Effect of Zoledronic Acid on Bone Pain Secondary To Metastatic Bone Disease

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You are in your office. Mr.X, a 64 year-old patient well known to you for over 10 years, comes for persistent severe bone pain despite palliative radiotherapy and recent opioid treatment. Six years ago, he was diagnosed with stage IV prostate cancer with metastasis in the right pubic bone. He was treated with surgery and pelvic irradiation including the right pubis. One year prior to presentation he had an orchiectomy with prompt relief of pain and a decrease in his **prostate specific antigen (PSA)**. He is taking morphine and dexamethasone was added recently with minimal effect. The pain has affected his sleep, appetite, and ability to enjoy life. He does not like the opiates' effect on his ability to make high level decisions.

The patient comes into the office noting that he just saw a commercial about a new medication, zoledronic acid, for treatment of cancer bone pain. He wants to know if this can help him.

What are the current treatment options for metastatic bone disease?

Bone metastases are frequent in patients with advanced cancer. The most common cancer which metastasize to bone are breast, lung, prostate, multiple myeloma, and renal. Skull, spinal column, rib cage, pelvis and femur are the most frequent sites of bone metastases.

Pain from cancer is a major problem. Thirty percent of patients with cancer have pain at the time of diagnosis; 65 to 85% have pain when their disease is advanced. The impact of cancer pain is magnified by its interaction with other common cancer symptoms: fatigue, weakness, dyspnea, nausea, constipation, and impaired cognition.[18] With an integrated program of systemic, pharmacologic, and anticancer therapy, cancer pain can be effectively treated in 85-95% of patients. Many of the remaining patients can be helped by the use of invasive procedures. In the final days of life, pain not controlled by therapies aimed at both comfort and function can be relieved by intentional sedation. No patient with cancer needs to live or die with unrelieved pain. Pain caused by bone metastases lowers the quality of life and performance status of patients, and causes disability occurring at rest or typically during movement.[14]

Treatment of bone metastases is aimed at reducing the risk of pathological fractures and other **skeletal related events (SREs)**, as well as reducing pain to maximize patients' quality of life. The options include surgery, radiation therapy, radiometabolic therapy, chemotherapy, hormone therapy, and other palliative treatment. Bisphosphonate therapy is now well established as a way of reducing morbidity from the lytic skeletal metastases.[19]

BISPHOSPHONATES

Metastatic bone disease is associated with a marked increase in bone resorption and formation rates, which can be evaluated by the measurement of biochemical markers of bone metabolism in the serum or urine.

Bisphosphonates inhibit osteoclastic bone resorption and control bone metabolism via several mechanisms that differ from those of other antiresorptive agents. They contain 2 phosphate groups linked to 1 carbon atom, forming a stable structure (phosphorus-carbon-phosphorus) resistant to the action of osteoclastic hydrolytic enzymes. This backbone and the presence of R1 and R2 chains allow bisphosphonates to bind calcium phosphate and inhibit bone resorption by osteoclasts.[14]

Bisphosphonates inhibit osteoclast maturation and function and ultimately cause osteoclast apoptosis. Initially bisphosphonates were developed to treat predominately osteolytic bone metastases. However histomorphometric and biochemical evidence show that osteoblastic lesions also lead to increased osteolysis and bone turnover and that bone resorption markers are significantly raised in patients with advanced prostate cancer.[14]

There are 3 different classes of bisphosphonates; the first is characterized by the absence of nitrogen atoms; the second contains only 1 nitrogen atom, and the third has 2 nitrogen atoms.[20] **Zoledronic acid (ZA)** is one of the most active nitrogen-containing bisphosphonates, the third generation intravenous bisphosphonate that is at least 100 fold more potent than pamidronate.[7] It inhibits the enzyme farnesyl diphosphonate synthase and has been approved for treatment of bone metastases. Recent studies suggest that ZA also has direct antitumor activity.[16]

We reviewed the literature, using Pubmed (January 1966-2007) and the keywords zoledronic and pain. The initial search yielded 162 articles. After selecting those clinical studies published in English, 25 articles met our review criteria. Thirteen articles were applicable to the current case. The majority of studies were conducted in the United States and Italy (n= 7 and 5 respectively). Others were from Canada, UK, and one study from South Korea. The time frame ranged from 2000-2007. Study populations were Caucasians, and the minority of study populations were black and Asians. Mean age ranged from 57-72 years old. Proportion of male to female was close to 1: 1 overall.

