Published in final edited form as:

Leuk Lymphoma. 2015 March ; 56(3): 615–621. doi:10.3109/10428194.2014.924117.

Comparative Effectiveness on Survival of Zoledronic Acid versus Pamidronate in Multiple Myeloma

KM Sanfilippo^{1,2}, B Gage³, S Luo¹, K Weilbaecher⁴, M Tomasson⁴, R Vij⁴, G Colditz⁵, and K Carson^{1,4}

¹Saint Louis Veterans Health Administration Medical Center

²Division of Hematology, Department of Medicine, Washington University School of Medicine Saint Louis

³Division of General Medical Sciences, Department of Medicine, Washington University School of Medicine Saint Louis

⁴Division of Oncology, Department of Medicine, Washington University School of Medicine Saint Louis

⁵Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine Saint Louis

Abstract

Zoledronic acid and pamidronate are the two bisphosphonates approved to reduce multiple myeloma skeletal complications in the United States. Little prior evidence exists comparing survival outcomes between the two. We evaluated the incidence of skeletal related events and overall survival in myeloma patients treated with zoledronic acid versus pamidronate using a cohort of 1,018 United States Veterans. At median follow-up of 26.9 months, patients receiving zoledronic acid had a 22% reduction in risk of death compared to pamidronate (hazard ratio (HR) 0.78; 95% CI, 0.67–0.92). The benefit persisted after controlling for potential confounders. Adjusted Cox modeling with inverse probability weighting and propensity score matching supported these findings. Zoledronic acid was also associated with a 25% decrease in skeletal-related events. Zoledronic acid is associated with increased overall survival and decreased skeletal related events compared to pamidronate in patients with multiple myeloma and should become the preferred bisphosphonate.

Keywords

Multiple Myeloma; Bisphosphonates; Mortality; Comparative Effectiveness Research

Corresponding Author: Kristen M. Sanfilippo, MD, MPH, Division of Hematology, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8125, St. Louis, MO 63110, Phone: 314-362-0233, Fax: 314-362-8813, ksanfili@dom.wustl.edu.

POTENTIAL CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest in relation to the work described.

INTRODUCTION

Multiple myeloma is a plasma cell malignancy that causes significant bone destruction. At the time of diagnosis, 80% of patients have osteolytic lesions.¹ Multiple myeloma cells express interleukin (IL)-6, macrophage inflammatory protein (MIP)-1 α , and dickkopf (DKK1), that recruit and activate bone-destroying osteoclasts and suppress bone-forming osteoblasts causing severe bone loss and decreased bone integrity.^{2,3} Bone destruction places patients at risk for skeletal-related events defined as, bone lesions requiring surgery or radiation, pathologic fractures, hypercalcemia and spinal cord compression.⁴ Skeletal-related events cause significant morbidity and increase mortality.⁵ Therapy directed at preventing bone loss in multiple myeloma decreases skeletal related events and has the potential to improve survival.

Bisphosphonates are the treatment of choice for prevention of bone destruction in multiple myeloma.^{6,7} The nitrogen-containing bisphosphonates, zoledronic acid and pamidronate, inhibit farnesyl diphosphate synthase thereby inhibiting protein prenylation, a process crucial for osteoclast formation and survival.⁸ Inhibition of protein prenylation also interferes with cell adhesion, migration, and proliferation with preclinical studies demonstrating anti-tumor activity of bisphosphonates through effects on tumor cells, myeloid derived suppressor cells, gamma-delta T-cells and angiogenesis.⁹⁻¹² Morgan et al showed increased overall survival in 1,970 multiple myeloma patients treated with zoledronic acid compared to a non-nitrogen containing bisphosphonate (clodronate).⁶ The increased survival was independent of the effect on prevention of skeletal related events, supporting the hypothesis that zoledronic acid has additional anti-tumor activity. Indeed, several randomized clinical studies have demonstrated that administration of bisphosphonates in high-risk early stage breast cancer or in selected patient subsets has been associated with improved survival.¹³⁻¹⁶ The molecular mechanism(s) for these effects remains under active investigation.

