Acute Kidney Injury and Bisphosphonate Use in Cancer: A Report From the Research on Adverse Drug Events and Reports (RADAR) Project

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Abstract

Purpose: To determine whether acute kidney injury (AKI) is identified within the US Food and Drug Administration's Adverse Events and Reporting System (FDA AERS) as an adverse event resulting from bisphosphonate (BP) use in cancer therapy.

Methods: A search of the FDA AERS records from January 1998 through June 2009 was performed; search terms were "renal problems" and all drug names for BPs. The search resulted in 2,091 reports. We analyzed for signals of disproportional association by calculating the proportional reporting ratio for zoledronic acid (ZOL) and pamidronate. Literature review of BP-associated renal injury within the cancer setting was conducted.

Results: Four hundred eighty cases of BP-associated acute kidney injury (AKI) were identified in patients with cancer. Two

hundred ninety-eight patients (56%) were female; mean age was 66 ± 10 years. Multiple myeloma ($n = 220$, 46%), breast cancer ($n = 98$, 20%), and prostate cancer ($n = 24$, 5%) were identified. Agents included ZOL ($n = 411$, 87.5%), pamidronate ($n = 8$, 17%), and alendronate ($n = 36$, 2%). Outcomes included hospitalization ($n = 304$, 63.3%) and death ($n = 68$, 14%). The proportional reporting ratio for ZOL was 1.22 (95% CI, 1.13 to 1.32) and for pamidronate was 1.55 (95% CI, 1.25 to 1.65), reflecting a nonsignificant safety signal for both drugs.

Conclusion: AKI was identified in BP cancer clinical trials, although a safety signal for BPs and AKI within the FDA AERS was not detected. Our findings may be attributed, in part, to clinicians who believe that AKI occurs infrequently; ascribe the AKI to underlying premorbid disease, therapy, or cancer progression; or consider that AKI is a known adverse drug reaction of BPs and thus under-report AKI to the AERS.

Introduction

Bisphosphonates (BPs) inhibit malignant osteolysis, compromise cancer growth, and prevent bone destruction.¹ BPs are powerful inhibitors of bone resorption and lead to a positive calcium balance and increase in bone mineral content.² Preclinical evidence suggests that nitrogen-containing BPs, like zoledronic acid (ZOL), might have inherent antitumor and antiangiogenic properties.^{1,3} Up to 75% of patients with breast and prostate cancer develop skeletal metastasis in stage IV disease.⁴ Among patients with lung cancer, bladder cancer, or melanoma, approximately 40% develop bone metastases during the course of their disease. It is therefore not surprising that BPs have become a core component of cancer care.

Multiple myeloma commonly results in the development of lytic lesions, anemia, renal failure, and hypercalcemia.^{5,6,7} By blocking growth factor release from the bone matrix, BPs can indirectly impede myeloma growth.⁸ ZOL extended survival in a murine model of myeloma.^{9,10} Gnani et al¹¹ demonstrated a 36% reduction in the risk of developing recurrent breast cancer from the addition of ZOL to endocrine therapy. The Cochrane

Breast Cancer Review Group identified eight studies involving 1,962 women with advanced breast cancer and existing bone metastases. Among these women, BPs reduced the risk of developing a skeletal event by 14% (95% CI, 0.80 to 0.91; risk ratio, 0.86).¹² BPs are therefore effective for prevention and control of skeletal metastasis and humoral hypercalcemia.

In September 2011, the US Food and Drug Administration (FDA) issued a drug safety communication warning about the risk of acute kidney injury (AKI) with ZOL. Manufacturers were subsequently required to modify the package insert for BPs. Because BPs have become an important supportive therapy for patients with skeletal metastases, and because many patients with cancer are older and have attendant comorbidities, including diabetes mellitus and hypertension, they are at higher risk for BP-associated AKI. Furthermore, in advanced cancer, renal effects are related to dose, infusion duration, and total number of infusions of ZOL.¹³ Oncology clinical guidelines have therefore addressed prevention of AKI with dose reduction of BPs in patients with chronic kidney disease (CKD). The objective of this study was to evaluate the FDA's

Adverse Event Reporting System (AERS) for the occurrence of reports of AKI in patients with cancer in the setting of BP therapy.

