

A multicenter randomized trial of ibandronate compared to single dose radiotherapy for localized metastatic bone pain in prostate cancer

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Abstract

Background

The radiotherapy or ibandronate (RIB) trial was a randomized multicenter non-blind two arm trial to compare intravenous ibandronate given as a single infusion with single dose radiotherapy for metastatic bone pain.

Methods

470 prostate cancer patients with metastatic bone pain and suitable for local radiotherapy were randomized to radiotherapy (single dose, 8Gy) or intravenous infusion of ibandronate (6mg) in a non-inferiority trial. Pain was measured using the Brief Pain Inventory at baseline and 4, 8, 12, 26 and 52 weeks. Pain response was assessed using WHO criteria and the Effective Analgesic Score (EAS); the maximum allowable difference was $\pm 15\%$. Patients failing to respond at 4 weeks were offered re-treatment with the alternative treatment. Quality of life (QoL) was assessed at baseline and 4 and 12 weeks. Because the trial was designed with a 5% one-sided test, we provide 90% confidence intervals (two-sided) for differences in pain response.

Results

Overall, pain response was not statistically different at 4 or 12 weeks (WHO: -3.7%, 90% CI -12.4 to 5.0%; and 6.7%, 90% CI -2.6 to 16.0%, respectively). Corresponding differences using the EAS were -7.5% and -3.5%. However, a

more rapid initial response with radiotherapy was observed. There was no overall difference in toxicity, although each treatment had different side effects. QoL was similar at 4 and 12 weeks. Overall survival was similar between the two groups but was better among patients having re-treatment than those who did not.

Conclusions

A single infusion of ibandronate had outcomes similar to a single dose of radiotherapy for metastatic prostate bone pain. Ibandronate could be considered when radiotherapy is not available.

Introduction

Bone metastases are a major cause of morbidity in prostate cancer. Treatment ranges from analgesics, androgen deprivation therapy and bisphosphonates to external beam radiotherapy and systemic isotope therapy. For localized bone pain, radiotherapy is the standard and most effective treatment.¹

There is increasing evidence that bisphosphonates are effective in the treatment of prostate cancer bone metastases. Oral clodronate has been shown to reduce the incidence of skeletal related events and even prolong survival in metastatic disease.² The use of bisphosphonates as an analgesic for bone pain is supported by only limited data relating to their efficacy.³⁻⁶

Ibandronate (ibandronic acid) is one of the new generation of bisphosphonate drugs. It is indicated for the prevention of skeletal events in patients with breast cancer bone metastases and for treatment of tumor-induced hypercalcaemia. A single arm phase II study showed that ibandronate is effective in controlling metastatic bone pain,⁷ and in clinical practice the use of bisphosphonates for pain relief has become common.

There has been no previous direct comparison between radiotherapy and bisphosphonates for pain relief from metastatic bone pain. This prospective randomized trial has therefore been undertaken to compare the standard treatment of radiotherapy with a bisphosphonate infusion in painful bone metastases from prostate cancer.

Methods

Study design and patients

The radiotherapy or ibandronate (RIB) trial is an open randomized, controlled phase III non-inferiority trial, comparing local radiotherapy with intravenous ibandronate in patients with metastatic bone pain. The trial was run according to the Declaration of Helsinki with the approval of all relevant ethical bodies and regulatory authorities of the centers listed in the Notes.

Eligibility criteria were: ≥ 18 years old; histological or cytological diagnosis of cancer; referral for palliative radiotherapy for localized bone pain; radiological bone metastasis confirmation using x-ray, isotope, CT or MR scan; predicted life expectancy > 3 months; and ability to comply with the pain chart, participate in quality of life assessments, and provide written consent. Exclusions were: patients unable to receive radiotherapy or ibandronate due to renal failure, hypocalcaemia, hypercalcaemia or known hypersensitivity to ibandronate or other bisphosphonates; allergy to aspirin; pregnancy or lactation (when breast and lung cancer patients were recruited); and any of the following previous treatments: radiotherapy with external beam to index site; high-dose chemotherapy; bisphosphonates within the previous 6 months; aminoglycoside antibiotics within 4 weeks of the study drug; change in systemic chemotherapy or hormone therapy within 4 weeks of trial entry; or any investigational drug within 30 days of study drug. After relatively poor accrual of breast and lung patients

was noted at an interim analysis, the entry criteria were modified to include prostate cancer patients only.

