Zoledronic acid therapy impacts risk and frequency of skeletal complications and follow-up duration in prostate cancer patients with bone metastasis

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Abstract

Purpose—To evaluate the effects of timing and length of zoledronic acid (ZA) treatment on outcomes for patients with prostate cancer in clinical practice.

Materials and methods—Patients with prostate cancer and first bone metastasis diagnosed from January 2003 to October 2006 were included. Patients were considered 'untreated' if no ZA was given, 'early ZA-treated' if ZA was initiated before skeletal complication (SC) occurrence or 'late ZA-treated' if one or more SC was documented before or at ZA initiation. Patients were classified with short (≤90 days), medium (91–180 days) or long (>180 days) treatment persistence. Assessments included follow-up duration (FUP) and risk of developing one or more SC.

Results—Among eligible patients, 847 were untreated, 243 were early ZA-treated and 218 were late ZA-treated. For untreated versus early ZA-treated groups, median FUP was 263 versus 357 days (*p*<0.0001), respectively, and time to first SC was 199 versus 273 days (*p*<0.0001), respectively. ZA treatment was associated with significantly longer FUP and lower SC risk. The early ZA-treated group had significantly longer FUP versus the late ZA-treated group (median days, 357 vs. 299.5); the late ZA-treated group experienced significantly higher SC risk vs. the early ZA-treated group (odds ratio, 1.51). Compared with the long-persistence group, FUP was 56% and 40% shorter in the short and medium groups, respectively (*p*<0.0001).

Conclusion—Treatment with and early initiation of ZA for patients with prostate cancer and bone metastasis significantly prolonged time to and reduced risk of developing SC, while extending FUP.

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Keywords

Bone metastasis; Prostate; Prostatic neoplasms; Skeletal complication; Zoledronic acid

Introduction

Prostate cancer is the second most common cancer diagnosed in men world-wide 1. It is characterized by the propensity for developing bone metastases (BMs), which occur in more than 80% of patients with advanced disease[2]. Patients with prostate cancer are at high risk for skeletal complications (SCs) from BM and bone loss induced by cancer treatments (e.g., androgen-deprivation therapy)[1,3].

With a median survival of 30–35 months after a BM diagnosis, patients with prostate cancer experience considerable morbidity, adversely affecting patients' health-related quality of life and substantially increasing medical costs[4]. One study reported significantly higher total treatment costs (excluding bisphosphonate therapy) for those patients experiencing one or more SC ($7522) compared with those not experiencing an SC ($4180) in year 2000 US dollars[5]. In a recent retrospective study, the annual economic impact of treating SC in patients with prostate cancer with BM in the year after initial SC diagnosis was $12 469[6].

A review of several prostate cancer studies reported that bisphosphonates reduced SC and bone pain and reduced the adverse effects of androgen-deprivation therapy[7]. Zoledronic acid (ZA) is approved for treatment of BM in patients with prostate cancer who have progressed after one or more hormonal therapy. ZA decreased SC in a randomized controlled trial of patients with hormone-refractory metastatic prostate cancer[8,9]. ZA significantly decreases the incidence, delays onset and reduces overall risk of SC compared with placebo and has a well-recognized safety profile[10]. Controlled clinical trials also have demonstrated the long-term efficacy of ZA in preventing or reducing the risk of SC in men with advanced prostate cancer and BMs[11,12]. In elderly patients with BMs from solid tumors, the benefits of ZA in reducing pain and increasing health-related quality of life were reported[13]. Moreover, a review of *in vitro* and *in vivo* studies on the antitumor activity of bisphosphonates suggests that ZA may stop disease progression and reduce tumor burden in bone[14].

Given the central role that ZA plays in managing SC in patients with prostate cancer, a drug use review was conducted using a nationally representative claims database to further quantify the effect of ZA and to address questions regarding when to start ZA therapy and how long to remain on treatment[15]. The results indicated that greater persistence on ZA was associated with reduced risk of SC and prolonged follow-up duration (FUP) in a cohort of patients with solid tumors having experienced BM and one or more SC[15]. The present study incorporates an additional year of follow-up data and takes into account the unique aspects of managing patients with prostate cancer as it pertains to the experience of SC within the context of using intravenous (IV) bisphosphonate in clinical practice settings.

