Vertebral fractures after denosumab discontinuation in breast cancer survivors—a single institution experience

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Abstract

Aim: To evaluate clinical vertebral fractures after denosumab discontinuation in patients with breast cancer. Methods: To evaluate the occurrence of clinical vertebral fractures after denosumab discontinuation, we conducted a retrospective chart review to identify patients with a history of breast cancer who were treated with denosumab between June 1, 2010 and July 18, 2018 at Memorial Sloan Kettering Cancer Center. We identified 335 postmenopausal female patients and one male patient with nonmetastatic breast cancer who received at least two doses of denosumab (60 mg) and had received their final denosumab injection at least 6.5 months earlier. Results: The median age of patients was 62 years (54–69). Patients received between two and 13 denosumab doses before drug discontinuation. The majority of patients (310; 92.3%) were also treated with aromatase inhibitors. Of the 194 patients with baseline bone-density data, 50 (25.8%) had normal bone density, 97 (50.0%) had osteopenia, and 47 (24.2%) had osteoporosis. The median follow-up duration from the last denosumab dose was 18.5 months (12.5–23.5). We identified one case of spontaneous vertebral fractures after denosumab stoppage. We found no cases of osteonecrosis of the jaw or atypical femur fracture. A majority of patients (88%) had a gap in denosumab dosing. Conclusions: Patients with breast cancer—especially those taking aromatase inhibitors—taking denosumab should be warned of the risks of delaying denosumab. Larger prospective studies are needed to fully evaluate the risks of stopping or delaying denosumab

INTRODUCTION

Denosumab, a monoclonal antibody against receptor activator of nuclear factor κ-β ligand (RANKL), is a potent antiresorptive agent that improves bone mineral density (BMD) and reduces fracture risk.[1] Denosumab, which is administered subcutaneously (60 mg) every 6 months, has been approved by the Food and Drug Administration (FDA) to prevent fragility fractures in both male and postmenopausal female osteoporosis patients at high risk for fracture and to prevent bone loss in patients with breast and prostate cancer who receive endocrine therapy. Denosumab therapy leads to immediate reductions in bone turnover, as measured by biochemical bone turnover markers (BTMs) such as pro-collagen type 1 N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type 1 collagen (CTX).

Discontinuation of denosumab results in a rapid rebound increase in BTM, with levels returning to baseline approximately 18–24 months after the final denosumab dose.[2, 3, 4] BMD gains are also lost after discontinuing denosumab, with BMD values returning to baseline 1 year after ending treatment.[2, 3, 4] A higher number of denosumab doses is associated with incremental BMD gains but is also associated with rapid bone loss once denosumab is stopped.[5] Single or multiple clinical vertebral fractures (MCVFs) have been reported after denosumab discontinuation and have been hypothesized to be related to the rebound increase in bone turnover and the rapid regression of bone density.[5-8]The antiresorptive effect of denosumab rapidly dissipates; MCVFs have been reported to occur 9 to 16 months following last denosumab injection.[6] Therefore, even a

gap in dosing (i.e. delaying the subsequent densumab dose by more than 6 months) could put the patient at risk for rebound fractures. Several retrospective studies have suggested that bisphosphonates given before or after denosumab discontinuation may reduce the rebound increase in BTMs and decrease in BMD. However, anecdotal evidence from case reports suggests that bisphosphonates may not be able to prevent MCVFs after denosumab stoppage.[9] To date, the risk factors for spontaneous MCVFs after stopping denosumab are largely unknown, though it appears that patients with a prior history of vertebral fracture may be at greatest risk for MCVFs upon drug discontinuation.[10]

A post-hoc analysis of the FREEDOM and FREEDOM extension trial evaluated 1001 postmenopausal women for seven or ten years after discontinuing denosumab and concluded that the risk of vertebral fractures was not significantly different after denosumab or placebo cessation.[7]After discontinuing denosumab, the rate of vertebral fractures increased to 7.1 per 100 participant-years (95% confidence interval [CI] 5.2–9.0), similar to the rate before and after discontinuing placebo (7.0 [95% CI 5.2–8.7] and 8.5 [95% CI 5.5–11.5] per 100 participant-years, respectively).[11] Of particular concern, a majority of participants who sustained a vertebral fracture after discontinuing denosumab had multiple vertebral fractures. This analysis may have been confounded by an unexpected observed increase in the risk of vertebral fracture after placebo discontinuation.