Methods

RADAR (Research on Adverse Drug Events and Reports) research methodology has been previously described.¹⁴ Methods included analysis of the FDA AERS database, comprehensive review of published cases in manuscripts and conference abstracts, and preclinical studies to ascertain the pathophysiology of a serious adverse drug reaction (sADR). Our literature review included diagnosis and treatment of BP-associated AKI from Medline, PubMed, and EMBASE searches. Search terms included *renal*, *renal failure*, *kidney injury*, *renal impairment*, *kidney disease*, *breast cancer*, *multiple myeloma*, *metastasis*, *cancer* and *bisphosphonates*, *zoledronic acid*, and *pamidronate*. We conducted searches of Web sites including the FDA, European Medicine Agency, Australian Adverse Drug Reactions Advisory Committee, and Canada Health. We also searched the FDA AERS (January 1998 to June 2009) using 76 terms relating to renal problems, combined with all drug names for BPs. We also evaluated international drug safety Web sites.

Cases identified in the FDA AERS were included if BP therapy was for cancer-related indications. We included Zometa (ZOL 4 mg). A total of 480 reports with cancer diagnosis in the FDA AERS were identified. These reports were identified by a cancer diagnosis and use of chemotherapy or unique adjuvant therapy (letrozole, thalidomide). Multiple myeloma, breast cancer, and prostate cancer were most commonly identified. Within the FDA AERS, we analyzed safety signal detection estimates of proportional reporting ratio (PRR) and empiric Bayesian geometric mean (EBGM) values with 95% CIs to determine whether the number of BP-associated AKI reports was greater than those for other drugs.¹⁵⁻¹⁷ The PRR is a statistical aid to signal generation based on the proportionate approach that also utilizes the stability of a large database. It involves calculation of the proportions of specified adverse reactions for drugs of interest in which the comparator is all other drugs in the database. Judgments about the presence of a signal and signal strength are made on the basis of three pieces of information: the PRR, the χ^2 or 95% CI of the PRR, and the number of cases. A signal is defined as a PRR of 2 or greater, a χ^2 of at least 4, and three or more cases.¹⁵ The empiric Bayesian geometric mean is a quantitative method for signal detection that stratifies by age, sex, and time, and is less prone to false-positive signals.¹⁵

Results

FDA AERS

In the FDA AERS, we identified 480 reports of BP-associated AKI in patients with cancer. The majority (298; 56%) of patients were female, and the mean age was 66 ± 10 years; case reports included multiple myeloma ($n = 220$, 46%), breast cancer ($n = 98$, 20%), prostate cancer ($n = 24$, 5%) and undefined ($n = 139$, 29%). Associated agents included ZOL

($n = 411$, 87.5%), pamidronate ($n = 8$, 17%), and alendronate ($n = 36$, 2%). Outcomes included hospitalization ($n = 304$, 63.3%), death ($n = 68$, 14%), and "other" ($n = 71$, 15%). The PRR for ZOL was 1.22 (95% CI, 1.13 to 1.32) and for pamidronate was 1.55 (95% CI, 1.25 to 1.65), reflecting non-significant safety signals.