Materials and methods

Study design

This retrospective cohort study utilized the PharMetrics integrated managed-care claims database, which is nationally representative of employer-based health plans. Claims of more than 55 million patients from more than 80 United States (US) health plans were compiled. Data from January 2002 to October 2006 were analyzed, and patients with prostate cancer who had their first BM diagnosed from January 2003 to October 2006 were selected from the database. Men with a diagnosis of prostate cancer (International Classification of

Diseases, 9th Revision [ICD-9] code 185) and BM (ICD-9 code 198.5: secondary malignant neoplasm of bone and bone marrow) and who had been enrolled in the plan for ≥6 months prior to the initial BM diagnosis were selected. SC claims, including radiation therapy to bone (Current Procedural Terminology, version 4, code 77413), spinal cord compression (ICD-9 code 336.9), pathologic fracture of vertebrae (ICD-9 code 733.13) and bone surgery (ICD-9 code 78.10) also were collected. To avoid counting a continuous SC event more than once, a 21-day window as previously reported in a controlled trial was applied[16]. The number of SCs was adjusted with FUP to derive a monthly SC rate. The 6-month baseline before BM was used to identify potential baseline comorbidities. Patients who had neoplasms other than prostate cancer or multiple cancers were excluded, as were patients treated with IV bisphosphonates other than ZA.

Three groups were evaluated: (1) untreated patients who did not have a diagnosis of SC before BM and were not treated with ZA or other IV bisphosphonates; (2) early ZA-treated patients who did not have a diagnosis of SC before BM and first ZA treatment; and (3) late ZA-treated patients who had one or more SC documented before or at the initiation of ZA. Based on the US label recommending a ZA dosing schedule of every 3–4 weeks[9], treatment persistence was defined as the number of days from ZA treatment initiation to the date of the first gap more than 45 days between consecutive treatments. Patients were categorized as having short (≤90 days), medium (91–180 days) or long (>180 days) treatment persistence.

Outcomes assessment

The impact of ZA treatment patterns on outcomes was evaluated in three steps. First, ZA treatment was compared with no treatment regarding impact on the following patient outcomes: (1) FUP from first BM diagnosis to last claim available; (2) time to first SC; and (3) rate of SC after BM. Analyses then were performed on early ZA-treated versus late ZA-treated to investigate the risk and rate of SC after ZA initiation and the impact of treatment timing on FUP. Finally, the impacts of persistence with ZA on FUP, time to first SC and rate of SC after BM were examined by grouping the early ZA-treated patients according to their degree of persistence.

Statistical analyses

The propensity score method was used to control for possible selection bias in ZA administration[17]. Age, score on Charlson Comorbidity Index (CCI)[18,19], geographic location, year of first BM diagnosis, other metastases, more than one BM claim and opioid or oral bisphosphonate use before first BM diagnosis were entered into a logistic regression model as predictors of ZA treatment. Factors significantly associated with ZA administration were combined to calculate propensity scores, grouped by quintiles and entered as covariates in multiple regression models.

Means, medians and interquartile ranges (IQRs) were reported and appropriate statistical tests were performed. Moreover, depending on the studied outcomes, several types of multiple regression analyses were performed.

Treatment with docetaxel, a first-line agent in patients having castration-resistant prostate cancer, was included to identify patients with hormone-refractory prostate cancer[20].

All analyses were conducted using SAS 9.0 statistical software (SAS Institute, Inc, Cary, NC, USA).

Results

Patient characteristics by treatment groups

Among patients who met the inclusion criteria, 847 were untreated, 243 received ZA treatment before the development of an SC (early ZA-treated) and 218 received ZA treatment after or at the same time as occurrence of an SC (late ZA-treated).

Comparisons between untreated and early ZA-treated patients

The untreated group was significantly older and had a higher mean CCI score than the early ZA-treated group (both $p<0.0001$; Table 1). The proportion of patients treated with docetaxel was significantly higher in the early ZA-treated than the untreated group (46.1 vs. 6.4%, $p<0.0001$). The median (IQR) FUP from BM to last claim was 263 (461) days in the untreated and 357 (398) days in the early ZA-treated group ($p<0.0001$). Time to first SC was 199 (394) days for the untreated and 273 (364) days for the early ZA-treated group ($p<0.0001$). No significant difference in the proportions of patients with one or more SC after BM was observed (22.7% in the untreated group vs. 27.2% in the ZA-treated group). However, when the number of SC was adjusted for the longer FUP experienced by the ZA-treated group, the rate was significantly lower in the early ZA-treated than the untreated group (mean [SD]: 0.02 [0.15] vs. 0.05 [0.16] per month, respectively; $p=0.012$).

Propensity score calculations revealed that patients more likely to receive early ZA therapy were those diagnosed with BM in more recent years, who used an oral bisphosphonate before BM, who had other metastases before BM, who had more than one claim for BM, who resided in the West region (compared with those in the Midwest), who were younger and who had lower CCI scores (all $p<0.05$; Figure 1).

