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EJC Supplements Vol 2 No. 5 (2004) 5–8

EJC Supplements

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Reducing skeletal complications and bone pain with intravenous ibandronate for metastatic bone disease

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Received 28 October 2003; received in revised form 19 January 2004; accepted 20 January 2004

Abstract

Complications of metastatic bone disease substantially compromise patient independence and mobility. The goals of management include reducing the rate of skeletal complications and alleviating bone pain, to improve morbidity and patient quality of life. In a 96-week, randomised, double-blind, phase III trial, intravenous (i.v.) ibandronate 6 mg administered over 1–2 h every 3–4 weeks significantly reduced skeletal complications (assessed by the skeletal morbidity period rate [SMPR]) compared with placebo ($P=0.004$). Individual components of the SMPR were also significantly reduced with ibandronate (vertebral fractures, $P=0.023$ and need for bone radiotherapy, $P=0.011$ versus placebo). Ibandronate 6 mg also significantly reduced bone pain scores and maintained them below baseline over 2 years ($P<0.001$), an effect not reported with other bisphosphonates for metastatic bone disease. Bone pain alleviation was accompanied by significantly improved quality of life compared with placebo ($P=0.004$). An independent pilot study used intensive i.v. ibandronate treatment (16 mg over 4 days) to treat opioid-resistant bone pain in patients with metastatic bone disease from various tumour types. Supporting the results of the phase III clinical trial, bone pain was significantly reduced ($P<0.001$ versus baseline), and patients experienced significant improvement in their quality of life ($P<0.05$ versus baseline). The results of these studies suggest that i.v. ibandronate effectively reduces skeletal morbidity rate and provides significant bone pain and quality of life benefits that have not been demonstrated so far with other bisphosphonates.

Keywords: Metastatic bone disease; Breast cancer; Bone pain; Bisphosphonates; Ibandronate

1. Introduction

Metastatic bone disease is a common manifestation of advanced malignant diseases such as breast cancer, prostate cancer, multiple myeloma and lung cancer, occurring in 30–90% of patients [1–3]. The condition is characterised by a high incidence of serious clinical problems including vertebral and non-vertebral fractures, need for bone radiotherapy and surgery, spinal cord compression and hypercalcaemia. These complications have a detrimental effect on patient quality of life, mobility and functioning. Bone pain is a particularly distressing symptom that is often severe and debilitating [4,5]. The key goals of management therefore include reducing the incidence of skeletal-related events, alleviating bone pain and improving overall patient well-being.

The symptoms and complications of metastatic bone disease may be treated with hormonal therapy, chemotherapy, radiotherapy and orthopaedic surgery [6,7]. Bisphosphonates target the underlying imbalance between bone resorption and formation to reduce the occurrence of new bone events [8,9]. Clinical trials support the significant benefits of bisphosphonate therapy in the management of skeletal events in patients with metastatic bone disease [10,11]. The older-generation bisphosphonates oral clodronate and i.v. pamidronate have been shown to exert significant analgesic effects in patients with bone pain arising from metastatic breast cancer or myeloma compared with placebo, although these effects were relatively short-term (<13 months) [4,12–17]. The effect on pain of zoledronic acid, a third-generation aminobisphosphonate, was reported to be similar to that of pamidronate in a phase III trial of breast cancer patients [18].

The clinical impact of i.v. ibandronate, another third generation aminobisphosphonate, has also been evaluated

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doi:10.1016/j.ejcsup.2004.01.002

in controlled clinical studies. This paper summarises the efficacy results of a phase III trial of i.v. ibandronate [19,20] and a pilot study of intensive i.v. ibandronate therapy in cancer patients with severe, opioid-resistant metastatic bone pain from various tumour types [21]. Implications for metastatic bone disease management are discussed.

2. Phase III trial of i.v. ibandronate in metastatic breast cancer

Patients with metastatic bone disease due to breast cancer were randomised into a multicenter, double-blind, placebo-controlled, parallel-group study (MF 4265) to assess the efficacy and safety of i.v. ibandronate 6 mg infused every 3–4 weeks ($n=312$). The safety results from this trial are detailed in this supplement [22]. Compared with placebo, patients receiving i.v. ibandronate 6 mg experienced a significant reduction in the number of 12-week periods with new bone complications (SMPR) ($P=0.004$). Although the study was not powered to show a benefit in the individual composite endpoints, vertebral fractures and the need for bone radiotherapy were also significantly reduced (Table 1). Supportive analyses revealed that the mean number of new bone events per patient over the 96-week study period was significantly reduced with ibandronate 6 mg (2.65 versus 3.64 with placebo, $P=0.032$), and the median time to first new bone event was significantly delayed in the ibandronate group compared with placebo (50.6 weeks versus 33.1 weeks, $P=0.018$). Multivariate Poission regression analysis revealed that ibandronate 6 mg reduced the risk of skeletal events by 40% compared with placebo (hazard ratio 0.60, $P=0.003$).