Procedures

Patients were randomly assigned to receive either local radiotherapy or ibandronate. Radiotherapy was megavoltage external beam therapy delivering a single dose of 8 Gy. The clinical target volume covered the painful site with a margin ≥ 3 cm; for a vertebral body, a margin of one vertebra above and below was recommended. Ibandronate was given as a single 6 mg intravenous infusion over 15 minutes; the recommended volume was 100mls but infusions up to 250ml were allowed. A crossover component was included. Patients randomized to receive ibandronate whose pain failed to respond at four weeks were allowed re-treatment within 4-8 weeks after randomization with radiotherapy and vice versa. Subsequent treatments outside this window were allowed at the treating clinician's discretion.

Outcomes

The primary endpoint was pain response at 4 weeks (but we were also interested at 12 weeks), compared to baseline, as measured by the World Health Organisation (WHO) pain ladder and the Effective Analgesic Score (EAS).

Baseline assessments included self-assessed pain score, using the Wisconsin Brief Pain Inventory (BPI) adapted by the RTOG for bone pain and analgesic

use, and the FACIT-G v4.0 quality of life (QoL) measure. These forms were collected either by posting the form to patients or were completed by them whilst in clinic (inpatient or outpatient). The pain score incorporates a visual analogue scale from 0-10, with zero as no pain and ten as the worst imaginable pain. Patients were asked to record their worst, average and least pain over the three previous days at their index site of pain (determined at baseline) as indicated on a body diagram on the form. The BPI also includes a section for patients to self-report all analgesic medication in the previous 3 days by name, strength (mg/pill) and number of pills per day or patch strength. These data were then weighted together with the BPI pain scores using the WHO pain ladder score and the EAS. Non-narcotics carried a fixed weight of 0.2 regardless of dosage. Morphine was weighted at 1, oxycodone at 2 and fentanyl at 3 to 3.6, with other narcotics rated between 0.2 and 1 (Supplementary Table 1, available online). Pain assessments and analgesic use were subsequently recorded at 4, 8, 12, 26 and 52 weeks post-baseline. QoL was assessed at 4 and 12 weeks post-baseline.

Pain response was assessed by analgesic use and self-assessed pain score, relative to baseline. Worst pain score was used in the primary analyses.

Complete response was defined as a pain score of zero with stable or reduced analgesic use. Partial response was defined as a reduction in pain score by ≥ 2 points with stable or reduced analgesic use, or a reduction in analgesic use by $\geq 25\%$ (with no change in pain of more than 1 point) (Supplementary Table 2).

Analgesic use was initially assessed according to the WHO pain ladder: ranked 1 as non-opioid, 2 as weak opioid and 3 as strong opioid. Analgesic use was scored between 1-3, based on the strongest pain medication taken at each time-point and also using the EAS, as described by Mercadante,⁸ taking into account patient pain score and the type and dose of pain medication used, expressed as a morphine equivalent (mg) [Supplementary Table 1]. This endpoint (on a continuous scale 0 to 150), was considered more sensitive to changes over time for a given patient and was therefore included in the trial protocol. Response using the EAS was defined by a score of zero at the time-point of interest, or a reduction of $\geq 20\%$ from baseline.

Secondary endpoints included long-term pain response at 26 and 52 weeks, quality of life at 4 and 12 weeks, crossover-rates, bone complications, toxicity using CTCAEv3.0, and overall survival. The predictive value of urinary markers will also be explored and these analyses are pending.

Sample size

An expected pain response rate of 70% at 4 weeks was assumed in both arms, and a maximum allowable difference of 15%, with 90% power. The initial target sample size was 580 patients, allowing for three interim analyses and a 20% non-evaluable rate. This was revised to 470 patients (12% non-evaluable rate, 90% power and 5% one-sided alpha) following planned interim analysis which revealed that the observed response rate was much lower than initially expected

(40% instead of 70%). Statistical significance tests were not used in the interim analyses.

