

Bone Scans, Bisphosphonates, and a Lack of Acute Changes Within the Mandible

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Purpose: The etiology of osteonecrosis of the jaw is poorly understood, but preferential mandibular uptake of intravenous bisphosphonates (IVBPs) has been implicated. We examined this association within a prospective study assessing the effect of IVBPs on radionuclide bone scanning.

Patients and Methods: Women with at least 3 osseous breast metastases on bone scanning and previous IVBP use within 8 weeks were eligible for the present study. After the first clinically indicated bone scan, the patients received zoledronic acid within 72 hours and underwent a second bone scan within another 72 hours. The regions of interest on the bone scan were read in triplicate, and the mean count per pixel was calculated for the mandible (C_M), left femur (C_{FL}), right femur (C_{FR}), and thigh (C_B). The mandibular bone turnover (MBT) was quantified as the ratio of $(C_M - C_B)/(C_F - C_B)$, where $C_F = (C_{FL} + C_{FR}/2)$. The MBT was compared before and after IVBP use.

Results: A total of 10 patients were enrolled (median age 51 years, range 40 to 71); none had known osteonecrosis of the jaw. Of the 10 patients, 8 had paired bone scans available for analysis. The previous zoledronic acid exposure was 48.6 mg (range 24 to 148) for a median of 13 months (range 6 to 35). The baseline mean MBT ratio was 2.33 (range 0.88 to 4.22). After IVBP administration, the mean MBT ratio was statistically unchanged at 2.23 (range 1.05 to 3.09). The MBT had declined in 4 patients and increased in 4. Only 1 patient had had an MBT of less than 1.0 before IVBP use, and no patient had an MBT ratio of less than 1.0 after IVBP use.

Conclusions: The mandibular region appears to be a site of increased uptake of technetium-99m bound to methylene diphosphonate-technetium. Acute changes in bisphosphonate binding in the mandible were not observed in our patients receiving chronic IVBP therapy.

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An estimated 200,000 women will have been diagnosed with breast cancer in 2009 in the United States,¹ and approximately 20% to 30% will develop

metastases (40,000 to 60,000 patients). Of these patients, approximately 70% will have metastases involving the bone (28,000 to 42,000 women).² Imaging with bone scintigraphy is 1 of the most commonly used modalities for assessing the osseous tumor burden in patients with metastatic breast cancer (MBC).^{3,4} Bone scan imaging typically uses a radiopharmaceutical, technetium-99m, bound to methylene diphosphonate (^{99m}Tc MDP), also known as technetium-99m medronate, which is preferentially taken up at sites of exposed hydroxyapatite where active bone formation is occurring.^{3,5}

Intravenous bisphosphonates (IVBPs) are potent inhibitors of osteoclast-mediated bone resorption and are routinely used in the treatment of patients with osseous metastases from advanced breast cancer because of their ability to decrease the risk of skeletal-related events (ie, fracture, need for surgery or radiotherapy to bone, spinal cord compression) and improve both bone pain and quality of life.^{6,7} Although the etiology is unknown, osteonecrosis of the jaw (ONJ) has been associated with the use of IVBPs.

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In patients with metastatic bone disease receiving high-dose IVBP therapy, the reported incidence of ONJ has varied widely from 1% to 10%,⁸ and, specifically, in patients with MBC, it might be approximately 1%.^{9,10}

No data are available on the sensitivity and specificity of bone scans in prospectively identifying patients at increased risk of ONJ¹¹; however, some reports have suggested that bone scans might reveal findings (both increased and decreased uptake) at the site of ONJ.^{9,11-13} Some have hypothesized that the rate of bone turnover seen in alveolar bone will be increased compared with other skeletal sites,¹⁴ such that IVBPs preferentially accumulate at this site, and that this increases the risk of necrosis of the jaw and/or surrounding soft tissues.¹⁵⁻¹⁷ However, in pre-clinical modeling with rats treated with ibandronate, no suggestion was found of preferential IVBP uptake in the jaw.¹⁸

To investigate whether the mandible is a site of preferential uptake of zoledronic acid compared with the long bone, we performed an analysis of the mandibular bone turnover (MBT) in patients with MBC undergoing bone scanning with ^{99m}Tc MDP. Patients were enrolled in an open-label, prospective, clinical study (clinical trial number NCT00582920) in which bone scans were obtained immediately before and after dosing with zoledronic acid.