The significant impact of ibandronate on skeletal complications was accompanied by a reduction in bone pain score (assessed on a 5-point scale from 0 = none to 4 = intolerable, mean change from baseline −0.21 with ibandronate versus +0.28 with placebo)[1] that was maintained below baseline throughout the 2-year study duration ($P<0.001$) (Fig. 1). Analgesic scores remained lower in the ibandronate group, suggesting that bone pain alleviation was not due to greater use of other pain-relieving drugs. Relief from bone pain was also indicated by a significant reduction in the need for radiotherapy over the study period ($P=0.032$). Deterioration in quality of life over time (assessed using the European Organization for the Research and Treatment of Cancer QLQ-C30 scale) was significantly reduced with i.v. ibandronate 6 mg (mean change in global score −10 with ibandronate versus −45 with placebo, $P=0.004$), with significant benefits observed for physical, emotional and social functioning ($P<0.05$).

Table 1
Mean SMPR (MF 4265): composite endpoints

	Placebo ($n=158$)	Ibandronate 6 mg ($n=154$)
All new bone events	1.48	1.19 $P=0.004$*
Vertebral fractures	0.82	0.71 $P=0.023$*
Non-vertebral fractures	0.81	0.72 $P=0.396$*
Events requiring radiotherapy	1.09	0.91 $P=0.011$*
Events requiring surgery	0.62	0.56 $P=0.075$*

*Pairwise comparison versus placebo using Wilcoxon rank sum test. Not adjusted for multiplicity.

3. Pilot study of i.v. ibandronate for 'intractable' bone pain

The effect of i.v. ibandronate on bone pain has been investigated further in a pilot study of patients with skeletal metastases and moderate to severe, opioid-resistant metastatic bone pain. A total of 18 patients with varying primary tumours (e.g. breast, adrenal, thyroid, liver, lung, head and neck, and prostate tumours) were included in the study, which was conducted in a supportive care setting. Because of the pain intensity, patients received a relatively high, non-standard dosing regimen of i.v. ibandronate (4 mg infused on four consecutive days, 16 mg total dose). Patients experienced a rapid reduction in bone pain scores (assessed on a visual analogue scale from 0 = none to 10 = severe pain) [23] within 7 days ($P<0.001$), which remained significantly below baseline levels at day 21 ($P<0.001$) and at endpoint (day 42: $P<0.05$) (Fig. 2). As in the phase III trial, pain reductions were not due to an increased use of analgesics.

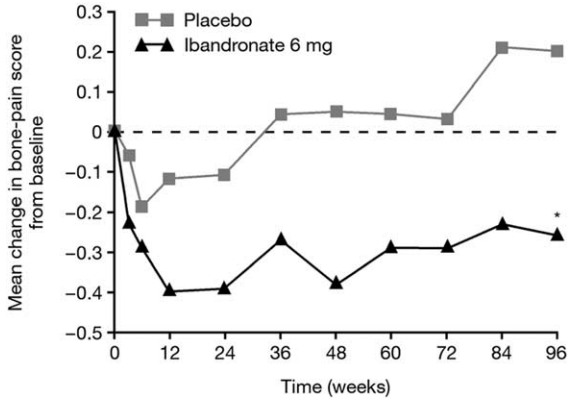

Fig. 1. Change in bone pain from baseline during the 2-year treatment period: i.v. ibandronate 6 mg versus placebo (MF 4265). *$P<0.001$.

[1] Missing data were carried forward from last observation.