Table 1 shows the types of study and demographic of patients in each study. Table 2 summarizes the methods and results of each study focusing on pain assessment and analgesic use in some clinical trials. A majority of patients received ZA 4

Table 1: Types of study and demographic

Study	Type of study	N	Age (mean age/ range)	Populations
Carteni et al.[1]	Multicenter, open-label study	316 pts screened, 312 pts enrolled	58.6+/- 11.7, 28-86	Breast cancer with newly diagnosed bone metastases
Facchini et al. [2]	Prospective study	60	76, 40-83	Breast and lung cancer
Hong et al. [3]	Prospective, multicenter, open-label trial	19	67.3/ 46-86	Hormone refractory prostate cancer
Ripamonti et al. [4]	Pilot study, prospective observational study	48	66/ 41-84	Breast and prostate cancer (N=34), (N=14)
Weinfurt et al. [5]	Randomized, double-blind, placebo-controlled, parallel-group study	422	71.8/72.2	Prostate cancer
Storto et al. [6]	Retrospective non-randomized trial	49	65(52-78), 70(58-82), 69(57-81)	prostate and breast cancer refractory to conventional treatment
Fulfaro et al. [7]	Prospective study	24	69, 45-75	Prostate cancer
Wardley et al. [8]	Randomized crossover study	101	60(37-87), 59(37-76)	Breast cancer
Berenson et al. [9]	Multicenter, open-label, dose-ranging, safety trial	59	N/A	Breast, MM, lung cancer, renal cell cancer
Berenson et al. [10]	Randomized, double-blind, double dummy, parallel group multicenter study	280	57.6+/-12.9, 56.5+/-13.6, 59.9+/- 11.3, 57.7+/-11.8	Breast cancer, MM
Clemons et al. [11]	Prospective study	31	58, 35-81	Breast cancer
Vogel et al. [12]	Open-label, prospective, multicenter study	638	66.4+/-11, 60+/- 13, 72.6+/- 9	Breast, prostate cancer, and MM
Saad et al. [13]	Randomized placebo controlled trial	458	72/73, 64/65	Prostate, renal cell cancer

mg, the standard dose intravenously every 3-4 weeks for a total of 3 months to 2 years depending on studies except study # 10 that used ZA dose ranged from 0.1-8 mg. pain assessment was evaluated before, while receiving treatment, and at the end of each study.

What is the benefit for this patient?

Of the 13 published studies, 7 focused on patients with metastatic, hormone refractory prostate cancer. Six out of the 7 studies demonstrated significant reduction in pain scores except that Ripamonti et al[4] showed that pain scores showed no statistically significant difference before and after treatment. This could be explained by the very small sample (N= 19) enrolled in this study.

Unlike bone metastases from other types of cancer, most bone lesions in prostate cancer are osteoblastic. However, recent studies showed that osteoblastic lesions not only have upregulated bone growth, but also concomitant increased osteolysis. The new bone created by tumor-stimulated osteoblasts is weak and poorly mineralized, and the osteopenia secondary to the increased osteolysis results in a bone matrix with severely compromised integrity. The risk of developing a skeletal complication is thus increased.[13] Fulfaro et al investigated the use of ZA in patients with bone metastases from prostate cancer and the effect on analgesic response and bone metabolism biomarkers. Besides the impressive pain control from ZA treatment, the bone metabolism biomarkers, C-telopeptide and bone alkaline phosphatase also decreased which confirmed the biochemical mechanism of action of zoledronic acid both on markers of bone formation and resorption.[7]

ZA is the only bisphosphonate confirmed to be effective in reducing skeletal complications associated with bone metastases from advanced prostate cancer.[13] The findings from these studies suggest that patients receiving ZA experienced a higher likelihood of clinically meaningful reductions in pain. Thus, ZA may help to avert the pain experienced by patients with progressing metastatic disease secondary to prostate cancer. The benefit from ZA therapy in terms of pain control and analgesic use from these 7 studies could potentially apply to Mr. X who has been through several modalities of treatment for his bone pain.

What are the risks?

ZA was well tolerated. Reported adverse events ranged from 2-60% of patients. These events were generally mild to moderate in severity and were consistent with known safety profile of i.v. bisphosphonates. From our review, we found that common adverse reactions were pyrexia (22-44%), fatigue (39%), skeletal pain (10-60%), nausea and vomiting (3%), headache (2-19%), hypocalcemia (9-33%), and confusion (7-13%).[1-13] All these events were mild in severity. Renal adverse events were noted, with an increase in serum creatinine levels from screening to final visit of < 0.5 mg/dL in 94.7% of patients from study #4 but all returned to within the normal range during follow-up.