Very few prospective studies have analyzed fracture incidence after denosumab therapy cessation, and none of them were specifically designed to assess fracture risk. A post-hoc study published by Zanchetta et al. observed 38 postmenopausal women for a mean duration of 17 months (range 16–20) between the last dose of denosumab and follow-up visit and found evidence for rapid bone loss after discontinuing treatment.[10] However, the incidence of fractures after stopping denosumab is still undefined because of the small number of patients and lack of power in these studies.

Many postmenopausal patients with breast cancer receive adjuvant endocrine therapy with aromatase inhibitors (AIs), which are known to decrease bone density and increase fracture risk.[12] In women with osteopenia who are not at high risk for fracture, denosumab is often discontinued after cessation of AI therapy. However, to our knowledge, there have been no published studies evaluating the effect of stopping denosumab in patients with breast cancer. A systemic review of 24 cases of vertebral fractures after denosumab discontinuation demonstrated that five patients were concurrently taking AIs and that fractures generally occurred eight to 16 months after the last dose of denosumab.[5] Most recently, Gonzalez-Rodriguez et al. reported a case series of 15 women that received AI for 5.0 years (± 0.6) and 8.2 doses (+- 2.0) of denosumab. The women were followed for 24.4 months (+- 9.5), and between one and 11 (mean 4.0 +- 1.9) clinical vertebral fractures within seven to 16 months after last denosumab injection were reported.[13] Pfeiler et al. recently presented data demonstrating that postmenopausal patients with hormone receptor positive–breast cancer treated with adjuvant AIs who stopped denosumab had a significantly higher risk of developing a clinical vertebral fracture (hazard ratio [HR] 2.44; 95% CI 1.12–5.32) and MCVFs (HR 3.52; 95% CI 0.98–12.64) than patients who stopped placebo. However, this increased risk was only observed in patients who ended AI treatment prior to or more than 6 months after the last dose of denosumab/placebo, whereas no difference was seen in patients who ended AI treatment within 6 months of stopping denosumab/placebo.[14]

We performed a retrospective chart review to identify postmenopausal patients with nonmetastatic breast cancer treated with denosumab at Memorial Sloan Kettering Cancer Center (MSK) in order to gain insight into the risk for, and incidence of, MCVFs in this population. The aim of the study was to evaluate clinical vertebral fractures after denosumab discontinuation in patients with breast cancer.

METHODS

With an institutional review board waiver, we conducted a retrospective review of charts of patients with a history of breast cancer who were treated with denosumab at MSK between June 1, 2010 and July 18, 2018 ($n = 469$ prior to exclusions). Patients were identified using MSK's pharmacy database. We conducted a detailed review of all healthcare provider notes and, if available, imaging studies, to identify any patients who had sustained either clinical fractures (both vertebral and nonvertebral).

All patients had a documented history of breast cancer and received at least two doses of denosumab (60 mg each), with the final dose of denosumab administered at least 6.5 months earlier. This captured patients who missed their scheduled denosumab dose and were effectively in an at-risk window for rebound fractures. Patients included in the study had to have at least one documented provider visit at MSK (with a nurse practioner [NP], physician assistant [PA], or medical doctor [MD]) after their last dose of denosumab. The documented provider visit at the furthest time point from the last administered dose of denosumab was used to compute the median duration of follow-up. All patients were followed until death or the time of the chart review.