Randomization

Patients were randomly assigned to treatment by the Cancer Research UK & UCL Cancer Trials Center. Randomization within this non-inferiority trial was computer-generated and stratified by center, with a 1:1 allocation using block sizes of four.

Statistical analysis

Statistical analyses were performed using Stata v12.1. The effect on pain response was estimated for both intention-to-treat (ITT) and per-protocol analyses (defined in relation to whether or not patients received their allocated treatment). The latter analyses excluded ineligible patients, those not receiving their allocated treatment, and those patients whose baseline site of pain did not match their index site of pain. In addition, patients with missing outcome data (at 4 or 12 weeks) were not included in the main analysis and therefore not analyzed by ITT (defined in relation to availability of data). To address this, we performed sensitivity analyses.

The treatment effect was the difference between the proportions who responded in each arm, using the WHO pain ladder score and the EAS (response was determined in relation to the baseline score; Supplementary Table 2), examined at 4 and 12 weeks. The difference in EAS was skewed at both time-points;

therefore, we provided the median pain score (Mann-Whitney test), as well as the mean pain score (for interest). We also used median regression to compare treatment medians at 4 and 12 weeks, separately, vs. baseline.

The treatment effect using average and least pain scores as reported by each patient were also examined using the above methods to check for consistency between the results. Because the trial was designed with a 5% one-sided test, we provide 90% confidence intervals (two-sided) for the differences in pain response.

Overall survival (OS) was assessed using the Kaplan-Meier method and Cox proportional hazard models for both treatment groups and the four (non-randomized) treatment/re-treatment groups. The latter comparison was found to violate the proportional hazards assumption, and so median survival was reported. The treatment effect on QoL at 4 and 12 weeks separately was assessed using analysis of covariance (ANCOVA), allowing for the baseline measure.

Results

470 prostate cancer patients were randomized between April 2003 and November 2009 from 58 centers across the National Cancer Research Network (235 radiotherapy and 235 ibandronate; Figure 1). Baseline characteristics were well balanced between treatment arms (Table 1) and are representative of

patients seen in routine practice. Seven patients were ineligible for the trial, but were included in the intention-to-treat analyses.

Treatment compliance

Ibandronate was received by 227/235 (97%) patients and 224/235 (95%) patients received radiotherapy, as randomized. The median time (25th, 75th centile) from randomization to start of treatment was 5 days (1, 8) with ibandronate and 7 days (3,12) with radiotherapy. One patient in the ibandronate arm received radiotherapy off-study and 18 patients received neither treatment, including seven ineligible patients (Figure 1). Twenty six patients failed to respond according to average pain score by four weeks, and could have been re-treated between 4-8 weeks. Of these, 14/26 (54%) patients received the other trial therapy. A further 114 patients, not meeting the criteria, were also re-treated at clinicians' discretion. There was no material difference in the cross-over rate between those who started with ibandronate (n=72, 31%) or radiotherapy (n=56, 24%). As expected, the response rate at 4 weeks was lower in those who crossed over (ibandronate then radiotherapy 33.8%, radiotherapy then ibandronate 32.6%), compared to those who did not (ibandronate only 58.1%, radiotherapy alone 59.8%). Also, several non-responders did not cross over, whilst a few responders did, indicating that the decision to switch treatment was not entirely based on pain response (Supplementary Table 3).

Pain response

i) WHO criteria

There was no treatment difference for worst pain response at 4 weeks (ibandronate 49.5% vs. RT 53.1%; difference =3.7%, 90% CI -12.4 to 5.0%; $p=0.49$), or 12 weeks (ibandronate 56.1% vs. RT 49.4%; difference = 6.7%, 90% CI -2.6 to 16.0%; $p=0.24$) [Table 2]. The 90% CI limits were within the maximum allowable difference of $\pm 15\%$ at 4 weeks (-12.4 to 5.0%) and almost at 12 weeks (-2.6 to 16.0%). Similar results were found at 26 weeks (ibandronate 48.8% vs. RT 52.8%; $p=0.53$), and 52 weeks (ibandronate 45.9% vs. RT 42.3%; $p=0.65$) [Supplementary Table 4]. The same conclusions were found when pain response was based on average or least pain scores for each patient (Supplementary Tables 4-5).