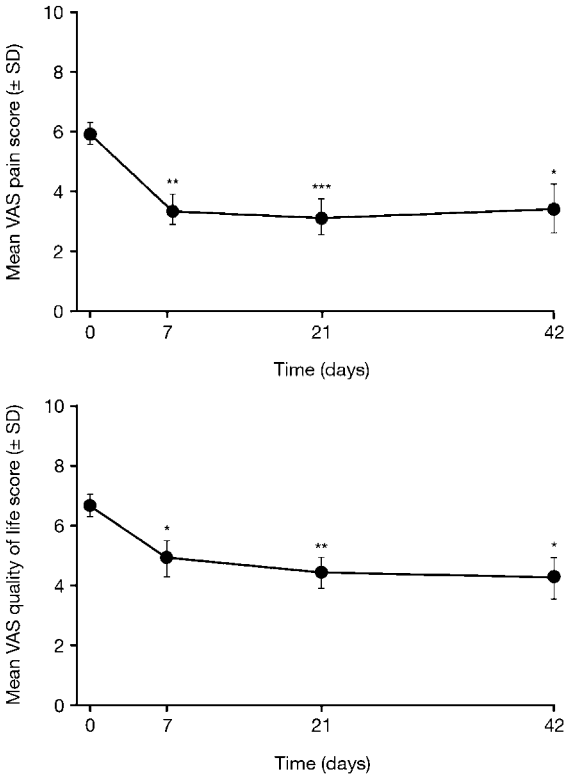

Fig. 2. Mean VAS bone pain and quality-of-life score: pilot study. *$P<0.05$; **$P<0.01$; ***$P<0.0001$.

Bone pain alleviation was accompanied by significant improvements in patient quality of life (as assessed on a 10-point 'wellbeing' visual analogue scale [VAS] [24], Fig. 2), patient functioning (Edmonton Functional Assessment Tool) [25] and performance status (Eastern Cooperative Oncology Group scale) [26] ($P<0.05$ versus baseline for all measures).

4. Discussion

The results of the phase III trial indicate that i.v. ibandronate significantly reduces skeletal complications, as measured by the SMPR. Although the study was powered to detect statistical significance for overall SMPR, ibandronate also had significant effects on some of the individual components (vertebral fractures and the need for bone radiotherapy), supporting the strength of the treatment effect.

Other bisphosphonate trials have used the skeletal related event or skeletal morbidity rate to assess the incidence of new bone events which, unlike the SMPR, do not discriminate between bone events that are likely to be related (e.g. those occurring in close time proximity, such as radiotherapy and bone surgery for a fracture) and unrelated events. By counting events occurring within a 12-week period as a single occurrence, the SMPR represents a more conservative (and potentially more accurate) measure of efficacy. As between-trials differences in the primary endpoint make it difficult to compare the efficacy of ibandronate with that of other bisphosphonates for metastatic bone disease, direct comparative trials are warranted. As well as reducing skeletal complications, ibandronate 6 mg infused every 3–4 weeks provided effective bone pain relief. Ibandronate is the first bisphosphonate to demonstrate bone pain relief that is maintained below baseline levels throughout 2 years of treatment. Sustained pain relief should improve mobility and functioning, thus allowing patients more freedom to go about their daily lives without relying on high doses of analgesics. Reductions in analgesic consumption and significant improvements in patient quality of life and performance status were observed in the studies reported here, even in patients with intractable bone pain at baseline. Long-term effects on patient functioning and quality of life have not been demonstrated for other i.v. bisphosphonates (pamidronate and zoledronic acid) in clinical trials [14–18].

Emerging evidence suggests that the pain relieving effects of i.v. ibandronate are not restricted to patients with metastatic bone disease from breast cancer. In a phase II study of patients with bone metastases from hormone-refractory prostate cancer [27], 40 out of 45 patients (89%) receiving i.v. ibandronate 6 mg on three consecutive days experienced significant pain reductions below baseline that were maintained for the 28-day study period. Approximately 25% of these patients ($n=11$) were pain-free following treatment. Pain relief was accompanied by reductions in daily analgesic requirement, and greater patient mobility. Based on these encouraging results, a phase III trial in patients with hormone-refractory prostate cancer is currently underway.

As reported elsewhere [22], the results of the phase III trial of i.v. ibandronate showed that a 6 mg dose infused every 3–4 weeks is well-tolerated, with no renal adverse events [22]. Even the intensive dose of i.v. ibandronate (16 mg in 4 days) that was used to treat opioid-resistant bone pain in our pilot study had no renal toxicity [21]. These results demonstrate the wide therapeutic window of ibandronate, which allows the use of high doses without compromising renal safety. The renal safety profile of ibandronate apparently contrasts with the potential for renal toxicity with other i.v. bisphosphonates (zoledronic acid and pamidronate) [28–29]. The absence of any notable side effects with intensive ibandronate therapy for severe bone pain also compares favorably with opioid analgesia. Therefore, ibandronate may provide an effective and well-tolerated supplementary therapy for the palliation of severe pain from skeletal complications.

Acknowledgements

This manuscript is supported by Roche.

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