Bone Marker-Directed Dosing of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Multiple Myeloma: Results of the Z-MARK Study


Abstract

Purpose: Zoledronic acid (ZOL) given every 3 to 4 weeks can reduce skeletal-related events (SRE) in patients with bone lesions from multiple myeloma. This study evaluated efficacy and safety of less-frequent ZOL dosing based on bone turnover markers in patients with 1 to 2 years of prior bisphosphonate therapy.

Experimental Design: Patients received ZOL (4 mg) every 4 or 12 weeks based on urinary N-telopeptide of type 1 collagen (uNTX) levels (every 4 weeks if uNTX ≥50 nmol/mmol creatinine, every 12 weeks if uNTX < 50).

Results: Of 121 patients enrolled (mean age, 63.8 years; median follow-up, 21 months), 4 patients started ZOL every 4 weeks and 117 received ZOL every 12 weeks based on uNTX at study entry. All 4 patients who initiated ZOL every 4 weeks switched to every 12 weeks due to decreased uNTX. Thirty-eight of 117 patients who initiated ZOL every 12 weeks switched to ZOL every 4 weeks due to disease progression (n = 20), increased uNTX (n = 14), and SREs (n = 4). Overall SRE incidence was low; 7 (5.8%) and 5 (4.9%) patients experienced an SRE during years 1 and 2, respectively. Mean (SD) SRE rate at year 2 was 0.01 (0.03) per person-year. The 2-year incidence rate for osteonecrosis of jaw was 3.3%. Four deaths were reported, none related to ZOL.

Conclusions: Less frequent ZOL dosing (every 12 weeks over 2 years) maintains a low SRE rate and can be safely administered for up to 4 years. Clin Cancer Res; 22(6); 1378-84. ©2015 AACR.

See related commentary by Fonseca and Jain, p. 1301

Introduction

Approximately, 80% of patients with newly diagnosed multiple myeloma have skeletal involvement and are at increased risk for skeletal complications (1, 2). The increased rate of bone resorption and suppressed bone formation associated with myeloma bone lesions severely impairs normal skeletal homeostasis. This often results in debilitating skeletal-related events (SRE), including pathologic fracture of bone, spinal cord compression, hypercalcemia of malignancy (HCM), and the need for radiotherapy or surgery to bone (3–5). These SREs have a negative effect on quality of life and significantly increase morbidity and mortality.

Current treatment guidelines recommend i.v. bisphosphonate therapy to delay the onset and reduce the risk of SREs (6–8). Although not routinely used in clinical practice, the pharmacologic effect of i.v. bisphosphonate therapy can be assessed by measuring circulating levels of bone resorption markers, including urine N-telopeptide of type 1 collagen (uNTX). Several studies have demonstrated that NTX levels correlate significantly with the extent of bone involvement in multiple myeloma (9, 10), wherein higher levels are associated with increased risk for skeletal complications and disease progression.

To date, zoledronic acid is the only bisphosphonate with widespread regulatory approval for reducing the risk and delaying the onset of SREs across a variety of tumor types, including multiple myeloma. The results of Medical Research Council Myeloma IX trial support the use of zoledronic acid in patients with newly diagnosed multiple myeloma regardless of bone disease status at baseline (11). In this setting, zoledronic acid infusions (4 mg, every 3–4 weeks) significantly reduced the risk of SREs, demonstrating a low SRE incidence rate of 27% after a median follow-up of 3.7 years (11). In addition, there is clinical evidence to support monthly zoledronic acid dosing to prevent SREs and improve survival, and these data are reflected in current guidelines (6, 12). Treatment with zoledronic acid also significantly improved progression-free survival and overall
Translational Relevance

Zoledronic acid is indicated for the treatment of patients with multiple myeloma in conjunction with standard anti-neoplastic therapy. Although standard monthly infusions are effective in reducing the risk of skeletal complications, patients with normal bone metabolism may not require as intense a treatment schedule as patients with accelerated bone resorption. A reduced dosing schedule of every 12 weeks may be adequate for patients with normal bone metabolism and may mitigate long-term toxicity. This study evaluated a tailored approach to zoledronic acid therapy that aimed at maximizing the benefit–risk ratio and allowing an effective, less frequent dosing based on bone turnover marker, urinary N-telopeptide of type I collagen. In this study, the low skeletal-related event rate maintained for every 12-week dosing supports the efficacy of less frequent zoledronic acid dosing in patients with multiple myeloma who have already received 1 to 2 years of prior intravenous bisphosphonate therapy.

survival by 5.5 months versus clodronate in patients with multiple myeloma (13).