ii) EAS

Worst pain response using the EAS was similar between treatment groups at 4 weeks (52.7% ibandronate vs. 60.2% RT; difference = -7.5%, $p=0.14$), and 12 weeks (56.7% ibandronate vs. 60.2% RT; difference = -3.5%, $p=0.51$) [Table 2]. The 90% CIs were within $\pm 15\%$ at 12 weeks (-12.3 to 5.3%) and almost at 4 weeks (-15.7 to 0.7%). Similar conclusions were found at 26 weeks (ibandronate 52.9% vs. RT 55.6%; $p=0.67$), and 52 weeks (ibandronate 44.6% vs. RT 45.3%; $p=0.92$) [Supplementary Table 4].

The analyses in Table 2 were only based on patients who had a pain score at 4 (or 12 weeks), so we conducted sensitivity analyses (Supplementary Table 6) with various assumptions about the missing data (mainly for patients who had died previously). The findings are consistent with those from Table 2.

Mean worst pain scores were not different between the two treatment groups at any time-point (Table 2; Supplementary Table 4; Figure 2). The Mann-Whitney test provided some evidence favoring radiotherapy at 4 weeks ($p=0.04$, i.e. just <0.05), but this effect was not found at 12 weeks ($p=0.48$) [Table 2] or at any other time-point (Supplementary Table 4). Consistent results were found when the data were analyzed using ANCOVA (with baseline score as a covariate; mean EAS difference: -4.55 (90% CI -8.8 to -0.32, $p=0.04$) and 1.34 (90% -4.47 to 7.15, $p=0.65$) at 4 and 12 weeks, respectively). Late pain responses based on

average and least pain scores are largely consistent with the worst pain score results (Supplementary Table 5). There was no appreciable difference in the interpretation of the results when median regression was used (Supplementary Table 7).

iii) Per-protocol analyses

The analyses in Table 2 were repeated after excluding the 25 patients who were ineligible (n=7), did not receive the treatment to which they were randomized (n=12), or whose baseline site of pain did not match their index site of pain (n=6). Per-protocol results (Supplementary Table 8) were similar to the intention-to-treat analyses. The differences in response at 4 weeks were -3.5% (90% CI (-12.2 to 5.3%)) and -6.6% (-15.0 to 1.7%) for WHO and EAS respectively; corresponding effects at 12 weeks were 5.5% (-3.8 to 14.8%) and -2.0% (-10.9 to 6.9%). The results at 12 weeks exclude patients who crossed over to the other trial treatment beforehand. We performed another per-protocol analysis at 12 weeks (when some patients had already crossed over treatment), but comparing patients who received radiotherapy alone or ibandronate alone: the differences in response at 12 weeks were -2.2% (90% CI -9.0 to 13.4%) and -0.1% (-10.5 to 10.7%) for WHO and EAS, respectively.

Spinal cord compression and pathological fracture

There was no statistical difference in the incidence of spinal cord compression at the index site, among patients with site of pain in the abdomen or thorax (ibandronate: 12 (5.6%) vs. RT: 7 (3.3%), $p=0.19$). Pathological fractures at the index site were also similar (ibandronate: 7 (3%) vs. RT: 5 (2%), $p=0.31$).

Quality of life

Overall quality of life at 4 weeks ($p=0.37$) or 12 weeks ($p=0.84$), including the physical, social, emotional and functional QoL subscales, were similar between ibandronate and RT (Table 3).

Toxicity

Toxicities including serious adverse events (SAEs) are given in Table 4. Twice as many patients reported diarrhea in the RT arm (12%) vs. ibandronate (6%, $p=0.014$) and there was some evidence of a higher nausea rate in the RT group (RT 26% vs. ibandronate 18%, $p=0.058$, i.e. just >0.05). However, this was balanced by a greater rate of other toxicities in the ibandronate arm (19% vs. 9%, $p=0.001$).