Patients and Methods

PATIENTS

Women with MBC involving the bone, who had at least 3 osseous lesions seen on a bone scan and who had had previous exposure to zoledronic acid within 8 weeks of enrollment, were eligible for the present study. Following approval by the institutional review board, the study was performed at the Memorial Sloan-Kettering Cancer Center, in accordance with the Helsinki Declaration. All participants provided written informed consent. Figure 1 outlines the study schema. The calculation of the MBT was performed retrospectively for the patients who participated in the clinical trial.

INTERVENTION

The first bone scan was obtained for clinical indications according to the standard clinical practice at the Memorial Sloan-Kettering Cancer Center. The bone scans were performed after an intravenous injection of 25 mCi of ^{99m}Tc MDP, followed 3 hours later by whole body and spot view images of the head and chest, obtained according to institutional policy. Both the pre- and postzoledronic acid bone scans were performed using the same dual-head gamma

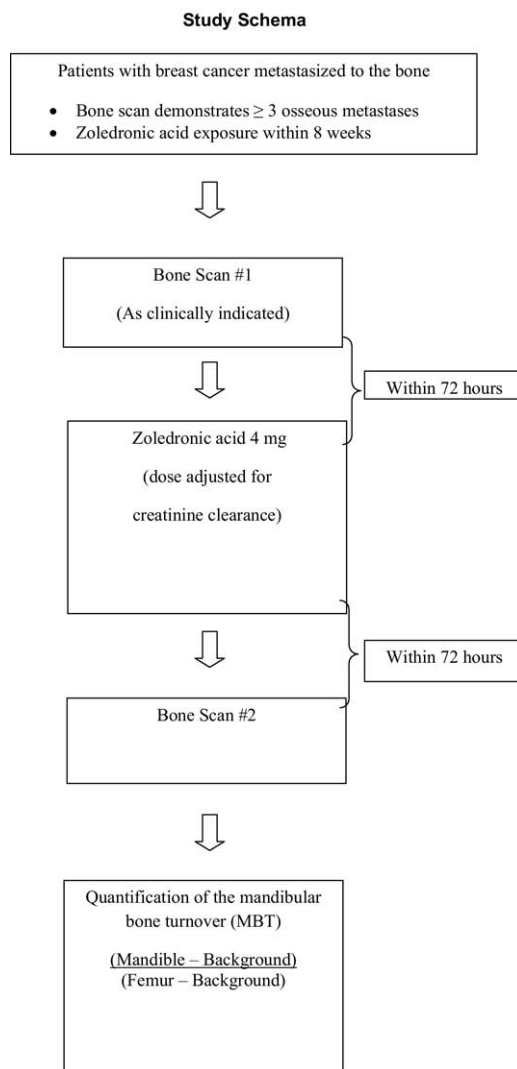


FIGURE 1. Study schema.

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camera and low-energy resolution collimator with isotope entry peak of 140 keV and a 20% energy window. The scan speed was 12.5 cm/min. A commercial supply of zoledronic acid (Novartis, East Hanover, NJ) was administered on the day of the first bone scan. The first bone scan and zoledronic acid infusions were performed according to the standard of care for clinical indications. The drug dose was determined according to the serum creatinine clearance (4 mg within not less than a 15-minute infusion, unless the dose had been adjusted according to the packet insert), with assessment for renal toxicity before infusion. To accommodate patient scheduling, the acceptable window for the zoledronic infusion was within 72 hours after the first bone scan. The day after the zoledronic acid infusion, the second bone scan was performed. Again, to allow for patient scheduling, a

window of 72 hours was permitted. These 2 bone scans were then compared in a blinded fashion, without information regarding the timing and sequencing of the 2 scans, as previously reported.¹⁹