Both zoledronic acid and pamidronate are widely used for prevention of bone destruction in multiple myeloma.⁷ In vitro studies show that zoledronic acid is 10 times more potent than pamidronate in the inhibition of farnesyl diphosphate synthase,^{17,18} a finding that may also translate to increased osteoclast and tumor cell apoptosis via increased inhibition of protein prenylation. A Cochrane meta-analysis of 20 trials found an association between higher bisphosphonate potency, measured by degree of inhibition of farnesyl diphosphate synthase, and overall survival in multiple myeloma.¹⁹ The VHA is the largest integrated health care system in the United States with facilities in all 50 states and Puerto Rico, providing care to a diverse population of patients. Healthcare is provided regardless of ability to pay, resulting in the care of a large number of medically underserved patients. This population represents an opportunity to compare the effectiveness of bisphosphonates in multiple myeloma in a pragmatic setting allowing analysis of patients who would have typically been excluded from randomized control trials, including those with multiple medical comorbidities. To test the hypothesis that zoledronic acid is associated with improved overall survival compared to pamidronate in multiple myeloma, we evaluated outcomes in a large cohort of United States Veterans with multiple myeloma treated within the VHA using the VHA Central Cancer Registry.

MATERIALS AND METHODS

STUDY POPULATION

Patients with newly-diagnosed multiple myeloma treated within the VHA system between October 1, 2002 and September 30, 2009 were identified in the VHA central cancer registry using international classification of diseases (ICD)-03 code 9732/3. The cohort was followed using administrative data through April 22, 2013. To exclude patients who may have had a multiple myeloma precursor disorder (i.e., monoclonal gammopathy of undetermined significance or smoldering myeloma), patients who did not receive therapy within 6 months of diagnosis date were excluded. Using Pharmacy Benefits Management records, we identified patients who had received zoledronic acid or pamidronate. Prior to cohort assembly, the Saint Louis VHA Medical Center and Washington University School of Medicine institutional review boards approved this study.

MEASUREMENTS AND DEFINITIONS

Treatment information was obtained using Pharmacy Benefits Management records, including dates of administration of all chemotherapy and/or bisphosphonates. Height and weight at diagnosis were determined as the values measured closest to and within one month of diagnosis. Using ICD-9-CM codes, the Romano adaptation of the Charlson comorbidity index was calculated for each patient at the time of diagnosis.²⁰ Hemoglobin, estimated glomerular filtration (eGFR) using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula, and albumin were measured at the time closest to but within two months of diagnosis and prior to treatment initiation. Patients with skeletal-related events were identified using a combination of ICD-9 and common procedural terminology codes using previously described methods.^{21,22} Overall survival was measured from the date of diagnosis of multiple myeloma until the date of death or end of the study follow-up period, whichever came first. Date of death was obtained from VHA vital status files. Patients with missing data were excluded from the study.

STATISTICAL ANALYSES

Baseline patient characteristics were compared between the zoledronic acid and pamidronate arms using Chi-square and Cochrane-Mantel-Haenszel tests on categorical variables and the unpaired Student's t-test on continuous variables. A two-tailed alpha significance level of less than 0.05 was used for all analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

The primary end point of the study was median overall survival at 5-years. Unadjusted survival curves were generated using the method of Kaplan-Meier with statistical comparisons using the log-rank statistic.²³ Cox proportional hazards regression modeling was used to assess association between bisphosphonate use and overall survival while controlling for known prognostic factors including continuous measured variables, age and Romano-Charlson comorbidity index, as well as categorical variables, race (black versus white), body mass index, era of diagnosis (before or after 2006), hemoglobin < 10 g/dL, eGFR < 30 mL/min/1.73m², albumin < 3 g/dL within 1 year of diagnosis, hematopoietic transplant status, and receipt of first line therapy with a novel agent. First line therapy with a

novel agent was defined as receipt of a thalidomide, lenalidomide, or bortezomib containing regimen within 60 days of initiating therapy.