After adjustment with regression models, it was found that ZA significantly increased FUP ($p<0.05$), while older age and higher CCI scores reduced FUP ($p<0.0001$). Docetaxel-treated patients also experienced significantly longer FUP ($p<0.05$). On average, the early ZA-treated group had 28.5% (95% CI: 4.2%, 58.6%) longer FUP compared with the untreated group. Regression modeling also found that early ZA treatment significantly reduced the risk of SC compared with the untreated group (hazard ratio: 0.463; 95% CI 0.280, 0.679; $p<0.001$), while age, CCI score and docetaxel-treatment status were not significant. Moreover, there was a significant trend for SC risk to increase over time ($p<0.05$). Regression model on SC incidence showed that early ZA use reduced the number of SC by 33% (95% CI 1.2%, 54.5%; $p<0.05$) compared with the untreated group, while age and CCI score increased SC incidence ($p<0.05$; Table 2).

Comparisons between early and late ZA-treated groups

Early and late ZA-treated groups were comparable in age and CCI scores ($p>0.05$, Table 1). Neither geographic location nor year of first BM diagnosis influenced the timing of ZA treatment initiation. The two groups had similar proportions of patients who were docetaxel-treated (46.1% in early-treated groups and 47.3% in late-treated, $p>0.05$). In the unadjusted analyses, the early ZA-treated group had significantly longer FUP days than the late ZA-treated group (median [IQR] days, 357 [398] vs. 299.5 [384], respectively, $p<0.05$). In addition, there was a smaller proportion of early ZA-treated patients (27.2%) than late ZA-treated patients who developed a SC (35.8%; $p<0.05$) and had a significantly lower monthly rate of SC after early ZA treatment compared with late ZA treatment (mean [SD]: 0.03 [0.07] vs. 0.08 [0.21], respectively; $p<0.005$).

After adjusting for age, CCI score and docetaxel treatment, the late ZA-treated group had 17.5% (95% CI: 2.9%, 30.0%; $p<0.05$) shorter FUP than the early ZA-treated group.

Additionally, higher CCI score was associated with reduced FUP, and docetaxel treatment was associated with increased FUP (both $p<0.001$). The risk of SC after initiation of ZA was 50% higher in the late ZA-treated group than in the early ZA-treated group (odds ratio [OR]: 1.508, $p<0.005$, Table 3). Docetaxel treatment was associated with a significantly higher risk of having one or more SC after ZA treatment (OR: 1.658, $p<0.05$). Regression modeling also showed that the SC incidence was significantly higher in the late ZA-treated group, who experienced 57.5% (95% CI: 9.3%, 126.8%; $p<0.05$) more SC than the early ZA-treated group.

Comparisons among outcomes of ZA treatment by persistence groups

The mean age, CCI score and docetaxel-treatment status of the 243 early ZA-treated patients evaluated by level of treatment persistence were generally comparable. Although the long-persistence group had the greatest proportion of patients who were docetaxel treated compared with the other persistence groups, the chi-square test result was not significant. Unadjusted outcomes showed statistically significant differences in proportions of patients with one or more SC (short persistence, 21%; medium persistence, 17%; long persistence, 39%), median FUP and median time to first SC after BM (all $p<0.05$), but not the mean monthly SC rate ($p>0.05$, Figure 2).

Using the long-persistence group as a reference, short and medium treatment persistence were associated with significantly shorter FUP after multivariate adjustment ($p<0.0001$; Table 4). Compared with the long-persistence group, FUP was 56% and 40% shorter in the short and medium groups, respectively. No significant differences were observed between the persistence groups in risk or rate of SC ($p>0.05$). Docetaxel treatment was associated with longer FUP ($p<0.0001$) but did not have a significant impact on either the risk or rate of SC ($p>0.05$).

Discussion

The present study evaluated the managing patterns in patients with prostate cancer and BM as it relates to the use of the IV bisphosphonate, ZA, in the clinical setting. The study found that ZA use in this patient population is associated with significantly reduced SC risk compared with no treatment and significantly prolonged time to SC onset. More important, the timing of ZA treatment initiation is associated with positive clinical outcomes, with the best outcomes achieved in patients initiating treatment earlier in the course of metastatic disease and persisting on treatment longer without gaps of more than 45 days between consecutive administrations. The degree of therapy persistence also may influence patient outcomes. The present study shows that persistence on ZA treatment at a frequency of every 3–4 weeks is associated with a patient's FUP, which are nearly 56% shorter in the short-persistence group and 40% shorter in the medium-persistence groups, compared with the long-persistence group. No significant differences in the risk or rates of SC were observed between-persistence groups.