ASSESSMENT OF MBT

Using the technique outlined by van den Wyngaert et al²⁰ for assessing the MBT, the present study focused on the bone scan findings within the mandible, bilateral femurs, and the soft tissue of the thigh (Fig 2). The regions of interest on the radionuclide bone scan were defined, and the minimal, maximal, and mean count per pixel were determined.¹⁹⁻²² Readings

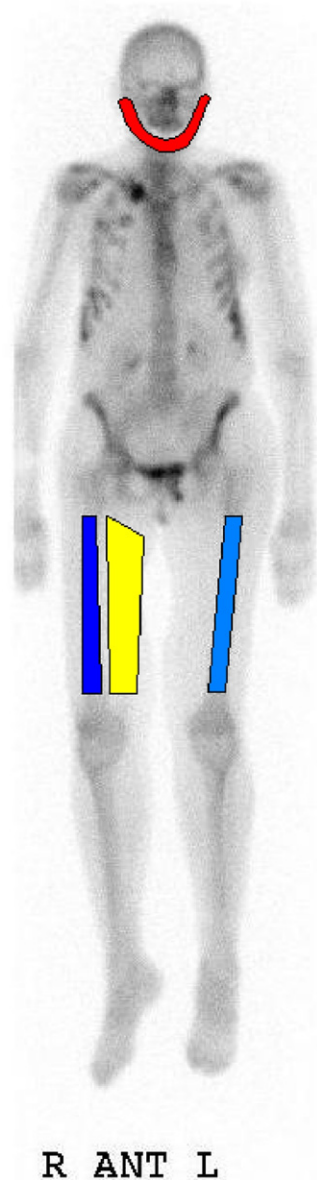


FIGURE 2. Regions of interest in mandible (red), right femur (dark blue), left femur (light blue), and background soft tissue (yellow).

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were taken in triplicate by a single investigator (P.M.), and the mean was calculated for the mandible (C_M), left femur (C_{FL}), right femur (C_{FR}), and soft tissue of the thigh (C_B) (Fig 2). For the femora, the readings were taken from the midshaft, avoiding any metastatic lesions. As described by van den Wyngaert et al,²⁰ the MBT was quantified as the ratio of $(C_M - C_B)/(C_F - C_B)$, where C_F is the mean of (C_{FL}) and (C_{FR}). The MBT was then compared before and after the IVBP infusion.

Results

A total of 10 patients were enrolled in the clinical study, and 8 had paired bone scans available for analysis. Of the remaining 2 patients, 1 had withdrawn consent and 1 was withdrawn owing to a protocol violation because she had not received the zoledronic acid before the second bone scan. The detailed patient demographics have been previously reported.¹⁹ In brief, the median age was 51 years (range 40 to 71). A total of 163 osseous lesions were identified (range 10 to 36 per patient, median 18) in the 8 patients with paired scans. The previous zoledronic acid exposure was 48.6 mg (range 24 to 148) for a median of 13 months (range 6 to 35). The period from the previous clinical dosing of zoledronic acid to the first study bone scan was 30 days (range 26 to 47). Zoledronic acid was the only IVBP administered to all study patients. The median period from the first bone scan to the study dosing of zoledronic acid was 1 day (range 1 to 2), and the median period from zoledronic acid administration to the second bone scan was 2 days (range 1 to 3). Of the 8 patients, 6 had evidence of femoral metastases (3 had right-sided lesions, 1 left-sided lesions, and 2 bilateral lesions).

No patients had been diagnosed with ONJ at the beginning of the present study. In addition, none of the patients had any evidence of mandibular metastases seen on the bone scan. Sixteen scans were reviewed for MBT assessment, and the results are outlined in Table 1. At baseline, the mean MBT ratio was 2.33 (range 0.88 to 4.22). After IVBP administration, the mean MBT ratio had decreased slightly to 2.23 (range 1.05 to 3.09; Fig 3). Overall, 4 patients had a decline in MBT and 4 had an increase. Only 1 patient had an MBT ratio of less than 1.0 before the IVBP infusion, and no patient had an MBT ratio less than 1.0 after the IVBP infusion. None of these subjects subsequently developed ONJ.