Secondary study end points included time from diagnosis to first skeletal-related event as well as development of osteonecrosis of the jaw. Cox proportional hazards regression modeling was used to assess association between bisphosphonate use and development of a skeletal-related event while controlling for the same prognostic factors used in the main analysis.

ADJUSTMENT FOR CONFOUNDING

Randomized controlled trials are considered the gold standard for assessing the effect of treatment on outcome with the ability of random treatment allocation to balance measured and unmeasured patient covariates. Balancing patient covariates minimizes potential confounders that would also influence the outcome of interest. It was anticipated that patient covariates would significantly differ between the zoledronic acid and pamidronate treatment groups given the observational nature of the study. While Cox proportional hazards adjustment can account for differences in measured covariates, use of propensity scores can balance unmeasured covariates and decrease confounding bias.²⁴

Propensity scores were generated using logistic regression to estimate the probability that each patient would receive zoledronic acid conditional on observed baseline patient covariates,²⁴ providing us with the probability that each patient in the cohort, regardless of treatment group, would have received zoledronic acid. This probability is the propensity score. The individual variables used in the propensity model included: age (continuous variable), race, sex, treatment at a VHA affiliated with a large academic center, county size of treating VHA, eGFR, autologous transplant status, recipient of dexamethasone monotherapy, BMI, and year of diagnosis (continuous variable). Treatment outcomes between patients with similar propensity scores in the zoledronic acid versus pamidronate group can then be fairly compared.

Propensity score analyses were performed using the inverse probability weighting approach of Cole and Hernan²⁵ and propensity score matching. The covariates for each propensity model were those used in the main analysis. A comparison of patient covariates before and after generation of the propensity score verified the performance of the inverse probability weighting and propensity score matching (Table I).

SENSITIVITY ANALYSES

In September 1995, the United States Food and Drug Administration (FDA) approved pamidronate for treatment of bone lesions in patients with multiple myeloma. Zoledronic acid was approved in February 2002 for the same indication. Because pamidronate and zoledronic acid were approved at different times, clinical implementation of zoledronic acid lagged behind pamidronate. Therefore an analysis including bisphosphonate treatment crossovers was performed. In this analysis, patients who started on pamidronate but switched over to zoledronic acid were included in the pamidronate only arm (n=191, for a total of n=826) while patients who started on zoledronic acid but switched to pamidronate were included in the zoledronic acid only arm (n=134, for a total of n=517).

RESULTS

A total of 1,369 patients with multiple myeloma received zoledronic acid and/or pamidronate, of which 26 were excluded for missing data (Figure 1). Of these patients, 383 received only zoledronic acid and 635 received only pamidronate, for a primary cohort of 1,018 patients. Patients receiving zoledronic acid were less likely to undergo autologous hematopoietic transplantation, had a higher eGFR at diagnosis, were more likely to receive a novel agent as first line therapy, were more likely to live in a larger county, were more likely to ever receive lenalidomide, and were less likely to receive dexamethasone monotherapy. After propensity score adjustment for these and other factors, characteristics were well balanced between the groups at baseline (Table I). The median follow-up time for the cohort was 26.9 months.

Multiple myeloma patients receiving zoledronic acid had significantly improved overall survival compared to patients receiving pamidronate (Figure 2). The median overall survival for patients receiving zoledronic acid was 32.4 months compared to 23.4 months for those receiving pamidronate. After controlling for age, BMI, comorbidity score, era of diagnosis (before or after 2006), baseline lab characteristics, first line therapy with a novel agent (thalidomide, lenalidomide, or bortezomib), and transplant status, overall survival was significantly improved in patients who received zoledronic acid compared to those who received pamidronate with patients receiving zoledronic acid having a 22% reduction in the risk of death compared to those receiving pamidronate (HR 0.78; 95% CI, 0.67–0.92) (Table II). Several factors were associated with decreased overall survival in Cox regression modeling including: higher Romano-Charlson score per point increase, BMI <18.5 compared to normal weight BMI, hemoglobin < 10 g/dL, and eGFR < 30 mL/min/1.73m²; while recipient of a stem cell transplant and first line treatment with a novel agent were all associated with improved overall survival (Table II).