Currently, monthly zoledronic acid therapy is recommended for at least 2 years in patients with active bone disease (6–8); however, there is no guidance regarding the optimum zoledronic acid dosing schedule after the 2-year treatment period. The Zoledronic Acid - Bone MARKer-Directed Dosing (Z-MARK) study evaluated whether patients with multiple myeloma, who had received 1 to 2 years of prior i.v. bisphosphonate therapy, would continue to benefit from i.v. zoledronic acid infusions and if bone turnover markers, such as uNTX, could guide the frequency of treatment, on a schedule of zoledronic acid every 4 weeks or every 12 weeks.

Materials and Methods

The Z-MARK was a prospective, single-arm, open-label, multicenter study conducted to evaluate clinical benefits of bone marker–directed zoledronic acid dosing in patients with advanced multiple myeloma (14). This study was conducted in accordance with the Declaration of Helsinki, and all patients gave written informed consent. The protocol was reviewed and approved by an appropriate institutional review board or ethics committee at each participating center.

Patients

The study included patients (aged ≥18 years) with confirmed diagnosis of multiple myeloma and life expectancy of ≥9 months. Patients were eligible for enrollment if they were on standard monthly i.v. bisphosphonate (zoledronic acid or pamidronate) treatment, having received a minimum of 4 doses within 52 to 104 weeks of study entry. Previous standard monthly bisphosphonate treatment had been initiated for treatment of osteolytic lesion, bone fracture, spinal compression, or osteopenia. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, serum creatinine <3 mg/dL, and calculated creatinine clearance ≥30 mL/min at screening were included. Key exclusion criteria were known hypersensitivity to zoledronic acid or other bisphosphonates, use of investigational drugs with a significant effect on bone turnover, or a concurrent malignancy or history of a malignancy in the past 2 years except for basal cell or squamous cell skin cancer, cervical carcinoma, or treated early stages of prostate or breast cancer. Patients with current dental issues, recent or planned dental/jaw surgery, and current or prior osteonecrosis of the jaw (ONJ) were excluded. Patients with peripheral blood stem cell/bone marrow transplantation within 2 months before treatment or uncontrolled congestive heart failure, hypertension refractory to therapy, with a diagnosis of metabolic bone disease other than osteoporosis, or a diagnosis of primary amyloidosis and immunoglobulin M–related disorders were also excluded.

Study treatment and assessments

Patients received i.v. zoledronic acid (4 mg) for 96 weeks on a schedule of every 4 weeks or every 12 weeks based on the patient’s most recent uNTX measurement. Zoledronic acid administration was carried out on a schedule of every 4 weeks if uNTX levels were ≥50 nmol/mmol creatinine and every 12 weeks if the levels were <50 nmol/mmol Cr. Patients could switch to the alternate zoledronic acid dosing schedule while on study based on a change in uNTX level as described above. If patients receiving zoledronic acid every 12 weeks developed an SRE or had disease progression requiring change in antmyeloma therapy, then zoledronic acid was administered every 4 weeks regardless of uNTX level.

The primary end point was the proportion of patients who experienced at least 1 SRE during study year 1. Secondary end points included the proportions of patients experiencing each type of SRE and SRE rate per patient. SREs were defined as pathologic fracture, radiotherapy to bone, surgery to bone, spinal cord compression, or HCM. SREs were assessed at baseline and on study every 12 weeks during year 1, and by clinical assessments throughout the study period. Other clinical assessments included change from baseline in uNTX. uNTX and urine protein were analyzed by a central laboratory and measured at baseline, every 12 weeks up to week 84, and at the end of study visit (week 100). The dosing schedule was based upon urine NTX measurement that is performed every 12 weeks. The patient’s most recent urine NTX measurement was used to determine the next dosing schedule to be implemented. SRE rate per patient was calculated as the number of SREs divided by the time on study for the patient. Bone fractures or vertebral compressions occurring in year 2 were analyzed by a local reader. A bone survey was performed as soon as possible if an SRE occurred (e.g., fracture or spinal cord compression) between bone survey visits that were conducted at screening and every 12 weeks during year 1.