We excluded patients who 1) had metastatic breast cancer; 2) received 120 mg of denosumab at any point; 3) had documented follow-up with a local endocrinologist and not at MSK 4) had concomitant second primary malignancy with bone metastases; 5) lacked at least one follow-up visit (or documented provider visit note) with an MSK NP, PA, or MD after their last dose of denosumab.

Continuous data were presented as mean with standard deviations or median with interquartile range (IQR), as appropriate, for each variable. Frequencies and proportions were calculated for categorical data. We conducted a subgroup analysis for patients who had BMD data from our institution. A paired t-test was performed to compare the mean BMD lumbar spine and hip T-scores at baseline and a minimum of 12 months after denosumab discontinuation. All p-values were two-sided with statistical significance evaluated at the 0.05 alpha level. Analyses were performed using SPSS software and R studio version 1.1.463.

RESULTS

The charts of 469 patients with breast cancer who were treated with denosumab were screened. Of these, 133 patients met the exclusion criteria and were excluded from the cohort (Figure 1), and 336 patients were included in the analysis. The median follow-up duration was 18.5 months (12.5–23.5) after the last denosumab injection. Patient characteristics are presented in Table 1. The median age of patients in the cohort was 62 years (IQR 54–69), and 335 (99.7%) were women. The median body mass index (BMI) was 26.7 (IQR 23.9–30.8). The majority of patients ($n = 184$; 60.5%) never smoked, 106 (34.9%) were former smokers, and 14 (4.6%) were current smokers. The number of denosumab doses ranged from two to 13 (median 3.0; IQR 2.0–4.0). The majority of patients ($n = 296$; 88%) had at least one period of more than 6.5 months between denosumab doses.

A total of 310 (92.3%) patients received treatment with AIs, of which 195 (62.9%) patients remained on treatment and 115 (37.1%) discontinued treatment. Of the patients who stopped AI treatment, 82 patients had their AI discontinued either prior to their last dose of denosumab ($n = 37$) or within six months of their last dose of denosumab ($n = 45$). Considering a 6-month period of effectiveness for denosumab treatment, most patients ($n = 228$; 73.5%) remained on AIs past 6 months after the last denosumab injection. The most common reasons for denosumab discontinuation were improved or normal BMD ($n = 56$; 23.4%), patient decision ($n = 49$; 20.5%), discontinuation of AI therapy ($n = 43$; 18.0%), or dental issue ($n = 34$; 14.2%).

One case of spontaneous vertebral fractures was detected. The patient was a 62-year old woman with a history of breast cancer, a history of osteopenia (diagnosed in 2014), and no prior history of fragility fractures. She was initiated on denosumab 60 mg every six months and adjuvant AI therapy in October 2013. Her bone density T-scores improved after 3.5 years on therapy (Table 3). Her final dose of denosumab was given in March 2018, and the patient was lost to follow-up after that dose. In September 2019, she developed severe low back pain and spasms while jogging. The pain was not fully relieved with corticosteroids and narcotic pain medications; magnetic resonance imaging (MRI) showed a T11 superior endplate fracture, and she was fitted for a back brace. Two months later, she was diagnosed with acute appendicitis. Her back pain increased postoperatively, and a second MRI showed new fractures of T3, T9, T10, T12, and L1. There was no evidence of metastatic bone disease, and AI therapy was discontinued. One month after teriparatide was initiated by her orthopedist, she presented to the MSK endocrinology clinic. Immunofixation and celiac antibodies were negative. The patient was treated with 5 mg of intravenous zoledronic acid.

There were no documented cases of osteonecrosis of the jaw or atypical femur fracture. We did identify

one case of traumatic spine fracture in a patient with osteoporosis (spine T-score -1.8, hip T-score -1.9, and radius T-score -2.6) that occurred after a fall down the stairs in a gap period between doses.