Discussion

Our data support 2 conclusions. First, the mandibular region is a site of increased uptake for ^{99m}Tc MDP (MBT ratio greater than 1.0 for 15 of 16 observations);

Table 1. MEAN TECHNETIUM-99m COUNT PER PIXEL BY REGION OF INTEREST (n = 8)

Pt. No., Scan No.*	Mean Count per Pixel					$(C_M - C_B)$	$(C_F - C_B)$	$(C_M - C_B) / (C_F - C_B)$ MBT	Change in MBT
	Mandible	Left Femur	Right Femur	Femur	Soft Tissue of Thigh				
1, 1	57.00	26.67	28.33	27.50	18.33	38.67	9.17	4.22	
1, 2	55.67	33.67	34.67	34.17	16.67	39.00	17.50	2.23	-1.99
2, 1	38.33	20.67	19.33	20.00	9.33	29.00	10.67	2.72	
2, 2	26.67	16.33	14.67	15.50	7.00	19.67	8.50	2.31	-0.41
3, 1	32.33	18.00	17.00	17.50	9.00	23.33	8.50	2.75	
3, 2	43.00	24.67	25.67	25.17	14.00	29.00	11.17	2.60	-0.15
4, 1	41.67	27.67	25.33	26.50	9.33	32.33	17.17	1.88	
4, 2	51.67	37.00	32.00	34.50	12.33	39.33	22.17	1.77	-0.11
5, 1	73.00	96.80	61.97	79.38	27.90	45.10	51.48	0.88	
5, 2	60.93	71.23	46.90	59.07	22.50	38.43	36.57	1.05	0.18
6, 1	48.67	21.00	23.67	22.33	7.00	41.67	15.33	2.72	
6, 2	54.33	19.33	25.33	22.33	7.00	47.33	15.33	3.09	0.37
7, 1	89.87	68.37	64.40	66.38	29.87	60.00	36.52	1.64	
7, 2	41.63	21.70	22.27	21.98	6.80	34.83	15.18	2.29	0.65
8, 1	66.20	48.43	47.03	47.73	24.77	41.43	22.97	1.80	
8, 2	46.97	23.80	24.47	24.13	8.83	38.13	15.30	2.49	0.69

Abbreviations: C_M , mean count per pixel for mandible; C_{FL} , mean count per pixel for left femur; C_{FR} , mean count per pixel for right femur; C_B , mean count per pixel for soft tissue of thigh; MBT, mandibular bone turnover ratio [determined by $(C_M - C_B) / (C_F - C_B)$].

*Patient 1, 1 indicates first patient, first (pre-bisphosphonate) bone scan; 1, 2 indicates first patient, second (post-bisphosphonate) scan, and so forth.

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and second, no consistent change was found in the MBT acutely after IVBP therapy. After administration of the IVBP, the mean MBT ratio was largely unchanged (2.23 compared with 2.33), with one half of the patients having an increased MBT and one half a decreased MBT. From our previous report, we know that IVBPs do not interfere acutely with tumor uptake of ^{99m}Tc MDP on bone scanning.¹⁹ It seems likely that calculation of the MBT before and after IVBP administration would not be affected by changes in the uptake of ^{99m}Tc MDP within known bone metastases, given what is known about bisphosphonate pharma-

cokinetics and pharmacodynamics.^{23,24} The present study calculated the mean pixel count within bone that had no evidence of metastases. Because each patient served as her own control, we believe we can be confident in our assertion that acute changes in ^{99m}Tc MDP do not occur in the jaw after IVBP administration.

The MBT results were not unexpected. Bone scans have commonly demonstrated increased uptake within the region of the jaws and sinuses. Bone scans can demonstrate positive uptake in areas of dental disease, including healing extraction sites and pulpal and periodontal infections, areas of irritation from ill-fitting dentures, sinusitis, Paget's disease of the bone, trauma, and areas of blastic or mixed osseous metastases.²⁵⁻²⁷ Bone scintigraphy might not permit exact, anatomic location of the site, or nature, of the tissue associated with the increased uptake.

