Published in final edited form as:
Cancer Invest. 2009 February ; 27(2): 221–226. doi:10.1080/07357900802208608.

Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents

Jeanny B. Aragon-Ching[1], **Yang-Min Ning**[1], **Clara C. Chen**[2], **Lea Latham**[1], **Jean-Pierre Guadagnini**[3], **James L. Gulley**[1], **Philip M. Arlen**[1], **John J. Wright**[4], **Howard Parnes**[5], **William D. Figg**[6], and **William L. Dahut**[1,*]

1 *Medical Oncology Branch, National Cancer Institute, Bethesda, MD 20892, USA*

2 *Department of Nuclear Medicine, Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA*

3 *National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, USA*

4 *Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD 20892, USA*

5 *Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20892, USA*

6 *Section of Molecular Pharmacology, National Cancer Institute, Bethesda, MD 20892, USA*

Abstract

ONJ is an important toxicity in cancer patients receiving bisphosphonate therapy. Here we report a higher than usual incidence of ONJ, 11 of 60 (18.3%, 95% Confidence Interval, CI: 9% – 28%) patients enrolled in a phase II clinical trial combining bevacizumab, docetaxel, thalidomide, and prednisone (ATTP) in chemotherapy-naïve men with metastatic castration resistant prostate cancer (mCRPC). The use of bisphosphonates was allowed at study entry. Our study suggests that anti-angiogenic and chemotherapy agents can predispose to the development of ONJ in men with mCRPC on zoledronic acid. Imaging modalities, such as bone scans, may be useful in following the clinical course of patients who develop ONJ.

Keywords

osteonecrosis of the jaw; bisphosphonates; anti-angiogenesis; chemotherapy; prostate cancer

INTRODUCTION

Osteonecrosis of the Jaw (ONJ) is a rare, but potentially debilitating condition, which has been described in cancer patients treated with various regimens (1). However, since 2003, there have been numerous reports that associate ONJ with intravenous (IV) bisphosphonate therapy (2, 3). While there is currently no consensus definition for ONJ (1), confirmed cases of ONJ have

Correspondence to: Jeanny B. Aragon-Ching, M.D. and William L. Dahut, M.D., Medical Oncology Branch, National Cancer Institute, NIH, Building 10, Rm 12N226, 9000 Rockville Pike, Bethesda, MD 20892, Phone: 301-435-8183; FAX: 301-435-3854, Email: chingj@mail.nih.gov; dahutw@mail.nih.gov.

COMPETING INTEREST

None of the authors have any financial and/or personal relationships with other people or organizations that could inappropriately influence or bias the work.

been defined as areas of exposed bone in the maxillofacial region that has failed to heal within six (4) to eight weeks after identification by a health care provider (5). Multiple risk factors have also been described in the development of ONJ, including a prior invasive dental procedure, infections, corticosteroids, renal osteodystrophy, and chemotherapy (6,7). Intravenous bisphosphonate use has emerged in the past few years as one of the most common associated factors in cancer patients. Bisphosphonates are currently indicated for a variety of patients with metastatic bone lesions, including multiple myeloma, breast cancer and prostate cancer. The exact mechanism for the development of ONJ remains unclear. However, others have hypothesized that this may be secondary to disruption of bony remodeling and angiogenesis inhibition in a region where excessive microtrauma occurs (2,7,8), in the presence of a microbiologically diverse oral environment, causing impairment of local healing (7,9). Chemotherapy has long been implicated in isolated case reports but a clear association is difficult to demonstrate (6,10–13), especially since the majority of patients with bone disease are receiving chemotherapy and bisphosphonates concurrently. The incidence of ONJ in patients who have been treated with bisphosphonates for non-malignant conditions, such as Paget's disease, had been around 0.8% (8). Although the incidence is variable among prostate cancer patients, it had been reported to occur around 6.5% (8,14). This manuscript describes a cohort of patients with metastatic prostate cancer treated with a multiagent regimen including docetaxel and two anti-angiogenesis agents who developed ONJ with an incidence that far exceeded previous reports in the current literature.