Prior to the use of denosumab, 29 (8.7%) patients had a history of fragility fracture. The majority of patients ($n = 311$; 92.6%) received calcium and vitamin D supplementation. The cohort had an average calcium level of 9.5 mg/dL (standard deviation [SD] 0.41) and vitamin D level of 34.5 mg/dL (SD 13.4) prior to starting denosumab. Sixty-nine patients (20.6%) were exposed to bisphosphonates either prior to starting denosumab or after denosumab discontinuation. Of the 228 patients who remained on AIs through their follow-up, only 29 (12.7%) received bisphosphonates after starting denosumab.

Baseline BMD data was available for 194 (57.7%) patients. Of those, 50 (25.8%) patients had normal bone density, 97 (50.0%) had osteopenia, and 47 (24.2%) had osteoporosis. Eighty-nine patients had bone density scans performed at MSK prior to denosumab initiation and a minimum of 12 months after denosumab discontinuation. In this subgroup, the baseline dual-energy X-ray absorptiometry (DEXA) was performed a median of 3.4 months prior to starting denosumab, and the follow-up DEXA was performed a median of 19.0 months after stopping denosumab. There was no significant difference between baseline and post-denosumab lumbar spine and total hip BMD values (Table 2).

DISCUSSION

We conducted this retrospective review to evaluate the occurrence of clinical vertebral fractures after denosumab discontinuation in postmenopausal patients with breast cancer. In our cohort of 336 patients, we identified a single case of multiple rebound fractures after denosumab discontinuation in a patient with breast cancer who was treated with an AI. In the entire cohort, the median duration of follow-up was 18.5 months after the last denosumab injection. In contrast with most published cohorts, patients in our cohort were younger, had relatively good BMD, and carried few risk factors for fractures.

Uniquely, in this cohort of patients with breast cancer, 92% received treatment with AIs. Because only a quarter of patients with baseline DEXA had osteoporotic BMD, treatment with AIs was the only fracture risk factor in most patients. When AIs are discontinued in postmenopausal patients with breast cancer, fracture risk decreases.[15] Of the 310 patients in the cohort who received AIs, 115 (37%) patients discontinued treatment. Of the 115 patients, 82 (71%) patients had their AI treatment end before their last dose of denosumab or within six months after the final denosumab dose. Those patients would be expected to have increased estradiol levels and mild antiresorptive effects, possibly mitigating the rebound increase in bone resorption and lowering the risk of MCVFs.

Importantly, a minority of our cohort (20.6%) was exposed to bisphosphonates either before or after denosumab discontinuation. This may have been bone protective by blocking rebound increases in bone turnover, though prospective studies evaluating timing of bisphosphonate admnistration are ongoing. One small cases series suggested that zoledronic acid was not effective at preserving BMD gains brought about by denosumab, whereas another study showed conflicting results.[16, 17] A randomized, open-label study investigating if zoledronic acid can prevent increases in bone turnover and bone loss in patients previously treated with denosumab is currently ongoing.[18]

Eighty-nine patients had BMD measurements at our institution before and after treatment with denosumab. There was no difference in the BMD of the lumbar spine and hip before and after denosumab treatment (median 3 months prior to starting denosumab and median 19 months after stopping denosumab, respectively). This is consistent with published literature showing that BMD gains are lost and that BMD returns to baseline one year after discontinuing denosumab.[5-8]

Our cohort contained only 47 (24.2%) patients with osteoporotic BMD at baseline and 29 (8.6%) patients with a documented history of fragility fracture; given that the absolute number of such high-risk patients in our cohort is relatively low, we recommend caution if denosumab must be stopped in patients with breast cancer with such risk factors.

In our study, we found that 88% of our cohort had at least one gap of more than 6.5 months between

their denosumab doses. Our study illustrates that gaps in dosing appear to be a common occurrence, which implies that most patients treated with denosumab are theoretically at risk of spontaneous rebound vertebral fractures at some point in their treatment course. However, the scarcity with which MCVFs have been reported implies that it is extremely rare. Our study demonstrates that although these gaps in dosing are common, they rarely result in MCVFs. Nevertheless, this risk, albeit seemingly small, does exist, so careful consideration needs to be taken to ensure continuity of dosing, and, before denosumab discontinuation. The patient who had MCVFs was a highly active, physically fit woman, and the MCVFs severely affected her quality of life. Treatment with an AI and osteopenic BMD were her only risk factors for fracture.