Overall survival

After a median follow-up of 11.7 months, 395 (84%) patients had died by June 2012 (ibandronate 200 deaths, RT 195 deaths). Median overall survival was 12.9 months (95% CI: 11.1–14.2) and 12.2 months (95% CI: 10.1–14.1) in ibandronate and RT, respectively (HR=0.89, 95% CI: 0.73-1.09, $p=0.25$; Figure 3A). 342 patients had no re-treatment, and among these 89% (ibandronate) and 82% (RT) had died. The corresponding rates among re-treated patients were 76% (ibandronate then RT) and 88% (RT then ibandronate). The proportional hazards assumption did not hold when comparing all four groups ($p=0.028$, Figure 3B), so HRs cannot be reliably estimated. Median OS times were 11.4 months (ibandronate alone), 11.8 months (RT alone), 16.8 months (ibandronate then RT) and 12.7 months (RT then ibandronate); logrank p -value=0.08.

Re-treated patients had a lower chance of dying, compared to those who were not (Figure 3B): unadjusted HR: 0.77, 95% CI: 0.61-0.96, $p=0.021$, and adjusted for initial treatment, HR: 0.77, 95% CI: 0.62-0.97, $p=0.025$. There was no indication of a treatment-re-treatment interaction effect ($p=0.50$). However, these results need to be interpreted with some caution because the reasons for re-treatment were largely at the clinicians' discretion.

Lung and breast cancer patients

Response rates among 49 lung cancer patients were 35.7% and 33.3% (ibandronate) and 31.3% and 50.0% (RT) at 4 and 12 weeks, respectively; the corresponding rates for the 38 breast cancer patients were 50.0% and 38.9% (ibandronate) and 64.2% and 63.6% (RT) (Supplementary Tables 9-10 and Figures 1A-B). No reliable conclusions can be made given the small patient numbers.

Discussion

The gold standard for treatment of localized metastatic bone pain is radiotherapy. There is an extensive literature evaluating different radiation dose fractionation schedules and meta-analysis data which shows single dose treatment as chosen here to be as effective as more protracted schedules.^{1,9} This trial has shown that a single infusion of ibandronate is also effective in achieving pain relief. Pain response was measured using a prospective validated patient completed pain score; however, because of the very different nature of the treatments, blinding was not used in the assessments, which may have introduced an element of bias.

The primary analyses presented here are based on worst reported pain using the BPI. The relationship between the different parameters collected with the BPI has previously been carefully analyzed.¹⁰ Worst pain had the best correlation with

functional interference and was recommended as the measure of choice for assessment of palliative radiotherapy in metastatic bone pain. The response criteria we used are those defined by an International Consensus Group¹⁰ to include analgesic use. The primary end point at 4 weeks may be regarded as a little early to capture all patients responding to radiotherapy [1] and may therefore have underestimated the radiotherapy effect. Overall the response rate was between 50 and 60% at 4 and 12 weeks, and the more detailed EAS method of analgesic summation gave a slightly higher response rate than the WHO classification. These response rates are similar to those seen in other studies of single dose radiotherapy.¹¹⁻¹³ In contrast, the efficacy of ibandronate is greater than that reported for older bisphosphonates such as pamidronate. Pooled analysis of two double blind trials of pamidronate compared to placebo showed no greater analgesic effect from pamidronate than placebo.¹⁵ However other studies which used clodronate or zoledronate have shown a modest but variable analgesic effect with regular administration of the bisphosphonate.¹⁶ Ibandronate and zoledronate are third generation bisphosphonates and considerably more potent in osteoclast inhibition than their predecessors, which may account for the greater analgesic effect seen with ibandronate in our trial. It would be reasonable to suggest that this is a class effect and also applicable to zoledronate. Prior use of bisphosphonates is unlikely to have an effect, because patients who had such treatment within 6 months were ineligible for the trial, and the number who had taken it before should be balanced between the two groups.

Although our trial focused on prostate cancer the mechanisms of pain and pain relief from the two treatment modalities are however not primary tumor-specific and it may be reasonable to extrapolate the findings of this study to other solid primary tumor types. The number of lung and breast-cancer patients in this study is, however, too small to comment further.

