

Efficacy and safety of intravenous bisphosphonates beyond two years

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Citation

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Abstract

Background: Metastatic bone disease, a common complication of malignancy, causes significant morbidity in affected patients. Intravenous bisphosphonates (IBPs) have shown efficacy in preventing skeletal morbidity, however few studies have investigated their efficacy and safety in cancer patients beyond 2 years of use. This retrospective study documents long term clinical use of IBPs among a variety of patient populations and clinical settings. Methods: This study is a multi-center retrospective chart review of patients who received IBPs (Pamidronate or Zoledronic Acid) for more than 24 months. Patients were at least 18 years of age and had tumor-associated bone disease. Data analysis focused on skeletal related events (SREs) and drug related toxicities such as renal failure and osteonecrosis of the jaw (ONJ). Results: Ninety-two patients were included with the most common diagnosis being multiple myeloma. A total of 44 SREs occurred among 23 patients. Mean time to first SRE was 515 days. The rate of skeletal events in the first 2 years of treatment was 0.70, while skeletal morbidity rate (SMR) in subsequent years was 0.16. Thirteen patients experienced renal toxicity; most patients' renal function normalized after brief or permanent cessation of IBP therapy. ONJ was associated with 5 patients. Conclusion: Continuation of IBP therapy for skeletal metastasis after 2 years of treatment may improve skeletal morbidity. Similar to the first 2 years of treatment, significant toxicities such as renal failure and ONJ are uncommon.

INTRODUCTION

Bone metastasis leads to significant morbidity, such as bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy.^{1,2} Optimal management of bone metastasis is important as it may significantly improve quality of life, while reducing healthcare-associated cost and resources. This may be especially true for patients receiving novel cancer therapies which have been successful in prolonging survival.

Intravenous bisphosphonates (IBPs) have been proven effective in reducing skeletal related events (SREs) by several randomized trials. Two IBPs [Zoledronic Acid (Zometa®, Novartis) and Pamidronate (Aredia®, Novartis)] are currently available and have FDA approval for use in metastatic bone disease. These drugs inhibit tumor mediated activation of osteoclasts and thus reduce bone resorption. In general, IBPs are well-tolerated; however, serious adverse reactions such as renal failure and osteonecrosis of the jaw

(ONJ) can occur in a small minority of patients.³⁻¹² Large randomized trials have evaluated the renal safety of IBPs in patients with skeletal metastasis and found that renal failure is rare when the IBPs are administered at the recommended doses and infusion rates.¹³⁻¹⁶

No randomized controlled trial of IBPs has evaluated the efficacy or safety of use beyond two years. As better cancer therapies allow patients to live longer with metastatic disease, it becomes more important to know the optimal duration of therapy with these bone-targeting agents. Without supporting evidence to clearly direct duration of therapy, the decision to continue treatments is often at the discretion of the clinician. The American Society of Clinical Oncology (ASCO) recommends continuing IBP therapy in women with breast cancer until a substantial decline in the patient's general performance status based on clinical judgment.¹⁷ In multiple myeloma patients, ASCO recommends discontinuing bisphosphonate therapy for

patients with responsive or stable disease, or to continue therapy at the clinician's discretion.¹⁸ Due to the relative scarcity of evidence regarding the safety and efficacy of continuing IBPs in patients with skeletal metastasis who survive beyond two years, further investigations are needed to evaluate the optimal duration of treatment.

METHODS

We conducted a multi-center retrospective chart review of cancer patients receiving IBPs for metastatic bone disease for a duration greater than twenty-four months. Institutional review boards approved the study at three sites located in Albuquerque, New Mexico: The University of New Mexico Cancer Center, The Albuquerque Veterans Affairs Medical Center Hematology/Oncology Clinic, and the private practice group Hematology Oncology Associates. Patient eligibility criteria included being of 18 years of age or older, having radiographic and/or cytologic confirmation of bone metastasis, receiving treatment with intravenous Pamidronate or Zoledronic Acid at regular intervals for more than 24 months, and having sufficient follow-up data throughout the course of treatment.

Demographic information included ethnicity, gender, age, baseline height and weight, baseline performance status, baseline pain level, cancer type and stage at diagnosis, date of diagnosis of bone metastasis and distribution of bone metastasis. Treatment information included, IBP drug used, dose, infusion dates, duration of use, total number of infusions received, reason for discontinuation, any documented SRE's and concomitant anti-cancer therapy.

Efficacy was measured by the incidence of SREs, including pathologic fracture, spinal cord compression, or hypercalcemia of malignancy. If two SREs occurred in the same 21 day period, only the first event was counted to ensure that linked events were not counted as separate occurrences. Efficacy parameters included characterization of SREs occurring in the first two years and beyond two years of IBP treatment, time to first SRE, and skeletal morbidity rate (SMR).

Renal toxicity was determined by changes in serum creatinine. A significant increase of serum creatinine was defined as an increased by ≥ 0.5 mg/dl with a baseline ≤ 1.4 mg/dl, by ≥ 1.0 mg/dl with a baseline ≥ 1.4 mg, or if the baseline doubled. Each patient's serum creatinine was documented at baseline, prior to each administration of IBP, and at discontinuation of therapy or last known evaluation. T-test comparison was used to for statistical comparison of

the mean baseline serum creatinine measurement, highest mean creatinine measurement, and final mean creatinine measurements. Diagnosis of ONJ was determined solely by documentation in physician progress notes stating if the patient developed or experienced the condition.