Safety assessments included recording of adverse events (AE) and serious AEs (SAE), collection of clinical laboratory data for hematology and blood chemistry, vital signs, physical condition, electrocardiogram, and pregnancy.

Statistical analysis

Sample size determination and power calculation were based on the primary efficacy variable, which was the proportion of patients with ≥1 SRE including HCM at the end of year 1. Assuming that approximately 37% of patients on the bone marker–directed dosing schedule would have at least 1 SRE as ascertained by bone surveys during the first year, the sample size required to estimate the proportion using a 95% confidence interval with a half-width of 10% was 90. Assuming a dropout rate of about 25%, 31 additional patients were enrolled bringing...
the total sample size to 121 patients. For each patient, the SRE rate was first calculated as the number of SREs divided by the exposure time in years. The efficacy variables were analyzed in the intent-to-treat population, which included all enrolled patients who received at least 1 dose of study drug and had at least 1 postbaseline assessment. All safety analyses were performed on the safety population, which included all enrolled patients who received at least 1 dose of study drug. Sample size estimation was performed using nQuery Advisor 4.0 (Statistical Solutions).

Results

Patients

This study was conducted at 67 centers in the United States. The first patient was enrolled in November 2007; the last patient completed the study in April 2012. Among the 121 patients enrolled, 84% (n = 102) and 57% (n = 69) completed the first and second year of treatment, respectively (Fig. 1). The reasons for study discontinuation prior to the planned 2-year duration include withdrawal of consent (14%), AEs (13%), elevated serum creatinine levels (7%), administrative problems (5%), death (3%), and abnormal test procedure results consistent with progressive disease (1%).

The baseline demographics and clinical characteristics of all enrolled patients are shown in Table 1. Approximately, half of the patients were male (52.9%) and the majority were Caucasians (76.9%), with a mean age of 63.8 years. Half of the patients (52.9%) had stage I multiple myeloma by the International Staging System. At baseline, 27% of patients had more than six osteolytic lesions localized predominantly to the femur (43%), humerus (40.5%), and skull (40.5%). The median duration of prior bisphosphonate therapy was 14 months (range, 1–36 months). Approximately, 86% of patients had received prior zoledronic acid therapy. Overall, 74.4% of patients had experienced ≥1 prior SRE, with vertebral fracture reported in 41.3% of patients.

At study entry, 4 patients initiated zoledronic acid every 4 weeks, and 117 patients initiated zoledronic acid every 12 weeks. The median dose per zoledronic acid infusion for both treatment schedules was 4.0 mg (range, 3.9–4.0). All patients received at least 1 zoledronic acid dose, with 87.6% (n = 106) of patients receiving at least 11 zoledronic acid doses (Table 2). Overall, 38 of

Figure 1. Consort diagram. *If a patient developed an SRE or had disease progression requiring a change in antinmyeloma therapy, zoledronic acid was administered every 4 weeks thereafter regardless of uNTX level. †Adverse events that led to discontinuation include back pain, dehydration, diarrhea, acute renal failure, respiratory failure, osteonecrosis of the jaw, and disease progression. Abbreviations: Cr, creatinine; ITT, intent-to-treat; q, every.
Multiple myeloma stage, a n (%) | N = 117
---|---
I | 64 (55.2)
II | 29 (24.0)
III | 20 (16.5)
Missing | 4 (3.4)

Time since diagnosis, months | Median 18.4
Range | 5–82

Number of osteolytic lesions, n (%) | N = 117
---|---
0 | 37 (31.6)
1–6 | 51 (43.4)
>6 | 33 (28.2)

uNTX, nmol/mmol Cr | Median 0.05
Range | 0.01–0.6

Prior bisphosphonate therapy, n (%) | N = 117
---|---
Zoledronic acid only | 104 (88.6)
Pamidronate only | 12 (10.3)
Zoledronic acid and pamidronate | 5 (4.3)

Duration of prior bisphosphonate therapy, months | Median 1.0
Range | 1–12

Change in uNTX | N = 117
---|---
Median | 0.044
25th, 75th percentile | 0.038, 0.052

Proportion of patients with ≥ 1 SRE | N = 121
---|---
Year 1 | 5.8%
Year 2 | 4.9%

Abbreviations: Cr, creatinine; CrCl, creatinine clearance.