Following RADAR methodology,¹⁴ we assessed the pathophysiology and case reports of AKI. Of note, BPs have been associated with the development of renal cell apoptosis.¹⁸ In patients with advanced cancer, renal compromise is related to the dose of BP given, infusion time, and total number of infusions administered.¹³ Because of the attendant comorbidities often seen in the setting of advanced cancer, kidney toxicity was attributed to many factors, including ZOL.¹⁹ An unusual case of AKI in which the patient developed diffuse extracapillary necrotizing crescentic glomerulonephritis after ZOL administration for small-cell lung cancer was reported. Dialysis was required, and renal function improved after withdrawal of bevacizumab-ZOL.²⁰

Case Reports and Case Series

In the literature, we found few case reports on AKI with BPs. One case of AKI (in 1997) occurred 1 month after alendronate administration in a patient with newly diagnosed multiple myeloma and normal renal function.²¹ The French system recognized seven cases of ZOL-associated AKI (January 1, 2001 to June 1, 2004).¹⁹ In 2001, six cases involving patients with multiple myeloma or breast cancer who developed nephrotic range proteinuria and AKI with the collapsing variant of focal segmental glomerulosclerosis (FSGS) after treatment with pamidronate were described. Mild to severe tubular injury was also noted in all cases.²² In 2003, six cases of AKI after treatment with ZOL in five patients with myeloma and one patient with Paget's disease were reported.²³ All patients received pamidronate before ZOL administration, and all but one had a baseline creatinine level between 1.3 and 1.9 mg/dL. Each case had widespread severe tubular injury on biopsy, with kidney injury becoming clinically evident within 4 months of ZOL administration. Non-nephrotic range proteinuria was noted, but biopsies showed no FSGS. One case report in a 53-year-old patient with metastatic breast cancer being treated with pamidronate showed a collapsing form of FSGS.²⁴ FSGS is usually not a medication-related kidney disease and is usually seen with use of interferon- α , nonsteroidal anti-inflammatory drugs, and lithium, as well as with heroin and cocaine use.^{25,26} Collapsing FSGS induced by pamidronate has etiologic similarities to HIV, with direct insult to the podocytes and apoptosis with possible mitochondrial toxicity^{27,28} (Table 1).

Safety Warnings

The FDA issued a "Dear Doctor" letter in 2009 warning about ZOL²⁹ and recommended ZOL doses for patients with reduced renal function (mild and moderate renal impairment; creatinine clearance < 60 mL/min; Table 2).²⁹ Renal deterioration was defined as an increase in serum creatinine of 0.5 mg/dL, and for patients with abnormal baseline creatinine, an increase

Table 1. Case Reports of Bisphosphonate-Associated AKI in the Cancer Setting

Author	No. of Cases	Agent	Diagnosis	Histologic Findings	Clinical
Zazgornik (1997) ²¹	1	ALN	Myeloma, normal kidney function		AKI
Markowitz (2001) ²²	6	PAM	Breast cancer, myeloma	FSGS and tubular injury	AKI, nephrotic syndrome
Markowitz (2003) ²³	6	PAM/ZOL	Myeloma, Paget's disease	Severe tubular injury, FSGS	AKI
Munier (2005) ¹⁹	7	ZOL			AKI
Yoshizawa (2011) ²⁴	1	ZOL	Breast cancer	Collapsing FSGS	AKI

Abbreviations: AKI, acute kidney injury; ALN, alendronate; FSGS, focal segmental glomerulosclerosis; PAM, pamidronate; ZOL, zoledronic acid.

Table 2. Dosage Adjustment of Zoledronic Acid Recommended by the US Food and Drug Administration³⁰

Baseline Creatinine Clearance (mL/min)	Recommended Zometa Dose (mg)*
> 60	4
50-60	3.5
40-49	3.3
30-39	3.0

* Doses calculated assuming target area under the curve of 0.66(mg × hr/L) (creatinine clearance = 75 mL/min).