PATIENTS AND METHODS

We reviewed the medical and dental records of 11 patients who developed ONJ out of 60 participants enrolled in a National Cancer Institute (NCI) Institutional Review Board (IRB) approved phase II clinical trial of bevacizumab, thalidomide, docetaxel, and prednisone (ATTP) for the treatment of mCRPC (15). All patients signed informed consent. The investigational drug regimen included docetaxel given as 75 mg/m^2 dose every 21 days, prednisone 10 mg daily, thalidomide 200 mg daily, and bevacizumab 15 mg/kg dose every 21 days. Thromboprophylaxis using enoxaparin at 1 mg/kg weight subcutaneous daily dose was also given. Patients who had been on bisphosphonates prior to study entry continued with its use during the clinical trial. Patients were seen in clinic every 21 days, with CT and bone scans obtained at baseline, after the first 2 cycles, and every 3 cycles thereafter, until disease progression. Basic laboratory tests and prostate specific antigen (PSA) were also obtained at each visit. Patients presenting with any dental problems, such as pain, swelling, infection of soft tissue, drainage, loosening of teeth, or exposed bone (sequestrum), were referred to the National Institute of Dental and Craniofacial Research (NIDCR) at the National Institutes of Health. Clinical diagnosis of ONJ was made by the NIDCR's dentists based on physical examination showing signs of bone death. Non-healing oral lesions were biopsied initially and reviewed by the pathology department at the National Institutes of Health. We used the NCI Common Terminology Criteria version 3 for clinical grading of ONJ as this was the standard adverse event reporting used for the clinical trial, which was compatible with the ONJ severity grading by Weitzman et. al. of asymptomatic, mild, moderate, and severe grading (1).

RESULTS

A total of 60 men with mCRPC were accrued as planned for the Phase 2 study from April 2005 to September 2007. Of the 60 patients, 11 developed ONJ while on-study, with an incidence of 18.3% (95% Confidence Interval, CI: 9% – 28%). One patient had been previously diagnosed with ONJ upon study entry. The severity of ONJ was moderate at diagnosis in all patients (Grade 2 according the NCI Common Terminology Criteria for Adverse Events version 3.0) except one with only Grade 1. One patient progressed to Grade 3, requiring surgical intervention.

The baseline characteristics of all patients are shown in Table 1. None of the patients had prior chemotherapy for mCRPC (see Table 2). Of the 60 study participants, 5 did not receive zoledronic acid (ZA) therapy (2 due to absence of bony disease, 1 patient was allowed to continue oral ibandronate rather than be changed to ZA and 2 due to refusal).

The incidence of ONJ for patients on ZA was 20% (95% CI: 9 – 30%). Of the 55 patients who received ZA, all but 4 were treated with ZA at a dose of 4 mg intravenously every 3 – 4 weeks. Two patients received only 3.5 mg ZA due to increased creatinine and 2 patients were treated with ZA every 3 and 6 months, respectively. One patient (patient 3) had been treated with an oral bisphosphonate (alendronate) for 3 years before being switched to ZA upon study entry. This patient developed ONJ after 5 months of ZA. Patients had a mean duration of ZA infusion of 18 months prior to suspicion or diagnosis of ONJ, with a median of 19 months. The mean duration of ATTP at the time of diagnosis of ONJ was 12.5 cycles, with a median of 13 cycles. Although only 3 out of 11 patients received full doses of all study drugs throughout the duration of the study, all patients received full doses of bevacizumab. Only one patient had a dose reduction of prednisone, 5 patients had reduction in thalidomide dose and 7 patients had docetaxel either held for a few cycles or dose reduced (see Table 2). Only four of the 11 patients had a biopsy done at the NIH revealing osteonecrosis with no evidence of metastatic disease. Four patients had gingival cultures showing overgrowth of *Haemophilus influenzae*, actinomyces, and clusters of mixed gram positive and gram negative bacteria. All patients on protocol were staged at baseline, after the first 2 cycles and then every 3 cycles. Analyses of the patients' bone scans are shown on Table 3. Of the 11 patients who developed ONJ, one patient (patient 7) had a positive uptake in the mandibular region at baseline, which persisted throughout the study period. This patient was found to have an infection requiring dental extraction at the time of the baseline bone scan. He had received ZA for only 3 consecutive months before developing persistent pain and a non-healing open tooth socket. Only two of the 11 patients had a positive bone scan prior to the clinical suspicion or diagnosis of ONJ (patient 6 is shown in Figure 1) but all patients except one eventually had increased uptake in the area of ONJ (Table 3). The intensity of technetium uptake correlated with the duration of symptoms and either resolved (n=5) or remained positive (n=5) at each patient's last recorded follow-up visit. Median follow-up time was 10.4 months (range 0.5 – 35 months). ZA was promptly discontinued in all patients with clinical symptoms or signs suggestive of ONJ and the majority did well with conservative treatment, which included maintenance of good oral hygiene, peridex cleaning, antibiotic administration, and removal of loose sequestrum. All of the patients remained functional and most were free of pain over time, as shown in Table 2.