*Based on the International Staging System.

Table 2. Average zoledronic acid dose per infusion

| Zoledronic acid dose, mg | N = 121
---|---
Median | 4.0
25th, 75th percentile | 3.9, 4.0

Number of doses, n (%) | N = 117
---|---
1–5 | 21 (17.4)
6–10 | 72 (59.5)
11–15 | 21 (17.4)
≥16 | 7 (5.8)

The median values were calculated based on the average dose per patient.

Incidence of SREs

During the first year on study, 7 of 121 patients (5.8%) experienced at least 1 SRE (Fig. 2). Some patients experienced more than 1 SRE, which included pathologic fractures (n = 3), spinal cord compressions (n = 3), radiation to bone (n = 4), surgery to bone (n = 1), and HCM (n = 1). During the second year on study, 5 of 101 patients (4.9%) experienced at least 1 SRE including 1 event of pathologic fracture and 4 events of radiation to bone. The mean (SD) SRE rates per patient during years 1 and 2, including hypercalcemia of malignancy or prior fracture, were 0.01 (0.049) and 0.01 (0.031). Of the 11 patients, who had an SRE on study, 6 had SREs while on every 12-week treatment.

Among the 11 patients, who experienced at least 1 on-study SRE, 5 patients had stage I multiple myeloma, 3 patients had stage II multiple myeloma, and 1 patient had stage III multiple myeloma at the time of study entry. Prior antineoplastic therapies reported for these patients included bortezomib, dexamethasone, thalidomide, cyclophosphamide, melphalan, doxorubicin, and vincristine. Two of the patients who experienced SREs were subsequently found to have disease progression approximately 4 months after presenting with SREs.

Change in uNTX

Overall, mean uNTX values generally decreased from baseline throughout the study period. The mean (SD) percentage

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The 117 patients (32.5%) initially assigned to 12-week dosing switched to 4-week dosing, and the remaining 79 patients continued the 12-week dosing schedule until study completion. The reasons for a change in initial zoledronic acid administration frequency included disease progression (n = 20), increased uNTX (n = 14), and SREs (n = 4). Disease progression was a prespecified protocol criteria for every 4-week dosing. No patient had progressive disease at study entry. Patients who switched to 4-week dosing remained on this schedule for the duration of the study regardless of their subsequent uNTX measurements.
change from baseline in uNTX was $13.36 (47.36)$ at the end of study ($P < 0.001$; Fig. 3). Throughout the study, only 14 patients had $uNTX/Cr \geq 50$, and these were observed during the first year of the study and these uNTX levels were moderate to high (range, 50–82 nmol/mmol creatinine). The majority of uNTX shifts observed were from normal to low levels or maintenance of low levels. Analysis using a Cox regression model demonstrated that baseline uNTX level was not predictive of SREs during the first year on study.

Safety

The most frequently reported AEs (all grades) included fatigue (26.4%), upper respiratory tract infection (24.0%), diarrhea (21.5%), and pneumonia (21.5%; Table 3). Grade 4 AEs were reported in 10.7% of patients and included thrombocytopenia ($n = 6$), neutropenia ($n = 4$), respiratory failure ($n = 3$), cardiac failure ($n = 3$), and leukopenia ($n = 2$). However, only 17 patients (14%) experienced at least 1 AE that was suspected to be related to the study drug.