In addition, we also found one case of traumatic spine fracture in a patient with osteoporosis that occurred in a gap period between doses. This fracture resulted from a fall down the stairs, but it is not possible to know whether the delay in denosumab dosing contributed to the development of this fracture. Our data, and that of others,[19] suggest that it may prove difficult for patients to receive an injection without delay every 6 months. Although the true risk of rebound MCVFs is still unknown, we urge clinicians to discuss the bone health consequences of discontinuing denosumab altogether and the risk of more than 6.5 months of time elapsing between doses. Although current data is limited, we agree with using bisphosphonate therapy following denosumab cessation in accordance with current clinical guidelines.[11]

Limitations of our study include its retrospective design, small sample size, and, for some subjects, limited duration of clinical follow-up. As with all retrospective studies, our study was limited by the accuracy of medical documentation and is subject to selection bias. Given that our institution is a specialized cancer center, we acknowledge that it is possible that patients who had spontaneous rebound vertebral fractures may have presented to an outside institution. In addition, given our unique cohort of patients with breast cancer, our findings may not be generalizable to the larger population receiving denosumab, many of whom have severe osteoporosis, defined as osteoporotic BMD and a history of fracture. Finally, ideally, clinical follow-up would have extended to 30 months after the last dose of denosumab to capture all possible rebound fractures.

The aim of our study was to evaluate the risk of clinical vertebral fractures after denosumab discontinuation in patients with breast cancer. We found that the risk of rebound vertebral fractures, although small, does exist. Additionally, delays in denosumab dosing are common in the real-world setting. Our findings underscore the consequences of discontinuing denosumab altogether and the risk of more than 6.5 months of time elapsing between doses.

CONCLUSION

In conclusion, the risk of spontaneous rebound vertebral fractures after denosumab stoppage in patients with breast cancer exists and needs to be further clarified in larger cohorts. These fractures have severe clinical consequences, so the need for strict compliance with dosing frequency should be discussed with patients when considering densumab treatment. Patients already receiving denosumab treatment should be encouraged to continue to do so every six months without delay. Prospective post-trial analyses of large randomized denosumab trials are needed to evaluate the risks and benefits of stopping denosumab, to identify the risk factors that put patients at higher risk for spontaneous rebound vertebral fractures after stopping denosumab, and to determine the appropriate management strategy in cases of denosumab discontinuation.

CLINICAL PRACTICE POINTS

The risk of vertebral fractures after stopping denosumab in patients with breast cancer is unknown. We conducted a retrospective review to evaluate the occurrence of clinical vertebral fractures after denosumab discontinuation in postmenopausal patients with breast cancer. In our cohort of 336 patients, we identified a single case of multiple rebound fractures after denosumab discontinuation in a patient with breast cancer who was taking an aromatase inhibitor. We also found that denosumab administration was frequently delayed. Clinicians should inform patients with breast cancer of the risk of stopping or delaying denosumab administration.