In addition to impact on overall survival, zoledronic acid reduced the risk of skeletal-related events compared to pamidronate by 25% (HR 0.75; 95% CI, 0.60–0.94). We also assessed the incidence of osteonecrosis of the jaw in the two-bisphosphonate populations. Of the 383 patients receiving only zoledronic acid, 10 developed osteonecrosis of the jaw (2.6%); while, 5 of the 635 patients who received only pamidronate developed osteonecrosis of the jaw (0.8%).

Using the propensity score with inverse probability weighting, the reduction in risk of death was maintained with zoledronic acid compared to pamidronate (aHR 0.84; 95% CI, 0.72–0.97) (Figure 3). This benefit was confirmed by the propensity score matched model (aHR 0.82; 95% CI, 0.68–0.97), although the statistical significance was borderline due to a smaller number of matched patients resulting in decreased statistical power.

Of the 1,343 patients initially identified, 517 started with zoledronic acid of whom 134 switched to pamidronate, while 826 started with pamidronate, of whom 191 switched to zoledronic acid. When bisphosphonate treatment crossovers were combined with the monotherapy cohort, the reduction in the risk of death from zoledronic acid remained significant (HR 0.76; 95% CI, 0.67–0.87).

DISCUSSION

In this large, multicenter cohort study of over 1,300 patients, zoledronic acid reduced the risk of death by 22% compared to pamidronate in patients with multiple myeloma (HR 0.78; 95% CI, 0.67–0.92). This benefit persisted even after controlling for potential confounders: Romano-Charlson comorbidity score, eGFR, hemoglobin, albumin, BMI, treatment with a first line novel agent, and receipt of an autologous stem cell transplant. Additionally, given the improvement of supportive care anticipated over the later part of the decade during which this study occurred, as well as the knowledge of the introduction of new, superior myeloma specific therapies during the later half of the decade studied, we adjusted for era of diagnosis to account for any survival benefit patients diagnosed later would have had. To account for inherent differences in baseline and treatment characteristics between the two treatment groups, propensity scores were used to balance the baseline covariates and minimize confounding. While there was significant overlap between the two groups, on average, patients who received pamidronate had a lower probability of being selected for zoledronic acid therapy (Figure 4). Zoledronic acid remained superior to pamidronate with inverse probability weighting (aHR 0.84; 95% CI, 0.72–0.97) and propensity score matching (aHR 0.82; 95% CI, 0.68–0.97) confirming its benefit. The benefit of zoledronic acid on overall survival persisted even after including patients whose bisphosphonate treatment crossed over. Additionally, zoledronic acid also reduced the risk of skeletal-related events by 25% (HR 0.75; 95% CI, 0.60–0.94).

Our results are consistent with those reported by Morgan et al., in which zoledronic acid reduced mortality by 16% (HR 0.84; 95% CI, 0.74–0.96) compared to clodronate.⁶ Prior to our study, limited data existed comparing the effectiveness of zoledronic acid versus pamidronate in multiple myeloma. A Cochrane meta-analysis of 20 trials found that higher bisphosphonate potency was associated with improved overall survival in multiple myeloma.¹⁹ No prior survival study directly compared zoledronic acid to pamidronate. A single phase III randomized control trial compared the efficacy of zoledronic acid versus pamidronate on skeletal-related events in patients with breast cancer or multiple myeloma.²⁶ Zoledronic acid was associated with a 16% reduction in the risk of a skeletal complication compared to pamidronate (HR 0.84; 95% CI, 0.72–0.98) in that cohort; however, the study was not powered to detect a difference in the myeloma only cohort ($n=194$) ($p = 0.59$). Thus, our findings add to the growing body of evidence that zoledronic acid is superior to pamidronate in patients with multiple myeloma.