Adverse events leading to zoledronic acid discontinuation occurred in 19.8% of patients, the most common being serum creatinine increase (5%), ONJ (3.3%), and acute renal failure (3.3%). Eleven patients required delay of zoledronic acid administration due to renal function deterioration, as indicated by changes in serum creatinine levels. Mean (SD) urine protein level at baseline was 14.43 (27.64) mg/dL. The mean (SD) urine protein change increased from baseline to 34.02 (80.10) mg/dL at study end. The mean (SD) corrected calcium at baseline was 9.36 (0.40) mg/dL. At study end, the mean change in corrected calcium from baseline to 34.02 (80.10) mg/dL. No specific trend was observed in changes over time or shift from baseline to higher or lower corrected calcium levels.

Overall, $39.7\%$ of patients had at least 1 SAE during the study. The most common SAEs were pneumonia (9.9%), acute renal failure (4.1%), anemia (3.3%), ONJ (3.3%), and congestive heart failure (3.3%). Fourteen patients (11.6%) discontinued from the study due to SAEs, the most common SAEs resulting in discontinuation of study drug were ONJ (3.3%, $n = 4$) and acute renal failure (3.3%; $n = 4$). The rate of ONJ was 3.3% at the end of 2 years; 1 patient had grade 3 and 3 patients had grade 2 events. Except for ONJ, none of the SAEs were suspected to be related to zoledronic acid treatment. Four deaths were reported on study, none of which were suspected to be related to zoledronic acid: 2 from disease progression, 1 from pneumonia, and 1 of unknown cause.

Discussion

In the Z-MARK trial, only 5.8% of patients experienced at least 1 SRE during the first study year, which was well below the initially expected 37%, despite the fact that the majority of patients received zoledronic acid every 12 weeks. The low incidence of SREs observed in Z-MARK compared with historic controls may lead to a more favorable benefit-risk profile.
be in part due to recent improvements in antimyeloma therapies, which are also known to have bone-protective effects. Overall, approximately 32% of patients who started on zoledronic acid dosing every 12 weeks switched to standard monthly dosing. The patients who had disease progression were switched to standard zoledronic acid dosing (every 4 weeks). These data suggest that patients who have already received 1 to 2 years of i.v. bisphosphonate therapy continue to derive SRE-protective effects from less frequent zoledronic acid dosing. This is the first prospective study in patients with multiple myeloma where the relationship between prolonged therapy with zoledronic acid treatment (3–4 years) and cumulative SRE incidence has been established. However, there are limited data on estimation of SRE reduction rates in patients with multiple myeloma with this duration of bisphosphonate therapy. Low SRE incidence during long-term zoledronic acid therapy has been previously reported in a retrospective claim analysis on 4,546 patients with bone metastases from a single tumor type (breast, lung, or prostate cancer; ref. 15). The monthly SRE rate decreased with increased durations of zoledronic acid therapy, with approximately 1 SRE occurring every 9 months in patients receiving zoledronic acid 4 mg every 3 to 4 weeks for longer than 1 year (15).

Changes in bone turnover markers may provide potential insight into bone destruction rates in patients with malignant bone disease. High baseline NTX serum concentrations have been shown to be associated with an increased risk of SREs and a negative effect on survival (16). In this study, mean uNTX values generally decreased throughout the study period. The low level of uNTX obtained at baseline in patients who had received 1 to 2 years of prior bisphosphonate treatment is consistent with the antiresorptive activity of standard monthly zoledronic acid dosing for 1 to 2 years in patients with advanced disease (17, 18). Hence, monthly dosing of zoledronic acid may be needed to suppress aggressive bone resorption as indicated by high NTX levels during initial therapy for bone lesions (19). In patients who had received 1 to 2 years of prior bisphosphonate therapy in Z-MARK, baseline uNTX levels were generally low, with levels above 50 nmol/L in only 4 patients. The low measurements of uNTX obtained as a baseline at study entry for these patients who had had 1 to 2 years of prior zoledronic treatment were consistent with reports demonstrating antiresorptive activity of ZOL standard dosing for 1 year (17). These low levels, suggestive of adequate bone suppression, may have contributed to baseline uNTX levels not being predictive of future skeletal complications. Consistent with our findings, a recent exploratory analysis suggests that increases in NTX levels may not precede SREs in zoledronic acid–treated patients with normal baseline NTX levels (20). In addition to the open-label study design, the study has limitations in that uNTX assessments were performed only every 3 months, which may not be frequent enough to capture a rapid increase in uNTX level that may precede an SRE. Of note, the uNTX measurements were performed at the time of an SRE but were performed at the prespecified every 3-month interval. It may be that low-grade bone destruction occurred over several years, resulting in the SREs observed in our study, and that increases in uNTX are not detectable even with more frequent monitoring in patients who have been on previous bone antiresorptive therapy. Therefore, the utility of bone resorption markers such as uNTX as a predictive marker after prolonged antiresorptive therapy is questionable and underscores the need to study other novel biomarkers. Another limitation was the fact that patients with progressive disease were switched to a more frequent dosing schedule based on the prespecified protocol requirements. It is therefore unclear if these patients would have done just as well with less frequent dosing of zoledronic acid treatment.