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TABLES

Table 1 Characteristics of patients with breast cancer treated with denosumab

Characteristic	
Age (years)—Median (IQR)	62.0 (54.0–69.0)
Sex Female	335/336 (99.7)
Body mass index—Median (IQR)	26.7 (23.9–30.8)
Number of Dmab doses—Median (IQR)	3.0 (2.0–4.0)
Follow-up (months) Mean (SD) Median (IQR)	21.2 (13.5) 18.5 (12.5–23.5)
Smoking status—*n* (%) Never Former Current	184/304 (60.5) 106/304 (34.9) 14/304 (4.6)
Alcohol intake—*n* (%) Yes	131/282 (46.5)
Baseline calcium (mg/dL)—Mean (SD)	9.50 (0.41)
Baseline vitamin D (mg/dL)—Mean (SD)	34.5 (13.4)
Calcium/vitamin D supplementation—*n* (%) Yes	311/336 (92.6)
History of fragility fracture—*n* (%) Yes	29/336 (8.6)
Baseline BMD—*n* (%) Normal Osteopenia Osteoporosis	
Aromatase inhibitor—*n* (%) Yes, and continued Yes, but stopped prior to last dose of Dmab Yes, but stopped within 6 mor	
Reason for Dmab discontinuation—*n* (%) Improved or normal BMD Patient decision Stopped aromatase inhibitor Dental is	
Timing of bisphosphonate exposure—*n* (%) Prior to Dmab After Dmab stoppage Both prior to and after Dmab	

Abbreviations: IQR, interquartile range; Dmab, denosumab; BMD, bone mineral density; SD, standard deviation

Table 2 Bone mineral density before and after denosumab

BMD (g/cm^3)	Before denosumab initiation[a]	After denosumab stoppage[b]	Least significant change range	95% confidence interval[c]
Lumbar spine Mean (SD) Median (IQR)	1.02 (0.18) 1.01 (0.90–1.1)	1.04 (0.15) 1.02 (0.93–1.12)	±0.0357	(-0.04, -0.002)

Hip Mean (SD) Median (IQR)	0.87 (0.12) 0.88 (0.78–0.96)	0.87 (0.13) 0.87 (0.79–0.97)	±0.0191	(-0.0055, 0.013)

Abbreviations: CI, confidence interval; BMD, bone mineral density; SD, standard deviation; IQR, interquartile range;

a. Bone mineral density assessed by dual-energy X-ray absorptiometry a median of 3.4 months prior to initiating denosumab.

b. Bone mineral density assessed by dual-energy X-ray absorptiometry a median of 19.0 months after denosumab stoppage.

c. 95% confidence intervals were calculated based on 2-sample paired t-test. No difference in scores was considered to be present if the upper or lower limits of the 95% confidence intervals overlapped with the least significant change range.

Table 3 T-score changes in patient on denosumab

	T-score before denosumab[a]	T-score on denosumab[b]	Percent change
L1–L4	-2.2	-1.7	7.1
Total Hip	-1.9	-1.6	3.8
Femoral Neck	-2.4	-2.3	2.3

a. T-score obtained close to the time of denosumab initiation

b. T-score obtained after 3.5 years on therapy

FIGURES

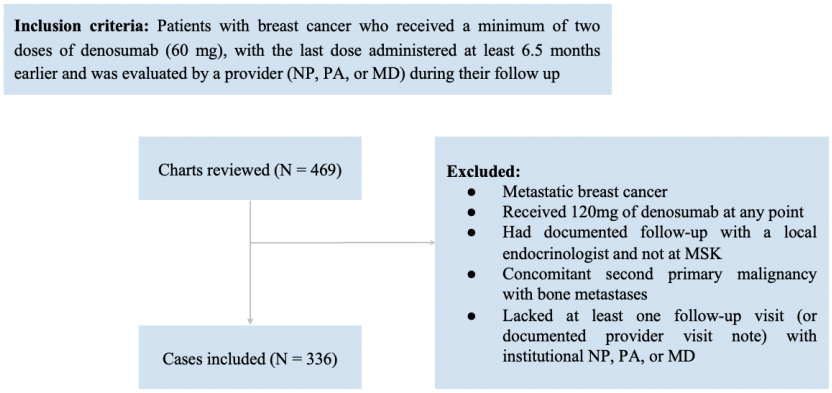

Figure 1 Identification of charts for review . The charts of 469 patients with breast cancer treated with denosumab at Memorial Sloan Kettering Cancer Center were reviewed. One hundred thirty-three charts were excluded for the indicated reasons, and 336 charts were included for review. NP, nurse practitioner; PA, physician assistant; MD, medical doctor; MSK, Memorial Sloan Kettering Cancer Center.

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