The mechanism by which zoledronic acid may decrease mortality cannot be determined by this observational study, but is worthy of investigation. Nitrogen-containing bisphosphonates promote osteoclast apoptosis via inhibition of farnesyl diphosphate synthase, an enzyme crucial for prenylation of proteins needed for cell survival, and this inhibition may exert an anti-tumor effect in multiple myeloma.¹¹ Zoledronic acid is the most potent FDA-approved bisphosphonate in inhibition of farnesyl diphosphate synthase.¹⁷ It is hypothesized that greater inhibition of this enzyme may in turn increase the anti-tumor effect. Multiple myeloma cells promote enhanced osteoclast mediated bone resorption, which results in the release of growth factors from the bone matrix. The released growth factors feed forward to promote tumor cell growth and survival.^{3,4} Additionally, the protein

families Ras and Rho are affected by inhibition of farnesyl diphosphate synthase, both of which have been linked to myeloma cell growth and survival. These mechanisms are hypothesized to be responsible for nitrogen-containing bisphosphonate anti-tumor activity.

There were several strengths associated with the use of the VHA cancer registry for this study. The VHA is the largest integrated health care system in the United States with facilities in all 50 states and Puerto Rico, providing care to a diverse population drawn from throughout the United States. Healthcare is provided regardless of ability to pay, resulting in the inclusion of medically underserved patients into the cohort. As a population-based study, this study was able to evaluate effectiveness in a real world setting. This diversity allows for generalization of our findings to a large population of multiple myeloma patients. Given the comprehensive benefits provided by the VHA, the records regarding survival status are well maintained and accurate.²⁷

The retrospective identification of covariates from medical records limits the data available for inclusion in the analyses. Consistent with routine care, only a fraction of patients had cytogenetic or fluorescence in situ hybridization testing performed, prohibiting us from including these results into our analyses. This study also does not address the optimal duration of bisphosphonate therapy. Current guidelines recommend continued administration of a bisphosphonate while patients have active multiple myeloma.⁷ While incidence of osteonecrosis of the jaw was higher in the zoledronic acid group (2.6%) versus the pamidronate group (0.8%), an association between bisphosphonate and risk of osteonecrosis of the jaw could not formally be assessed. While the VHA is a comprehensive care facility, not all institutions have available a dental service to provide dental care and diagnose osteonecrosis of the jaw. Thus, a significant proportion of patients in our cohort may have received dental care outside of the VHA, and thus could have been missed in our assessment. The median overall survival noted in our cohort is less than that observed in recent randomized prospective trials. This is likely attributable to the presence of an older patient population with increased co-morbidities compared to the selective population of patients eligible for clinical trials. This is supported by the frequency of autologous stem cell transplantation within this study cohort, which is less of that than the general population.²⁸ Lastly, while we incorporated multiple methods to adjust for the presence of confounding, adjusted analyses can only address these issues partially. Zoledronic acid was more commonly the agent of choice in the second half of the study period analyzed. Patients entering the cohort in the second half were also more likely to receive more modern, effective therapies first line which invariably impacted their survival. Additionally, patients with renal insufficiency are more likely to receive pamidronate given prescriber concern regarding adverse effects of renal insufficiency associated with the more potent bisphosphonate zoledronic acid. While we performed adjustment for these variables, they may have still influenced to a degree our outcome. Finally, it is possible that unmeasured confounders were present in the groups that could influence the outcome of interest. These limitations notwithstanding, our data strongly suggests that zoledronic acid improves overall survival compared to pamidronate in patients with multiple myeloma.