The incidence of AEs and SAEs in this trial is consistent with that previously reported for this patient population. Overall, the rate of acute renal failure was low, and no events were suspected to be related to zoledronic acid treatment. In this study, zoledronic acid dose adjustment guidelines based on creatinine clearance appeared to be sufficient to maintain renal tolerability with long-term zoledronic acid treatment. This is consistent with relative renal safety demonstrated in other long-term studies of zoledronic acid in patients with multiple myeloma (13, 20).

ONJ has been reported as a complication in patients receiving nitrogen-containing bisphosphonates, such as pamidronate and zoledronic acid. In Z-MARK, the prospective analysis of ONJ revealed an incidence rate of 3.3% beyond 3 years. This result is consistent with the ONJ incidence (<5%) reported in long-term studies in patients receiving monthly zoledronic acid treatment for more than 2 years (20, 21). ONJ incidence has been shown to increase with longer duration of zoledronic acid exposure and is often triggered by invasive dental procedures or tooth extraction (22). Per treatment guidelines, patients are advised to proactively monitor and maintain good oral hygiene by regular dental examinations with preventive dentistry to reduce ONJ risk while receiving zoledronic acid therapy (23, 24). In conclusion, Z-MARK is the first trial to provide prospective clinical evidence to support the efficacy of less frequent zoledronic acid dosing during years 3 and 4 in patients who have already received 1 to 2 years of i.v. bisphosphonate therapy. Although uNTX levels were not predictive of SREs in this patient population, this study provides information about the use of zoledronic acid beyond 2 years of therapy, and it shows that a low SRE rate can be maintained in patients receiving zoledronic acid every 12 weeks. The overall low incidence of SREs clearly demonstrates that less frequent ZOL dosing beyond 1 to 2 years continues to provide SRE-prevention benefits and may reflect changing treatment patterns in the context of newer antimultiple myeloma therapies with some bone-protective effects. It, however, also highlights important information demonstrating continued risk of SREs in a patient’s lifetime albeit very low. Further studies will be required to identify other bone turnover markers that can be used as surrogates for predicting SREs and to tailor bone-directed therapy.

Disclosure of Potential Conflicts of Interest
N. Raje reports receiving consulting fees from Amgen, Celgene, Millennium, and Onyx, and research funding from Acetylon and Eli Lilly. R. Vescio reports receiving speakers bureau honoraria from Novartis. N. Mushli reports receiving consulting fees from Celgene, Janssen, and Onyx. K.C. Anderson reports receiving consulting fees from Celgene, Gilead, Millennium, Onyx, and Sanoﬁ-Aventis; and is a scientiﬁc founder of Acetylon and Oncopep. No potential conﬂicts of interest were disclosed by the other authors.

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Raje et al.

Authors’ Contributions


Acquisition of data (provided animals, collected, acquired and/or managed patients, provided facilities, etc.): N. Raje, R. Vescio, C.W. Montgomery, A. Badros, N. Munshi, R. Orofino, K.C. Anderson

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Raje, J.T. Hadala, G. Warsi, E. Argonza-Aviles, S.G. Ericson, K.C. Anderson


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.T. Hadala, G. Warsi, E. Argonza-Aviles, S.G. Ericson


K.C. Anderson

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Noopur Raje, Robert Vescio, Charles W. Montgomery, et al.


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