In a case-control study using a similar method to assess MBT, van den Wyngaert et al²⁰ examined patients who had bone metastases from solid tumors who had received IVBP therapy (n = 40), patients with cancer without IVBP exposure (n = 40), and controls with neither cancer nor a history of IVBP therapy (n = 40). The 3 groups were matched for factors that could affect bone turnover, and the study excluded patients with ONJ. The mean MBT was lower in those who had bone metastases and had received IVBP therapy (MBT ratio 2.49) than that of

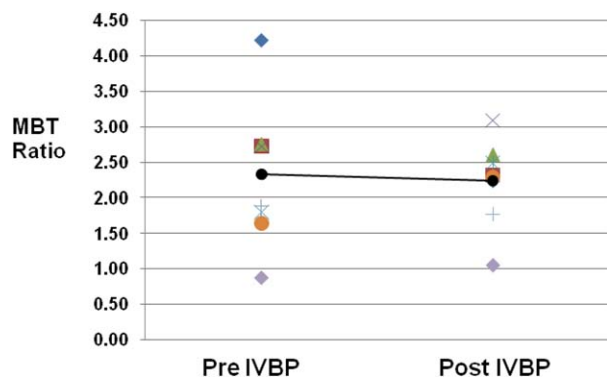


FIGURE 3. MBT ratio before and after IVBP administration for 8 patients. Black line indicates mean.

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the matched controls from patients with cancer without IVBP use (MBT ratio 2.84) and the patients without cancer or IVBP exposure (MBT ratio 3.00). The investigators concluded that their data suggest that IVBPs produce a greater inhibition of bone turnover in the mandible relative to the femur and that their findings support the hypothesis that the inhibition of bone turnover might be important in the pathophysiology of ONJ. In the study by van den Wyngaert et al,²⁰ the timing of IVBP administration was not specified, in contrast to our study, in which we examined the MBT of patients with MBC immediately before and after the administration of IVBP therapy. The results of the present study did not demonstrate a pattern of change in MBT with IVBP use. Hence, the MBT data we obtained are inconsistent with the results from van den Wyngaert et al,²⁰ because our sequential assessment of MBT did not demonstrate a uniform pattern of inhibition of bone turnover in the mandible relative to the femur.

A critical aspect of the present study was the timing of the bone scans, which provided uniform and rapid assessment of bone uptake of the radionuclide tracer. The elimination of IVBPs has been modeled using 3 compartments, with the initial plasma levels showing a rapid decrease from peak concentrations at the end of infusion to less than 1% of the maximal concentration within 24 hours,^{28,29} with the bone surface and deep bone the other 2 compartments. Because we obtained the postinfusion bone scan immediately after zoledronic acid infusion, we can be confident that the acute changes secondary to rapid bone metabolism likely had not occurred. The present study did not examine the bone scans immediately after the initial dosing of zoledronic acid; therefore, data on the uptake in naive bone are lacking from our study. In our data from examining 163 osseous metastases from breast cancer for changes in bone scan tracer uptake after zoledronic acid administration, we demonstrated that IVBP therapy did not appear to interfere with the ^{99m}Tc MDP bone scan results or suggest saturation of bone.¹⁹

The small sample size in the present study limited the extent of the analysis; however, our findings are consistent with other data, as well as supportive of clinical experience. In the analysis of the MBT, the data would have been enriched if serum or urine marker data of bone metabolism were available; however, they were not. Because no patient in the present study was diagnosed with ONJ, we could draw no conclusions about the changes in mandibular binding of IVBP when ONJ has occurred. For patients receiving chronic IVBP therapy, these data suggest that acute changes in bisphosphonate-binding in the mandible do not occur.

Bone scans have been an important tool in the diagnosis of ischemic necrosis. However, bone scans have a low resolution, and regions of inflammation can obscure other regions that might be more avascular. The role of bone scans in the assessment of ONJ has not been defined.⁸ Our MBT results and that of our recent report provide data suggesting that the timing of zoledronic acid infusions does not affect the bone scan results in metastatic foci¹⁹ and that acute bisphosphonate uptake is not necessarily preferential to the jaw.

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