Current guidelines recommend use of a nitrogen-containing bisphosphonate, zoledronic acid or pamidronate, for prevention of skeletal-related events in patients with multiple myeloma.⁷

With little prior evidence supporting use of zoledronic acid over pamidronate, some institutions prefer pamidronate due to reduced drug acquisition costs. However, with the recent expiration of the patent on zoledronic acid, generic versions of zoledronic acid will reduce cost.²⁹ The shorter infusion time of zoledronic acid (15-minute infusion) compared to pamidronate (120-minute infusion) is another advantage that is more attractive to patients and decreases drug administration costs.³⁰ In summary, zoledronic acid is associated with improved overall survival and fewer skeletal related events, has comparable drug cost, and has a shorter infusion time compared to pamidronate. Based on these benefits, zoledronic acid should become the preferred bisphosphonate for most patients with multiple myeloma.

Acknowledgments

FUNDING

Funding that supported completion of this study includes: NHLBI/5K12HL087107, Barnes Jewish Hospital Foundation, NCI/KM1CA156708, and NHLBI/U54 HL112303.

References

1. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003; 78(1):21–33. [PubMed: 12528874]
2. Oranger A, Carbone C, Izzo M, Grano M. Cellular mechanisms of multiple myeloma bone disease. *Clin Dev Immunol.* 2013; 2013:289458. [PubMed: 23818912]
3. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004; 350(16):1655–1664. [PubMed: 15084698]
4. Weilbaecher KN, Guise TA, McCauley LK. Cancer to bone: a fatal attraction. *Nat Rev Cancer.* 2011; 11(6):411–425. [PubMed: 21593787]
5. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer.* 2007; 110(8):1860–1867. [PubMed: 17763372]
6. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet.* 2010; 376(9757):1989–1999. [PubMed: 21131037]
7. Terpos E, Morgan G, Dimopoulos MA, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol.* 2013; 31(18):2347–2357. [PubMed: 23690408]
8. Russell RG, Xia Z, Dunford JE, et al. Bisphosphonates: an update on mechanisms of action and how these relate to clinical efficacy. *Ann N Y Acad Sci.* 2007; 1117:209–257. [PubMed: 18056045]
9. Corso A, Ferretti E, Lazzarino M. Zoledronic acid exerts its antitumor effect in multiple myeloma interfering with the bone marrow microenvironment. *Hematology.* 2005; 10(3):215–224. [PubMed: 16019470]
10. Croucher PI, De Hendrik R, Perry MJ, et al. Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. *J Bone Miner Res.* 2003; 18(3):482–492. [PubMed: 12619933]
11. Guenther A, Gordon S, Tiemann M, et al. The bisphosphonate zoledronic acid has antimyeloma activity in vivo by inhibition of protein prenylation. *Int J Cancer.* 2010; 126(1):239–246. [PubMed: 19621390]
12. Shipman CM, Rogers MJ, Apperley JF, Russell RG, Croucher PI. Bisphosphonates induce apoptosis in human myeloma cell lines: a novel anti-tumour activity. *Br J Haematol.* 1997; 98(3):665–672. [PubMed: 9332325]

13. Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol*. 2013; 24(2):398–405. [PubMed: 23047045]
14. Coleman R, Gnani M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. *J Natl Cancer Inst*. 2012; 104(14):1059–1067. [PubMed: 22752060]
15. Gnani M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med*. 2009; 360(7):679–691. [PubMed: 19213681]
16. Lipton A. Zoledronic acid: multiplicity of use across the cancer continuum. *Expert Rev Anticancer Ther*. 2011; 11(7):999–1012. [PubMed: 21806323]
17. Green JR, Muller K, Jaeggi KA. Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res*. 1994; 9(5):745–751. [PubMed: 8053405]
18. Widler L, Jaeggi KA, Glatt M, et al. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). *J Med Chem*. 2002; 45(17):3721–3738. [PubMed: 12166945]
19. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database Syst Rev*. 2012; 5:CD003188. [PubMed: 22592688]
20. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol*. 1993; 46(10):1075–1079. discussion 1081–1090. [PubMed: 8410092]
21. Velde NV, Wu EQ, Guo A, et al. The benefits of timely intervention with zoledronic acid in patients with metastatic prostate cancer to bones: a retrospective study of the US Veterans Affairs population. *Prostate Cancer Prostatic Dis*. 2011; 14(1):79–84. [PubMed: 21173792]
22. Krupski TL, Foley KA, Baser O, Long S, Macarios D, Litwin MS. Health care cost associated with prostate cancer, androgen deprivation therapy and bone complications. *J Urol*. 2007; 178(4 Pt 1):1423–1428. [PubMed: 17706711]
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assn*. 1958; 53(2):257–281.
24. Rosenbaum PRR, DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983; 70:41–55.
25. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004; 75(1):45–49. [PubMed: 15158046]
26. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003; 98(8):1735–1744. [PubMed: 14534891]
27. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr*. 2006; 4:2. [PubMed: 16606453]
28. McCarthy PL Jr, Hahn T, Hassebroek A, et al. Trends in use of and survival after autologous hematopoietic cell transplantation in North America, 1995–2005: significant improvement in survival for lymphoma and myeloma during a period of increasing recipient age. *Biol Blood Marrow Transplant*. 2013; 19(7):1116–1123. [PubMed: 23660172]
29. ANDA (Generic) Drug Approvals. 2013. Retrieved October 1, 2013, from <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/andagenericdrugapprovals/ucm349492.htm>
30. Berenson J, Hirschberg R. Safety and convenience of a 15-minute infusion of zoledronic acid. *Oncologist*. 2004; 9(3):319–329. [PubMed: 15169987]

Figure 1.
Study Cohort Flow Diagram

Figure 2.
Kaplan-Meier Estimates of Overall Survival in the Unadjusted Zoledronic Acid Versus Pamidronate Cohorts

Figure 3. Inverse Probability Weighted Propensity Score Adjusted Kaplan-Meier Estimates of Overall Survival in Zoledronic Acid Versus Pamidronate Cohorts

Figure 4. Propensity Scores for receipt of zoledronic acid in the pamidronate and zoledronic acid treatment groups

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Baseline Characteristics stratified by bisphosphonate group among US veterans diagnosed with MM from 2002 to 2009