of 1.0 mg/dL.³⁰ Pre-existing renal insufficiency and multiple cycles of ZOL and other BPs were risk factors for subsequent renal deterioration with ZOL. Predisposing factors included dehydration or the use of other nephrotoxic drugs.³⁰ In September 2011, an FDA safety communication recommended monitoring of renal function with Reclast (ZOL).³¹ The European Medicine Agency also included ZOL dose adjustments in the package insert. Patients with serum creatinine of > 400 μ mol/L or > 4.5 mg/dL were excluded from clinical trials. Caution was advised when administering Aclasta (ZOL), on the basis of increased AKI risk.³² Since ZA was approved for use in patients with cancer in 2002, for Paget's disease in 2006, and for osteoporosis in 2008, there has been a trickle of reports to bodies such as the Australian Adverse Drug Reactions Advisory Committee (ADRAC) and the WHO database, some of which concern transient renal impairment, most of which occur in patients with cancer.^{32a} ADRAC also received a significant number of reports of AKIs after ZOL use in patients ranging in age from 44 to 88 years (median, 63 years). Time to onset was between 1 and 3 months after starting ZOL. The precautions listed within the Zometa (ZOL) product information include recommendations to monitor renal function and to adjust dose in patients with pre-existing renal impairment. Risk factors for renal adverse events include dehydration, pre-existing renal impairment, multiple cycles of BPs, use of other nephrotoxic drugs, and short infusion duration (< 15 minutes).³³ In Canada Health, dosing adjustments of ZOL in the setting of CKD were made in the package insert in 2005. Further warning recommending monitoring of renal function for Aclasta (ZOL) were recently publicized³⁴ (Appendix Table A1, online only).

Pathophysiology

Preclinical and clinical observations reveal that all BPs can potentially cause acute tubular necrosis.^{18,22,35,36} In clinical trials,

such as a phase II double blind randomized trial comparing three doses of ZOL administered over 5 minutes with 90 mg pamidronate, an increase in serum creatinine of 0.5 mg/dL was noted in 37 (13%) of 280 patients. This toxicity was most apparent at the highest dose (4 mg). Renal damage and elevations in serum creatinine levels were observed in the phase III trial of this drug, especially at the 8-mg dose tested initially.³⁷ The renal safety committee subsequently recommended abandonment of the 8-mg dose of ZOL, and the infusion time was extended from 5 to 15 minutes. Despite the increased infusion duration, some patients still experienced renal impairment. For example, of patients enrolled in a phase III trial for breast cancer and multiple myeloma, 9% of those treated with ZOL, given as 4 mg infused over 15 minutes, experienced deterioration in renal function. This rate compared with 8% of patients who received pamidronate (90 mg infused over 2 hours).³⁷ Rosen identified pamidronate as being less nephrotoxic. However, although pamidronate is generally well tolerated, some patients experienced renal function decline in the succeeding 12 months.^{37,38} In an uncontrolled study of 22 patients treated with pamidronate (n = 18) or ZOL (n = 4) for > 2 years (median, 3.6 years), the last serum creatinine level was significantly higher than baseline values.³⁹

BPs are excreted unmetabolized via the kidneys, although the exact mechanism is unknown. In rats and mice, the influx of these drugs into tubular cells is passive and is dependent only on the drugs' serum concentration and protein binding (Table 2). Excretion into the tubular lumen involves an active, limited transport mechanism, as has been shown in animal studies with pamidronate and alendronate.⁴⁰⁻⁴³ The renal histopathology associated with individual BPs can vary greatly, depending their degree of accumulation within the renal parenchyma, which in turn depends on their pharmacokinetics and pharmacodynamics.⁴⁴ In studies of patients with multiple myeloma with renal impairment undergoing renal biopsies, the most common cause was cast nephropathy (40%–63%), followed by light chain deposition disease (19%–26%) and amyloidosis (7%–30%).⁴⁵

Discussion

Our analysis of BP-associated AKI reports for cancer cases within the FDA AERS failed to demonstrate a significant safety signal. This was an unexpected finding, given prior preclinical and clinical findings that suggested a causal association between BPs and AKI. Furthermore, it contrasts with the FDA report of AKI in patients with osteoporosis treated with ZOL, which