The study findings are relevant in the context of the clinical picture for patients with prostate cancer who develop BM and in light of earlier reported studies[11,12]. With the high prevalence for BM in these patients, health-care professionals are faced with multiple challenges in complication management. Malignant bone lesions affect skeletal structural integrity, resulting in SC (i.e., pathologic fracture, spinal cord compression and severe bone pain), all of which adversely affect patients' health-related quality of life[21]. For this reason, maintaining skeletal integrity and preventing SC are essential to the well-being of patients with prostate cancer. Consequently, early diagnosis and treatment of bone loss and BMs with bisphosphonates are recommended[1]. It also is recommended that bisphosphonate therapy be sustained throughout disease duration[22].

In an analysis of three large, randomized controlled trials, ZA was associated with a significant reduction in the cumulative SC incidence compared with placebo in patients with prostate cancer[23]. Long-term ZA treatment also afforded continuing clinical benefits in patients with advanced prostate cancer, even after the occurrence of SC[11]. Recent data suggest that early treatment with ZA before the onset of bone pain may be associated with anti-tumor effects and may positively affect survival in subsets of patients with elevated levels of N-telopeptide of type I collagen, a biochemical marker of bone resorption[24]. In the majority of patients with prostate cancer or other solid tumors who received ZA, normalization of elevated N-telopeptide of type I collagen levels was observed and correlated with extended survival[24].

In the present study, the significantly increased FUP associated with ZA treatment, especially in patients who persisted longer on ZA therapy, is notable when considering preliminary evidence suggesting both antitumor/antimetastatic properties and improved patient survival associated with ZA. The antitumor/antimetastatic properties include the inhibition of angiogenesis, tumor cell invasion and bone adhesion and antitumor synergy with cytotoxic chemotherapy[25,26]. Additionally, one recent study found that adding ZA to adjuvant endocrine therapy improved disease-free survival in premenopausal women with estrogen-responsive early breast cancer, while another showed that adding ZA to a combination chemotherapy regimen increased overall survival in patients with advanced (stage IV) lung cancer and BMs[25,26]. The latter study also showed that longer ZA persistence correlated with longer survival and time to progression[26].

In addition to the long-term data establishing ZA efficacy and safety in patients with prostate cancer from clinical trials[11,12], the seemingly positive impact of treatment with ZA in the clinical setting has been previously reported[15]. A recent retrospective claims study, which was used as a foundation for the current study, reported an association between ZA treatment and both the reduction in the skeletal morbidity rate and the delay in time to occurrence of SC in a combined cohort of patients with a diagnosis of BM and a solid tumor who experienced one or more SC[15]. Greater persistency of ZA use was also associated with lower monthly rates of SC[15].

The present study has several limitations. The PharMetrics database has a potential bias toward employer-type managed health plans, which may limit the generalizability of the results to other populations. Being an observational study, the selection bias might not be fully accounted for even with the use of the propensity score method. The severity of the patients' clinical status, BM and SC and the disposition of patients after disenrollment could not be fully ascertained in the claims data. Despite these limitations, the use of a claims database permitted the examination of a larger patient sample than would be possible using a chart review-based study.

Conclusions

The results of this study suggest that ZA therapy in patients with prostate cancer is associated significantly and positively with prolonged time to and reduced risk for developing SC, while extending FUP. Best outcomes were observed in patients who initiated ZA treatment earlier in the course of metastatic disease and persisted on indicated dosing frequency (i.e., no gaps of >45 days between two consecutive administrations). These findings may argue for earlier intervention and longer persistence with ZA in patients with prostate cancer with BMs.

Acknowledgments

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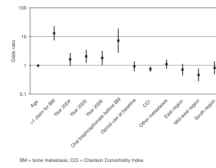
Figure 1.
Odds ratios and 95% confidence interval estimated from logistic regression on the propensity to receive early ZA treatment compared with no treatment (i.e., untreated). Comparison group was younger and had only one BM claim, BM diagnosed in 2003, no use of oral bisphosphonate before BM, no use of opioids at baseline, lower CCI score, no other metastases and residence in the West region. Significant variables were younger age, more than one claim before BM, BM diagnosed in 2005 or 2006, use of oral bisphosphonate before BM, lower CCI score and residence in the Mid-west region.
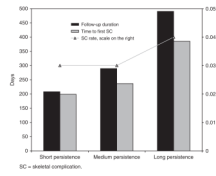
Figure 2.
Outcomes of early ZA-treated patients by level of treatment persistence. There was a significant difference among the three groups in median time of FUP and median time to first SC (*p*<0.05) but not in mean monthly SC rate.