Both zoledronate and clodronate, when given long term, have been shown to have a small but statistically significant effect on survival in men with established bone metastases from prostate cancer^{2,15}. It is therefore of interest that the crossover groups receiving both ibandronate and radiotherapy (in particular, ibandronate then radiotherapy) appear to have better survival than the groups receiving only one treatment. These patients may represent a selected subgroup with better performance status or survival to the point of re-treatment. This may suggest an important synergism between the two treatments, but it should be noted that these findings were based on a non-randomized comparison. Clearly the potential synergism between the two modalities is an important area for future research and may have particular implications for those patients on regular long term bisphosphonates, which is today the more common use of such drugs.

The decision to offer crossover treatment was not entirely associated with the response rate at four weeks, indicating that there were other considerations. Recently it has been shown that re-treatment with radiotherapy is effective.¹⁶ It is therefore not possible to recommend the best option for poor initial responders;

both radiotherapy and bisphosphonates appear to be of value. Furthermore, given that about a quarter of patients crossed over to the other trial treatment after 4 weeks, it could be argued that the results at 12 weeks represent a treatment policy, rather than a direct comparison of only radiotherapy and bisphosphonates.

Bisphosphonates work through reducing the overall number of functioning osteoclasts. Binding to apatite crystals in the bone they reduce osteoclast numbers by enhanced apoptosis and recruitment of osteoblasts; they also reduce the activity of remaining osteoclasts. The mechanism of action of radiotherapy in achieving pain relief remains elusive. It has been proposed that it is not directly due to tumor shrinkage but the result of a reduction in chemical mediators of pain and osteoclast activation. Within the RIB study urine samples were collected for measurement of markers of osteoclast activity which may inform the fundamental mechanisms of pain relief in these patients and provide a basis for treatment selection between radiotherapy and third generation bisphosphonates such as ibandronate.

Recently a new osteoclast inhibiting agent working through blockade of the RANKL pathway, denosumab, has been approved for use.¹⁷ The interaction between this drug and bisphosphonates in pain relief has yet to be studied but radiotherapy appears to be effective in patients receiving denosumab.

There is a possibility that RT is more effective in the first four weeks, but data on this are not strong (median EAS $p=0.04$). Otherwise the therapeutic ratio for each intervention is well balanced with broadly equivalent but different toxicities. Most reported side effects were mild, but there were 16 and 11 ungraded SAEs for ibandronate and radiotherapy, respectively, and one grade 3 diarrhea (radiotherapy). A 2002 Cochrane review of 32 randomized trials concluded that bisphosphonates can provide pain relief for bone metastases, but there was insufficient evidence for first-line therapy at the time.¹⁸ Our data therefore lend support for their use.

In conclusion, prostate cancer patients with localized pain from bone metastases should continue to be offered single dose radiotherapy, which may give optimal pain relief in the first 4 weeks after treatment, but a third generation bisphosphonate such as ibandronate given as a single dose could also give effective overall pain relief. It is plausible that these findings are applicable to metastases from other primary sites. This study did not address the efficacy of a combination of radiotherapy and bisphosphonate. A synergistic effect cannot be excluded and this should be explored in future trials.

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Figure Legends

Figure 1. CONSORT diagram for the Radiotherapy or Ibandronate (RIB) trial.

*Includes one patient randomized to ibandronate who did not receive this treatment, but received radiotherapy off-study. † Includes the ineligible patients (who did not receive either ibandronate or RT), as they were already randomized and are few in number.

Figure 2. Mean worst Effective Analgesic Score, over time and by treatment

Figure 3. Overall survival. **(A)** By treatment. Hazard ratio = 0.89 (95% CI: 0.73 – 1.09), $p=0.25$. The median survival in the ibandronate and radiotherapy arms is 12.9 months (95% CI: 11.1 – 14.2 months) and 12.2 months (95% CI: 10.1 – 14.1 months), respectively. **(B)** By treatment-re-treatment (non-randomized).

Proportional hazards assumption does not hold. The median survival in the four crossover groups is: ibandronate alone 11.4 months (95% CI: 9.2 – 13.2 months); ibandronate to radiotherapy 16.8 months (95% CI: 11.6 – 19.1 months); radiotherapy alone 11.8 months (95% CI: 10.0 – 14.2 months); radiotherapy to ibandronate 12.7 months (95% CI: 7.9 – 15.3 months).

Table 1. Baseline characteristics

Characteristics		Ibandronate 235 patients	Radiotherapy 235 patients
		No. (%)	No. (%)
Age at randomization:	< 65 years	42 (18)	41 (17)
	≥ 65 years	193 (82)	194 (83)
	(median, range)	(72, 50-97)	(73, 47-91)
Site of pain:	Abdomen	183 (78)	180 (77)
	Thorax	33 (14)	35 (15)
	Leg (left or right)	11 (5)	14 (6)
	Arm (left or right)	4 (2)	0 (0)
	Head and neck	2 (1)	2 (1)
	Not reported	2 (1)	4 (2)
Chemotherapy at randomization:	Yes	6 (3)	4 (2)
	No	223 (95)	224 (95)
	Not reported	6 (3)	7 (3)
Recent/current hormone therapy at randomization*:	Yes	215 (91)	210 (89)
	No	18 (8)	22 (9)
	Not reported	2 (1)	3 (1)
Performance status (WHO) at start of treatment	0	40 (17)	32 (14)
	1	133 (57)	143 (61)
	2	47 (20)	40 (17)
	3	8 (3)	11 (5)
	Not reported	7 (3)	9 (4)
Quality of life score	Median (range)	73	71
		(32-101)	(36-103)
Pain score	Median (range)	7 (0-10)	7 (0-10)

*Within 4 weeks of randomization to the trial (so patients may have been on hormonal therapy before this time)

Table 2. Analyses based on worst pain scores for each patient, at 4 and 12 weeks after randomization, using the WHO based pain-ladder score and the EAS*

	Individual treatment effects at:				Outcome (effect size) at:	
	4 wks		12 wks		4 wks	12 wks
	IB (n)	RT (n)	IB (n)	RT (n)	IB – RT (90% CI); p-value	IB – RT (90% CI); p-value
WHO response rate (%)†:						
	49.5 (182)	53.1 (175)	56.1 (157)	49.4 (156)	-3.7% (-12.4 to 5.0%); 0.49	6.7% (-2.6 to 16.0%); 0.24
EAS response rate (%)†:						
	52.7 (201)	60.2 (191)	56.7 (171)	60.2 (166)	-7.5% (-15.7 to 0.7%); 0.14	-3.5% (-12.3 to 5.3%); 0.51
Mean EAS‡:						
	1.16 (201)	-3.23 (191)	-1.67 (171)	-0.19 (166)	4.39 (-0.07 to 8.86); 0.11	-1.48 (-8.52 to 5.57); 0.73
Median EAS§:						
	-0.02	-0.12	-0.06	-0.08	0.38 (0.02 to 1.44); 0.04	0.08 (-0.10 to 0.84); 0.48

*EAS = Effective Analgesic Score; Ibandronate (IB); radiotherapy (RT).

† Comparison of proportions is used to assess the treatment effect for the WHO and EAS response rates;

‡ Unpaired t-test is used to assess the treatment effect for the baseline-adjusted difference in mean scores (these are given for interest, acknowledging that the distribution of the difference in scores is skewed);

§ Mann-Whitney test is used to assess the treatment effect for the baseline-adjusted difference in ranked scores. Note that the given treatment effect and its confidence interval is based upon the Hodges-Lehmann test and so the confidence intervals are not symmetric.

Non-inferiority trials are evaluated using the 90% confidence intervals, by observing where they lie in relation to the maximum allowable difference (here, -15%, for WHO and EAS response rates)

Table 3. Quality of life at 4 and 12 weeks, adjusting for baseline quality of life.

Quality of life function*	Mean quality of life score (change from baseline)		Difference in quality of life† (99% CI) IB - RT	p-value
	Ibandronate	Radiotherapy		
4 weeks				
Physical Well-Being	-0.1	0.6	-0.4 (-1.7 to 0.9)	0.38
Social Well-Being	-0.1	-0.5	0.4 (-0.5 to 1.2)	0.26
Emotional Well-Being	-0.2	0.4	-0.5 (-1.5 to 0.4)	0.12
Functional Well-Being	-0.7	-0.2	-0.5 (-1.6 to 0.7)	0.29
Overall Quality of Life	-0.9	0.3	-1.0 (-4.0 to 2.0)	0.37
12 weeks				
Physical Well-Being	0.1	0.6	-0.2 (-1.7 to 1.3)	0.72
Social Well-Being	-0.0	-1.0	1.0 (-0.2 to 2.1)	0.03
Emotional Well-Being‡	-0.3	0.2	-0.5 (-1.6 to 0.6)	0.25
Functional Well-Being	-0.9	0.1	-0.9 (-2.3 to 0.4)	0.08
Overall Quality of Life	-0.5	-0.1	-0.3 (-3.8 to 3.3)	0.84

* Physical, Social and Functional Well-Being scores range from 0-28, whereas Emotional Well-Being has values 0-24. The Overall Quality of Life score is the summation of these 4 scores, 0-108. A clinically important difference on these scales could be ± 5 units, and none of the differences above exceed this.

† Analysis of covariance was used to assess the treatment effect on the change in quality of life from baseline to 4 and 12 weeks, separately. A difference in quality of life score >0 indicates that the ibandronate patients have better QoL, whereas a difference <0 indicates that radiotherapy patients have a better quality of life.

‡ There is some evidence of treatment difference in effect of baseline score on 12 week score (interaction treatment and emotional well-being: $p=0.02$).

Table 4: Adverse events (all were grade 1-2, except where indicated)

Event	Ibandronate N=235 N (%)	Radiotherapy N=235 N (%)	P-value *
Toxicity			
Diarrhea †	13 (6)	28 (12)	0.014
Nausea ‡	43 (18)	60 (26)	0.058
Vomiting ‡	5 (2)	10 (4)	0.19
Fatigue	11 (5)	14 (6)	0.54
Constipation ‡	10 (4)	14 (6)	0.40
Thrombotic Event	6 (3)	2 (1)	0.29
Myocardial infarction ‡	2 (1)	1 (<1)	
Pulmonary embolism ‡	1 (<1)	0 (0)	
Cerebrovascular accident ‡	2 (1)	0 (0)	
Deep vein thrombosis ‡	1 (<1)	1 (<1)	
Other	44 (19)	20 (9)	0.001
Fever/anorexia ‡	17 (7)	6 (3)	
Urinary symptoms ‡	5 (2)	3 (1)	
Chest symptoms ‡	4 (2)	2 (1)	
Gastro-intestinal bleeds ‡	1 (<1)	1 (<1)	
Other ‡,§	20 (9)	8 (3)	
Any toxicity -	91 (39)	97 (41)	
Absolute risk difference (95% CI)	-2.6% (-11.4 to +6.3%)		0.57

* Toxicities were compared using the χ^2 test of association, and where the expected frequencies were ≤ 5 , Fisher's Exact test was used.

† This includes one grade 3 diarrhoea toxicity (treatment) for Radiotherapy.

‡ The reported serious adverse events for ibandronate include: MI (2); CVA (2); urinary symptoms (2); paresthesia (2); PE (1); DVT (1); anemia (1); dysphasia (1); abscess (1); bloating (1); dehydration (1); chest symptoms (1); and for radiotherapy: chest symptoms (2); MI (1); DVT (1); nausea (1); vomiting (1); constipation (1); gastro-intestinal bleeds (1); anorexia (1); ataxia (1); seizure (1).

§ Further ibandronate toxicities include: anemia (3); dizziness (3); paresthesia (2); shivering (2); itchy skin (2); dysphasia (1); edema (1) bruised chest (1); tender abdomen (1); abscess (1); bloating (1); dehydration (1); swollen tongue (1); bruising at cannulation site (1); restlessness (1); out of body sensation (1); and for radiotherapy: ataxia (1); seizure (1); dizziness (1); erythema (1); itchy skin (1); hypocalcaemia (1); edema (1); abdominal discomfort (1); stomach ache (1).

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