than that of clodronate and only needs to be administered once a day with the tablets being much smaller in size. Thus it would appear that some of the issues surrounding non-compliance with oral clodronate could be disregarded when treating patients with oral ibandronate.

Future studies of ibandronate in prostate cancer

In the UK, along with bisphosphonates, the current treatment for metastatic bone pain is single dose radiotherapy. The RIB trial, which has been developed by the NCRI and funded by Cancer Research UK, is being carried out to determine whether ibandronate, given as a single 6 mg i.v. infusion, can provide comparable relief from bone pain as a single 8 Gy dose of local radiotherapy in patients with primary prostate cancer and localised metastatic bone pain. The trial is still ongoing and it is hoped that accrual will be completed by the end of 2009.

Conclusion

Bisphosphonates still remain the standard of care for treating skeletal complications caused by metastatic bone disease. Zoledronic acid is the only licensed bisphosphonate for the treatment of prostate cancer. A rare but serious side effect associated with zoledronic acid use is nephrotoxicity. Whilst it is not clear how significant or common this problem is, it would appear that for prostate cancer patients, who have pre-existing renal impairment, zoledronic acid maybe deemed unsuitable. In such instances, there is a need for an alternative bisphosphonate. Phase III

clinical trials treating MBD from breast cancer patients show ibandronate is highly efficacious and safe. Ibandronate is not currently licensed for use in prostate cancer treatment and data on its use for this disease is severely limited with most studies carried out on small, non-randomised patient populations. However, the preliminary data that is emerging from these few studies appear to suggest that the use of ibandronate in prostate cancer is efficacious and well tolerated with no evidence of renal toxicity, even in patients with pre-existing renal impairment. These preliminary results need to be confirmed in larger randomised and placebo controlled trials to thoroughly investigate ibandronate as a serious treatment option for prostate cancer patients in order to improve the clinical management of their disease.

Declaration of interest: Professor John Wagstaff has been an advisor for Roche.

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