Demographic clinical characteristics	Unadjusted Data			Propensity Score Matching			Adjusted with the Use of IPW		
	Pamidronate n=635	Zoledronic acid n=383	P-value	Pamidronate n=357	Zoledronic acid n=357	P-value	Pamidronate n=635	Zoledronic acid n=383	P-value
Age (mean yrs ± SD)	67.5 ± 10.6	67.9 ± 10.2	0.55 [†]	68.4±10.5	67.8±10.2	0.46 [†]	67.8 ± 9.5	68.1 ± 11.6	0.67 [†]
Male Sex (%)	98	96.1	0.08 [*]	96.9	96.6	0.83 [*]	97.4	97.1	0.81 [*]
Race (%)			0.12 [*]			0.56 [*]			0.89 [*]
White and other	74.5	70		73.1	71.2		73	73.4	
Black	25.5	30		26.9	28.9		27	26.6	
BMI			0.97 [§]			0.76 [§]			0.85 [§]
<18.5	3.3	3.4		3.6	3.4		3.3	3.5	
18.5 – <25	31.3	32.9		31.7	32.2		31.5	30.8	
25 – <30	40.2	36.6		36.1	37.8		39.1	39.0	
>=30	25.2	27.2		28.6	26.6		26.1	26.8	
Comorbidities (mean Charlson score)	2.6	2.4	0.19 [†]	2.7	2.4	0.12 [†]	2.6	2.5	0.37 [†]
Treatment (%)									
Autologous Stem Cell Transplant	15.6	11	0.04 [*]	10.9	11.5	0.81 [*]	13.7	13.3	0.84 [*]
First Line Treatment with Novel Therapy ^{‡§}	61.1	70.8	0.002 [*]	64.5	70.2	0.11 [*]	62.9	68	0.09 [*]
Melphalan	35.3	36.8	0.62 [*]	36.2	35.5	0.81 [*]	38.4	36.7	0.64 [*]
Lenalidomide	21.7	27.4	0.04 [*]	23.4	23.9	0.85 [*]	24.7	27.6	0.39 [*]
Thalidomide	51.3	52.7	0.66 [*]	51.5	51.3	0.94 [*]	51.1	52.8	0.65 [*]
Dexamethasone Monotherapy	22.7	16.2	0.01 [*]	20.5	20.8	0.91 [*]	19.0	17.1	0.49 [*]
Bortezomib	34.3	32.9	0.64 [*]	33.7	32.9	0.78 [*]	34.1	33.2	0.81 [*]
Laboratory Characteristics									
Hemoglobin g/dL (mean)	10.7	10.7	0.74 [†]	10.9	10.8	0.34 [†]	10.8	10.6	0.21 [†]
eGFR < 30 mL/min/1.73m2 (%) [†]	21.6	9.4	<0.0001 [§]	15.1	10.1	0.04 [§]	18.6	13.1	0.02 [§]
eGFR < 60 mL/min/1.73m2 (%) [†]	58	37.3	<0.0001 [§]	50.1	50	0.99 [§]	42.3	40.1	0.54 [§]
Albumin g/dL (mean)	3.3	3.3	0.88 [†]	3.3	3.2	0.83 [†]	3.3	3.2	0.65 [†]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Demographic clinical characteristics	Unjusted Data			Propensity Score Matching			Adjusted with the Use of IPW		
	Pamidronate n=635	Zoledronic acid n=383	P-value	Pamidronate n=357	Zoledronic acid n=357	P-value	Pamidronate n=635	Zoledronic acid n=383	P-value
Calcium mg/dL (mean)	9.7	9.5	0.06 [†]	9.6	9.5	0.48 [†]	9.7	9.6	0.41 [†]
Academic			0.23 [§]			0.55 [§]			0.71 [§]
Major Academic Center Affiliated VHA	70.4	65.5		63.6	65.6		67.4	65.9	
Minor Academic Center Affiliated VHA	16.2	20.4		20.7	20.2		18.8	20.1	
Insufficient or Non-Academic Affiliatd VHA	13.4	14.1		15.7	14.3		13.8	14.0	
County size			<0.0001 [§]			0.65 [§]			0.78 [§]
<1400000	44.9	59.3		58.3	56.6		50.7	51.6	
>=1400000	55.1	40.7		41.7	43.4		49.3	48.4	

* Chi-square test

[†] T-test

[§] Cochran-Mantel-Haenszel (Row Mean Score) test

^{%%} Defined as first line treatment with a thalidomide, lenalidomide, or bortezomib containing regimen

^γ Calculated using CKD-EPI

Table 2

Multivariate Cox Proportional Hazard Model for Overall Survival, Zoledronic Acid versus Pamidronate

Variable	Hazard Ratio	95% Confidence Interval	p value
Zoledronic Acid	0.78	0.67, 0.92	0.002
Body Mass Index			
BMI < 18.5	1.86	1.26, 2.74	0.002
25 BMI < 30	0.91	0.77, 1.09	0.18
BMI ≥ 30	0.83	0.68, 1.01	0.06
Age (Continuous)	1.01	1.00, 1.02	0.05
Race			
African American	0.88	0.74, 1.04	0.14
Charlson Comorbidity Index	1.10	1.07, 1.14	<0.0001
Diagnosis Year 2006	0.89	0.77, 1.04	0.15
Laboratory Data			
Hemoglobin < 10g/dL	1.21	1.03, 1.42	0.02
eGFR < 30 mL/min/1.73m ² [£]	1.37	1.14, 1.65	0.001
Albumin g/dL (within 1 year of diagnosis)	1.23	0.98, 1.55	0.08
Treatment History			
Autologous Transplant	0.46	0.35, 0.61	<0.0001
First Line Therapy With A Novel Agent [¥]	0.65	0.56, 0.76	<0.0001

[¥] First line therapy with a novel agent defined as receipt of a thalidomide, lenalidomide, or bortezomib-containing regimen within 60 days of initiating therapy.

[£] eGFR calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula