Ibandronic acid gives a bone in cancer metastases

– Suzanne Sullivan –

Bone metastases can cause severe pain and disability requiring treatment with radiotherapy and analgesics. Pooled analyses of data from phase II and III studies showed that oral and IV ibandronic acid [Boniva, Bonviva, Bondronat] effectively relieves metastatic bone pain in patients with breast cancer for up to 2 years, and reduces the requirements for analgesics and radiotherapy. In another study, oral ibandronic acid was as effective as IV zoledronic acid [Aclasta, Zometa] in reducing bone turnover markers, indicating that ibandronic acid may have comparable benefits in preventing skeletal-related events. These studies were presented recently at the 13th European Cancer Conference (ECCO) [*Paris, France; October–November 2005*].

An estimated 65–75% of patients with breast cancer have bone metastases, resulting in pain, a reduction in quality of life and reduced mobility. Current standard treatments for bone pain associated with metastases include focal radiotherapy and opioid analgesics. However, pain often persists despite these therapies and > 20% of patients have uncontrolled pain. Previous studies have shown that ibandronic acid reduces the incidence of skeletal events in patients with breast cancer and bone metastases. Two pooled analyses were conducted to determine whether ibandronic acid reduces the requirements for radiotherapy and analgesics, and to evaluate the onset and duration of pain relief, respectively.

Reduced analgesic requirements

The first pooled analysis was prespecified and included data from three randomised, double-blind, phase III studies involving patients with breast cancer and bone metastases.[1] In the first study, 312 patients received IV ibandronic acid 6mg (n = 154) or placebo, infused over 1–2 hours every 3–4 weeks. The other two studies included 564 patients who received oral ibandronic acid 50mg (n = 287) or placebo, once daily.

At baseline, the mean bone pain score was 1.37 (range 0–4, where 0 = none and 4 = intolerable) and the mean analgesic score was 1.03 (range 0–6, where 0 = none and 6 = morphine dose of ≥ 100 mg/day or equivalent).

At 2 years, the IV and oral ibandronic acid groups had significantly greater reductions from baseline in mean bone pain scores, compared with the corresponding placebo groups [*see table 1*]. The reduction in the use of analgesics, according to mean analgesic scores, was greater in the ibandronic acid groups than the placebo group; the difference was statistically significant for oral ibandronic acid. The IV and oral ibandronic acid groups had significantly lower incidences of events requiring palliative radiotherapy, compared with the corresponding placebo groups, with risk reductions of 16.5% and 25.5%, respectively.

Table 1. Effects on bone pain and analgesic requirements, according to therapy

	IV study		Oral studies	
	Placebo	Ibandronic acid 6mg	Placebo	Ibandronic acid 50mg
Mean change from baseline at 2 years:				
Pain scores	+0.21	–0.28*	+0.20	–0.10*
Analgesic score	–0.90	–0.51	–0.85	–0.60**
Events requiring radiotherapy:				
Incidence after 2 years	1.09	0.91**	0.98	0.73**

* $p \leq 0.001$ vs corresponding placebo
** $p < 0.05$ vs corresponding placebo

"*Both intravenous and oral* [ibandronic acid] *significantly reduced bone pain even with the concurrent reduction in the use of analgesics and radiotherapy,*" concluded the investigators. "*This suggests that pain relief was not due to these factors and* [ibandronic acid] *was responsible for pain palliation.*"

Fast and sustained pain relief

In the second analysis, data were pooled from two phase II studies and the same three phase III trials as in the first analysis.[2] The phase II studies involved 98 patients with bone pain due to metastatic urological cancer (n = 53) or hormone refractory prostate cancer. Patients in these two studies received loading doses of IV ibandronic acid 6mg on 3 consecutive days, followed by doses of 6mg every 4 weeks thereafter. Bone pain was assessed on a visual analogue scale of 0–10 and analgesic use was recorded in a diary.

In the phase III studies, reductions from baseline in mean bone pain scores were observed as early as week 4 and maintained for up to 2 years with IV and oral ibandronic acid, compared with placebo.

Similar effects were noted in the phase II studies, although the onset of pain relief was faster [*see table 2*]. In both studies, bone pain scores were significantly reduced from baseline by day 3 and remained below the baseline score throughout the study periods.

Table 2. Onset and duration of pain relief with ibandronic acid in phase II studies

	Urological cancer	Prostate cancer
Mean bone pain score:		
Baseline	6.8	6.8
Day 3	2.5*	2.5*
Response rates:		
Significant pain reduction	83	89
Pain-free	25	25

* $p < 0.001$ vs baseline

Among the patients with urological cancer, 83% of patients had pain relief from as early as day 2 and 25% of patients became pain-free during the study period. In addition, 64% of patients had a reduction in analgesic use of ≥ 50%.

In the group of patients with prostate cancer, 89% had significant pain relief. By the end of the study period, 25% of patients were pain-free and daily analgesic requirements were reduced in 62% of patients.

The reduction from baseline in bone pain scores within 3 days suggests that ibandronic acid "*offers rapid relief of bone pain to patients who need it the most,*" commented the investigators.

An equal to zoledronic acid

Serum levels of biochemical markers are useful for evaluating the clinical response to bisphosphonates in patients with bone metastases. The suppression of bone turnover markers by these agents is thought to be correlated with a reduction in skeletal-related events. The third study presented at ECCO was designed to compared the effects of oral ibandronic acid and IV zoledronic acid on levels of bone turnover markers.[3]

Table 3. Effects on bone turnover markers, according to therapy

	Zoledronic acid	Ibandronic acid
Mean reduction from baseline at week 12 (%):		
S-CTX[a]	73	76
U-CTX[b]	82	76
Bone specific alkaline phosphatase	26	37
P1NP[c]	39	47
osteocalcin	26	35

[a] serum levels of cross-linked C-terminal telopeptide of type I collagen
[b] urinary levels of CTX
[c] amino-terminal procollagen propeptides of type I collagen

This randomised, open-label, multicentre study included 254 patients with advanced breast cancer, at least one osteolytic or mixed bone lesion, and a WHO performance status of 0–2. In this 12 week study, patients received oral ibandronic acid 50 mg/day (n = 128) or IV zoledronic acid 4mg every 4 weeks. The primary endpoint was the mean change from baseline in serum levels of the bone resorption marker cross-linked C-terminal telopeptide of type I collagen (S-CTX). Secondary outcome measures included urinary levels of CTX (U-CTX) and serum levels of bone specific alkaline phosphatase (BAP), amino-terminal procollagen propeptides of type I collagen (P1NP) and osteocalcin.

At week 12, patients in both groups had reductions from baseline in S-CTX; there were no significant differences between the two groups [*see table 3*]. In the ibandronic acid group, of the 26 patients who had high levels of S-CTX at baseline, all had normal or low levels at week 12. Among the 22 patients in the zoledronic acid group with high levels of S-CTX at baseline, 19 patients had normal or low levels at week 12 and the other three patients continued to have high levels of S-CTX.

There were no significant differences between patients receiving ibandronic acid and those in the zoledronic acid group in the reductions from baseline in U-CTX, BAP, P1NP and osteocalcin levels at week 12.

"*As markers of bone turnover are prognostic indicators of skeletal complications, the data presented here suggest comparable efficacy for* [ibandronic acid] *and zoledronic acid for preventing skeletal-related events,*" concluded the researchers.

1. Tripathy D, et al. Effect of intravenous and oral ibandronate on the need for analgesic interventions for metastatic bone pain: phase III trial results. EJC Supplements 3: 113 (plus poster) abstr. 404, No. 2, Oct 2005.
2. Heidenreich A, et al. Duration of onset of metastatic bone pain relief with ibandronate: phase III and phase II trial results. EJC Supplements 3: 368 (plus poster) abstr. 1276, No. 2, Oct 2005.
3. Lichinitser M, et al. Phase III trial of oral ibandronate and intravenous zoledronic acid in breast cancer patients with bone metastases: comparison of bone turnover markers. EJC Supplements 3: 113 (plus poster) abstr. 405, No. 2, Oct 2005.

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