Overall, ZA is the most broadly active i.v. bisphosphonate, and is the only one approved for preventing skeletal complications of malignancy in patients with bone metastases from all solid tumor types.[15] ZA is well tolerated with long-term use. It has an overall safety profile similar to other i.v. bisphosphonates and the renal safety profile is comparable with pamidronate when administered in accordance with treatment guidelines.[17] ZA is associated with a minimal risk of increased serum creatinine in patients with advanced prostate cancer and not influenced substantially by prior bisphosphonate exposure.[13]

Discussion

ZA has demonstrated statistically significant long-term efficacy and has the broadest clinical utility for pain palliation in a variety of tumor types of ZA therapy for bone pain secondary to bone metastases. The number needed to treat for bone pain calculated from available data from our review was 1.92 (indicating that 2 patients need to be treated with ZA to obtain improvement in 1), which strongly confirmed the superior benefit of this new drug treatment. ZA was extremely well tolerated in most clinical trials. Renal toxicity was the only serious safety finding after ZA treatment. Renal toxicity was related to dose (more with 8 mg than 4 mg), infusion duration (more with infusion over 5 minutes than 15 minutes), and total number of infusions. But no long- term complications were observed from the clinical trials.

Hypocalcemia is a side effect common to all bisphosphonates, regardless of administration method. However, it can be controlled with calcium and vitamin D supplements. Other adverse reactions were generally mild to moderate. Some patients reported only a single episode following the first infusion of ZA.

Table 2: Methods and results

Study	Dose/regimen	Parameters	Pain assessment	Results
Carteni et al.[1]	ZA 4 mg q 3-4 weeks* 12 months	BPI/ analgesic use	Every 12 weeks	3.3+/-2.2→2.6+/-2.3 -58% pain decreased -19% pain unchanged -37% decreased analgesic use -46% unchanged analgesic use
Facchini et al. [2]	ZA 4 mg q 3-4 weeks * 12 months	VAS	Before and 1 year after treatment	-Mod pain : 38.6% → 20.4 % -Severe pain: 38.6% → 9.1%
Hong et al. [3]	ZA 4 mg q 3-4 weeks * 6 months	BPI/ analgesic use	Every 4 weeks	1.5+/-0.5→1.7+/-0.5 -no statistically sig different in pain scores -use less strong opioids 6.6%-->0% -use less mild opioids 20→7.1%
Ripamonti et al. [4]	ZA 4 mg q 28 days * 6 months	VRS/analgesic score(six- level)	Every 2-4 weeks	VRS At rest: pain reduction=0.59 On movement: pain reduction= 0.86 Analgesic use decreased: At rest: 31% On movement: 27%
Weinfurt et al. [5]	ZA 4/8 mg q 3 weeks * 15 months	BPI	Every 4 weeks	Decreased pain in 33%
Storto et al. [6]	Gr.A ZA 4 mg q 3-4 weeks Gr.B ZA 4+^{89}Sr-Cl Gr.C^{89}Sr-Cl	VAS	Every week *2 months then 6 months later	Improvement of VAS: Gr. A 96% Gr. B 84% Gr. C 72%
Fulfaro et al. [7]	ZA 4 mg q 3-4 weeks* 1.5 years	VAS	0, 1st, and 3rd month	VAS 7.8+/-0.29→3.0+/-0.4
Wardley et al. [8]	ZA 4 mg q 4 weeks* 9 months	BPI	Every month	No BPI reported but significant pain reduction observed
Berenson et al. [9]	ZA 0.1,0.2,0.4,0.8,1.5,2,4,8 mg q 4 weeks * 3 months	Undefined pain scale/ analgesic score	Every week	No detectable improvement/worsening of pain scores
Berenson et al. [10]	ZA 0.4,2,4 and pamidronate 90 mg q 4 weeks * 10 months	BPI	Every 4 weeks	Decrease in pain scores in both groups, 67% & 50%
Clemons et al. [11]	ZA 4 mg q 4 weeks * 3 months	BPI	Every 4 weeks	Pain reduction 41.9% at 8 weeks
Vogel et al. [12]	ZA 4 mg q 3-4 weeks *6 months	VAS	Every 4 weeks	MM: 33.3+/-27→24.6+/-23 Breast: 32.8+/-24.5→26+/-24 Prostate: 34.7+/-25→33.2+/-29
Saad et al. [13]	ZA 4 mg q 3 weeks *2 years	BPI	Every 3 weeks	No BPI reported but less bone pain in ZA group

These clinical trials have confirmed the favorable benefits of ZA for bone pain secondary to multiple types of malignancy. Moreover, ZA was likely to be associated with clinical reductions in pain not only at rest but also on movement. This supports the consideration of ZA for bone pain reduction in metastatic bone disease due to prostate cancer. Taken altogether, the results of the contemporary randomized controlled trials indicate that ZA decreases the risk of skeletal complications and pain palliation in men with androgen-independent prostate cancer and bone metastases while other bisphosphonates: pamidronate, ibandronate, and clodronate, although tested, seem to be ineffective in this setting.[21,22]

What is this patient's decision for his next step of treatment?

The patient was treated with ZA, with improvement of his pain and reduction in his opiate dose.

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The author has no financial interests to disclose.

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