Table 3. RIFLE Criteria for AKI⁶⁹

Category	GFR Criteria	UO Criteria	
Risk	Increased creatinine $\times 1.5$ or GFR decrease $> 25\%$	UO < 0.5 mL/kg/h $\times 6$ hr	High sensitivity
Injury	Increased creatinine $\times 2$ or GFR decrease $> 50\%$	UO < 0.5 mL/kg/h $\times 12$ hr	
Failure	Increase creatinine $\times 3$ or GFR decrease $> 75\%$	UO < 0.3 mL/kg/h $\times 24$ hr or anuria $\times 12$ hr	High specificity
Loss	Persistent AKI = complete loss of kidney function > 4 wk		
ESKD	End-stage kidney disease (> 3 mo)		

Abbreviations: AKI, acute kidney injury; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; RIFLE, risk, injury, failure, loss, end-stage kidney disease; UO, urine output.

resulted in numerous hospitalizations and four deaths.²⁹ Relevant guidelines and BP package inserts consider renal status in dosing and underscore the fact that AKI is an ongoing concern. The recent Bisphosphonate Management in Breast Cancer guidelines⁴⁶ published in 2011 recommended no change in the dosage of BPs for patients with glomerular filtration rate (GFR) of > 60 mL/min. These guidelines were established to determine the use of BPs in preventing and treating bone metastases. Furthermore, the package insert for ZOL provides information on dosing guidelines when GFR is 30 to 60 mL/min, and mandates the monitoring of renal function, hemoglobin, and albuminuria.⁴⁶

BP therapy prevents osteolytic bone involvement, aids in palliation of bone-related pain, delays bone metastases, and prevents cancer treatment-induced bone loss.⁴⁷⁻⁴⁹ The ASCO myeloma guidelines recommend that patients with bone destruction be administered pamidronate (90 mg) over 2 hours or ZOL 4 mg over 15 minutes every 3 to 4 weeks.⁵⁰ Furthermore, for patients with pre-existing renal disease (CKD) and serum creatinine < 3.0 mg/dL, no change in dosage, infusion time, or interval dosing of pamidronate or ZOL is required.⁵¹ The FDA, however, recommends BP dosing adjustment based on creatinine clearance. (Table 1) More recent 2007 guidelines for myeloma recommend administering pamidronate 90 mg over 2 hours or ZOL 4 mg over 15 minutes every 3 to 4 weeks for bone destruction or spinal compression fractures. Because the risk of osteonecrosis of the jaw is 9.5 times higher with ZOL, pamidronate is the recommended agent. Patients with estimated creatinine clearance of 30 to 60 mL/min should receive a reduced dosage of ZOL. Pamidronate should be substituted for patients with creatinine clearance < 30 mL/min. If renal deterioration occurs, BPs should be withheld, and renal indices and albuminuria should be monitored.⁵² Increasingly, oncologists are determining doses of BPs on the basis of creatinine clearance and GFR, rather than serum creatinine. Arguably, this change in treatment management could account for the lower risk of AKI in patients with cancer.

Patients with cancer are often older, and the physiologic changes of aging present many challenges in the setting of BP use. Decreased lean muscle mass, higher fat content, and decreased total body water affect drug metabolism and increase the risk of developing ADRs. Decline in GFR, coupled with decreased renal blood flow, leads to reduced drug clearance and increased concentration of drugs in the renal medulla.^{53,54} The loss of muscle mass can result in misleadingly lower serum

creatinine values, leading to significant morbidity and mortality from resultant drug toxicities.⁵⁵ In 2004, the Acute Dialysis Quality Initiative II group and representatives from three nephrology societies established the Acute Kidney Injury Network to facilitate international, interdisciplinary, and inter-societal collaborations and to ensure progress in the field of AKI, including the development of uniform standards for the definition and classification of AKI. As part of this process, the RIFLE (risk, injury, failure, loss, end-stage kidney disease) nomenclature and classification was modified to a staging/classification system that differentiates between AKI stage I, II, and III. In addition, a 48-hour time window for the diagnosis of AKI was introduced to ensure the kidney injury is an acute event.⁵⁶⁻⁵⁸ (Table 3).