Table 1

Characteristics of the untreated and ZA-treated groups.

Treatment group	Patients, *n*	Age, mean (SD)	CCI score, mean (SD)	Docetaxel treatment, *n* (%)
Untreated	847	68.03 (13.66)	8.88 (1.30)	54 (6.38)
Early ZA-treated	243	64.51 (11.19)	8.49 (0.85)	112 (46.09)
Late ZA-treated	218	66.19 (11.63)	8.60 (0.91)	103 (47.25)
Short ZA persistence	87	66.74 (12.47)	8.63 (1.11)	34 (39.08)
Medium ZA persistence	58	63.78 (11.49)	8.47 (0.71)	25 (43.10)
Long ZA persistence	98	62.96 (9.48)	8.37 (0.63)	53 (54.08)

SD, standard deviation; ZA, zoledronic acid.

Table 2

Results of regression models comparing untreated and early ZA-treated groups.

	Log of FUP: coefficient (SE) from multiple regression	Time to first SC: HR (95% CI) from Cox regression	No. of SCs: coefficient (SE) from Poisson regression
Age	−0.014 (0.003)[*]	1.008 (0.997–1.019)	0.016 (0.006)[†]
CCI score	−0.143 (0.033)[*]	1.097 (0.974–1.235)	0.134 (0.066)[†]
Docetaxel treatment	0.281 (0.118)[†]	1.291 (0.911–1.830)	0.116 (0.207)
Early ZA treatment	0.251 (0.107)[†a]	0.463 (0.280–0.679)[‡]	−0.399 (0.198)[†b]
Time × early ZA treatment[c]	Not included	1.002 (1.001–1.003)[†]	Not included

[*]$p<0.0001$;

[†]$p<0.05$;

[‡]$p<0.001$.

[a]Because the dependent variable is log-transformed follow-up duration, the exponential of this regression coefficient represents ratio of follow-up duration of the late ZA-treated group to that of the early ZA-treated group. The exponential of 0.251 is 1.285. Therefore, the early ZA-treated group had a follow-up duration about 28.5% longer than the untreated group.

[b]In Poisson regression, the exponential of this regression coefficient represents the ratio of skeletal complications in the late ZA-treated group to those in the early ZA-treated group. The exponential of −0.399 is 0.671; therefore, the early ZA-treated group had about 33% fewer skeletal complications than the untreated group, after controlling for follow-up duration.

[c]The interaction term between time and early ZA treatment was included only in the Cox regression model.

CCI, Charlson Comorbidity Index; CI, confidence interval; FUP, follow-up duration; HR, hazard ratio; SC, skeletal complications; SE, standard error; ZA, zoledronic acid.

Table 3

Results of regression models comparing early and late ZA-treated patients.

	Log of FUP: coefficient (SE) from multiple regression	Risk of SC after ZA: OR (95% CI) from logistic regression	No. of SCs: coefficient (SE) from Poisson regression
Age	−0.004 (0.004)	1.001 (0.982–1.020)	<0.001 (0.009)
CCI score	−0.143 (0.049)*	0.901 (0.704–1.155)	0.012 (0.118)
Docetaxel	0.340 (0.076)*	1.658 (1.106–2.485)†	0.025 (0.191)
Late ZA-treated	−0.193 (0.083)†	1.508 (1.010–2.251)†	0.454 (0.186)†

*
$p<0.001$;

†
$p<0.05$.

CCI, Charlson Comorbidity Index; CI, confidence interval; FUP, follow-up duration; OR, odds ratio; SC, skeletal complications; SE, standard error; ZA, zoledronic acid.

Table 4

Results of regression models comparing the three ZA-persistence groups.

	Log of FUP: coefficient (SE) from multiple regression	Time to first SC: HR (95% CI) from Cox regression	No. of SCs: coefficient (SE) from Poisson regression
Age	0.002 (0.005)	0.988 (0.963–1.013)	−0.004 (0.014)
CCI score	−0.092 (0.060)	1.157 (0.843–1.589)	0.092 (0.173)
Docetaxel treatment	0.421 (0.100)[*]	1.458 (0.881–2.412)	0.147 (0.270)
Short ZA persistence	−0.819 (0.114)[*]	0.683 (0.382–1.222)	−0.280 (0.315)
Medium ZA persistence	−0.510 (0.126)[*]	0.551 (0.273–1.112)	−0.284 (0.342)

[*] $p < 0.0001$.

CCI, Charlson Comorbidity Index; CI, confidence interval; FUP, follow-up duration; HR, hazard ratio; SC, skeletal complications; SE, standard error; ZA, zoledronic acid.