RESULTS

A total of 92 patients met study inclusion criteria. The majority of our patients were white males (62%), and the most common cancer diagnosis was multiple myeloma (43%). Additional patient and treatment characteristics are presented in Tables 1 and 2, respectively.

Figure 1

Table 1: Patient Characteristics

Characteristic	N	%
Number of Patients	92	100
Sex:		
Male	57	62
Female	35	38
Age, years		
Median		62.5
Range		25 - 87
Race/Ethnicity:		
White	57	62
Hispanic	24	26
Native American	6	6.5
Other	5	5.4
Primary Diagnosis:		
Prostate	24	26
Breast	24	26
Multiple Myeloma	40	43
Other	4	4
Concurrent Cancer Treatments:		
Surgery	21	23
Radiation	31	34
Chemotherapy	69	75
Hormones	49	53
Biologic agents	17	18
Transplant	11	12
Site of Bone Metastasis:		
Upper Extremity	35	38
Lower Extremity	44	48
Axial skeleton	80	87
Calvarium	35	38

Figure 2

Table 2: IBP Treatment characteristics

Treatment Characteristics	Median	Range
Number of Treatments	36	13 - 97
Duration of Treatments, Months	42.1	24.7 - 128
Frequency of Treatments, Weeks	4.8	3.5 - 15
Reasons for Discontinuation	N	%
Hospice/Death/Performance Status	40	43.5
Renal Toxicity	5	5.4
Osteonecrosis of the Jaw	5	5.4
Other / Un-Documented	17	18.5
Patients Continuing Treatments	25	27.2

A total of 44 SREs occurred among 23 (29.3%) patients. Seventeen (74%) patients developed an SRE in the first two years of treatment, while 6 (24%) experienced an SRE after two years of treatment. Mean time to first SRE was 515 days

(95% confidence interval: 248 - 782). Overall SMR in the first two years was 0.70, while SMR in subsequent years was 0.16.

The most common reason for discontinuation of IBP therapy was deterioration of patient's condition due to disease progression. Several records failed to identify a reason for discontinuation of treatment. Furthermore, the physician's decisions to discontinue IBP treatments in these patients were not associated temporally with changes in the patient's performance status or development of adverse drug effects. Many patients' IBP treatments had yet to be discontinued at time of chart review.

Significant renal toxicity and ONJ were both uncommon and reported as reason for treatment discontinuation in only 10 patients. Significant differences were found between the mean baseline and mean highest creatinine levels ($p < 0.001$), but no significant differences were found between the baseline and final creatinine levels ($p = 0.0713$). Of the 13 patients who experienced renal toxicity (of all grades), serum creatinine returned to normal in 9 of the patients after brief or permanent cessation of IBP therapy. Only five patients permanently discontinued IBP treatments secondary to developing renal toxicity. Additionally, physicians suspected or documented a diagnosis of ONJ among five patients. No other unexpected significant toxicities related to IBP treatment were reported beyond 2 years of use apart from renal toxicity and ONJ.

DISCUSSION

This retrospective study documents clinical use of IBP despite limited evidence or guidelines endorsing such use in three different practice settings: a military facility, an academic facility, and private practice. Clinicians have chosen to continue IBP treatments to many patients (43.5%) until death or significant decline in performance status. Physicians infrequently attributed drug toxicity, either renal dysfunction (5%) or ONJ (5%), as reason to discontinue treatment. Although the median duration of therapy is 3.5 years, we documented patients receiving treatment for as long as 10 years. Although the interval between treatments increased over time, the reason for lengthening the time interval between treatments was poorly documented by physicians.

As expected, the SREs occurred less frequently as treatments continued. Although multiple factors may have influenced the incidence of SREs overtime, we have little reason to suspect there was a loss of efficacy of IBP therapy after two

years. Until more rigorous studies are conducted that prove otherwise, we conclude from our study that patients benefit from continued IBP treatment.

There does not seem to be a trend towards a cumulative renal toxicity as there was no significant difference between initial and final serum creatinine values. Our patient population had multiple risk factors for developing renal toxicity such as their underlying malignancy, use of cytotoxic chemotherapy, advanced age, and medical comorbidities; yet, almost all elevations in creatinine returned to baseline after brief or permanent cessation of IBP therapy. The relatively low incidence of renal toxicity observed in this study suggests that IBPs have little nephrotoxicity even beyond two years of use.

The mechanism of toxicity and predisposing risk factors for developing ONJ merits further research; however, it is reassuring to note that the rates remain low even among patients with prolonged IBP treatments. Establishing the pathophysiology underlying ONJ and identifying predisposing factors may assist in recognizing which patients are at increased risk. Many questions regarding the risks of ONJ and use of IBP remain unanswered and fall outside of the scope of this study.

It is important to note our study is consistent with two previously published retrospective reviews in terms of maintained efficacy and low incidence of toxicity.^{19,20} In contrast to those studies, we evaluated IBP use among a more diverse patient population with a higher percentage of males diagnosed with multiple myeloma and a larger representation of minorities. This is an important distinction considering the possible confounders of gender and underlying diseases on skeletal morbidity. In addition to confirming previously documented results, our study strengthens the ability to generalize such results to a larger patient population.

In short, this study provides additional evidence suggesting patients benefit from IBP therapy beyond two years without an increased risk of developing serious toxicities. While research is needed to determine the true efficacy of prolonged IBP treatments, clinicians are choosing to continue treatments in hopes that benefits outweigh known risks.

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