sADRs, like those seen with BPs, are a frequently unrecognized cause of morbidity and mortality among patients with cancer. Although adverse events reported in preapproval clinical trials are likely to be included in the drug's initial package insert, in the postmarketing phase it takes a median of 7 years before adverse events are described by pharmaceutical suppliers or the FDA.⁵⁹ Detection of sADR signals for oncology therapies is especially challenging, as noted herein with BPs, because of the complexity in obtaining high-quality reports about the associated clinical events and the difficulty in determining whether the underlying cancer, comorbid illness, or suspect cancer agent should be assigned causality. In this era of increasingly shortened review periods, postmarketing pharmacovigilance is of paramount importance.⁶⁰⁻⁶³

The FDA AERS is an important source of adverse event reports, but physician reporting to MedWatch has decreased since its inception in 1993.⁶⁴ Only 1% to 10% of all physician-identified ADRs are reported to MedWatch.⁶⁵ Even with mandatory reporting requirements, physicians frequently fail to comply. Furthermore, the FDA is often unable to conduct follow-up investigations for many of the 300,000 reports it receives annually as a result of missing information and confidentiality constraints.^{65,66} A recent study assessing adverse event reporting to the institutional review board (IRB) at 49 comprehensive cancer centers found that of the 55 items considered for ADR evaluation, one item (event description) was present on the IRB ADR forms. Event severity and clinical outcome were noted on only 41% of the forms, and demographics and links between the ADR report and source documentation were frequently absent, which hampered oversight and auditing efforts by the IRBs.⁶⁷ In addition, in another study

on imatinib ADR reporting, IRB reporting was found to be half as effective as reporting from clinical records using a structured case report form.⁶⁸ These reporting deficits continue to overshadow potential adverse event signals, hamper assignment of causality, and exert negative downstream effects on patient safety.

This study has several limitations. The analysis was done from a self-reported pharmacovigilance database, the FDA-AERs. Thus, reports vary in comprehensiveness (eg, comorbidity, concomitant medications, hospital course) provided by the reporter. Reporters to the database were from various groups, including patients, physicians, pharmacists, and drug company representatives. Reports are de-identified, which hinders investigators' ability to obtain additional information from the patient and the family. In addition, many reports contain missing data elements.

Our findings may be attributed to low adverse event reporting to the FDA by clinicians who believe that AKI occurs infrequently and ascribe AKI to underlying premorbid disease, therapy, or cancer progression, or deem renal dysfunction (AKI) to be a well-known adverse effect of BP therapy and thus not subject to reporting as an adverse event. In addition, the newer AKI criteria (RIFLE and Acute Dialysis Quality Initiative II) have not been well disseminated among oncologists or integrated into the cancer literature, and the monitoring of renal function continues to be primarily through use of serum creatinine, resulting in an underdiagnosis of AKI. Undoubtedly, BPs are highly effective supportive therapy within the oncology arena, but their potential to cause AKI remains a challenge, and practicing oncologists need to be highly vigilant in terms of appropriate and guideline-driven renal monitoring when using these agents. BP use among patients with established CKD and associated adverse event outcomes in this setting remain as areas for further research.

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Appendix

Table A1. Serum Creatinine Increase Criteria Indicating Temporary Interruption of Therapy With Zoledronic Acid

Serum Creatinine	Withhold
Normal baseline (≤ 1.4 mg/dL)	Withhold zoledronic acid if serum creatinine increases by ≥ 0.5 mg/dL
Abnormal baseline (≥ 1.4 mg/dL)	Withhold zoledronic acid if serum creatinine increases by 1 mg/dL

NOTE. Resume the same dose when serum creatinine returns to within 10% of baseline value.