DISCUSSION

We present a unique series of patients with metastatic prostate cancer being treated with a combination of chemotherapy, prednisone, and novel therapies that target angiogenesis, with an apparently higher than usual incidence of ONJ. The increasing frequency of ONJ associated with the use of bisphosphonates has resulted in heightened awareness of the toxicity although the exact underlying mechanism remains unknown. The development of ONJ in association with bisphosphonates has been attributed to faulty bone remodeling (16). Since the jaws have a rich vascular supply and are the site of frequent significant microtrauma causing a rapid bone turnover, bisphosphonates highly concentrate in the jaws(8). The inhibition of resorption by osteoclasts leads to acellularity and necrosis, with involution of small capillaries within the bone. The combination of this faulty remodeling, with other factors such as chronic dental disease, thin overlying mucosa, diverse oral microbial flora, with any form of injury or invasive surgery, would result in exposure of a poorly healing avascular bone (7,17). The jaw is particularly susceptible to hypoxia since this is a site that sustains significant microtrauma on a routine basis. The mandible, in particular, is a more frequent site because of single blood supply source as compared to the dual blood supply to the maxilla. Another theory for the

development of ONJ is the inhibition of capillary angiogenesis (7). ZA, an intravenous bisphosphonate, has been shown to exhibit anti-angiogenic properties in *in vitro* studies (18–22). We hypothesize that coupled with known anti-angiogenic therapies such as bevacizumab and thalidomide, the effects of ZA on avascularization may be enhanced, accounting for the high rate of ONJ in our patients. In a large systematic review of ONJ by Woo et. al. (8), 85% of affected patients had multiple myeloma or breast cancer, and only 6.2% of patients with ONJ had metastatic prostate cancer. The incidence of ONJ in prostate cancer patients on bisphosphonates has been variable, ranging from 2.9% to 6.5% (9,14,23–25). A higher than usual incidence (12%) had been reported with docetaxel use (26). We report an incidence of 18.3% (11 of 60 patients) and 20% (11 of 55 patients who received ZA). This high incidence rate may be related to the unique combination of the treatment regimen, as hypothesized above. In addition, it may also be associated with increased vigilance for recognition and reporting of ONJ by trained specialists at the NIDCR. In this study, the majority of patients presented with pain at the ONJ site (Table 2) and all patients had ZA held at the first symptom or suspicion of ONJ. Only the patient who developed the mandibular fracture had any of the ATTP drugs held because of the ONJ. Thus, most patients had mild symptoms and were managed conservatively. This contrasts with another series where the majority of patients had to be treated surgically (3). This suggests that our diagnostic criteria for ONJ may differ from other series, perhaps explaining the increased incidence of ONJ in our study. Furthermore, the prolonged exposure to the combination treatment due to good tumor responses may also have contributed to the increased incidence of ONJ. Notably, four of the patients who were biopsied had evidence of ONJ. These patients also had some overgrowth of bacteria suggesting the possible mechanistic role of areas of poor vascular supply compromising the healing of open wounds leading to necrosis (3). The majority of patients who developed ONJ had predisposing infection or poor dentition.

Since the promising results of ZA in retarding the skeletal complications of malignancy were reported (27,28), bisphosphonates have been in widespread use. Reports of ONJ have also increased significantly since 2003, with numerous studies linking use of bisphosphonates and ONJ. However, there are also data suggesting other possible etiologies, including chemotherapy and steroids. For example, the concomitant use of chemotherapeutic agents and steroids in multiple myeloma confounds the association between bisphosphonates and ONJ in this clinical setting. Several etiological associations have been made with the use of chemotherapy, thalidomide, or steroid use (8,23,26,29) to ONJ, although there are conflicting data (30). Despite the occurrence of ONJ, none of the patients had to discontinue protocol treatment because of ONJ. Perhaps close follow-up done every 3 weeks, as mandated by protocol in this cohort of patients, allowed for better and earlier detection of ONJ, suggesting that earlier intervention may significantly impact and bring about better outcomes. In addition, technetium-99m bone scanning was routinely performed every 3 cycles after the first 2 cycles. We retrospectively determined whether the use of bone scans could predict early development of ONJ, as some studies have suggested (31,32). Our results showed that patients either experienced symptoms or had clinical signs of ONJ before any abnormality was detected in bone technetium scan. However, once it developed, the intensity of the uptake on bone scan correlated with the severity of patients' symptoms and resolution. Therefore, this modality can perhaps be used as an adjunct in following clinical symptoms of patients.

Our study has several limitations. First, since ONJ was not an anticipated event at the outset for this clinical trial, information regarding exact duration of ZA administration and eliciting known risk factors such as poor dental hygiene in patients who never developed ONJ was difficult to ascertain since dental examination was not mandated as part of the clinical protocol. In addition, incidence of higher ONJ in this metastatic prostate cancer patient population is difficult to estimate due to lack of a true control group. The drug regimen used in this clinical trial was also distinct from the current standard of care and the use of enoxaparin as

thromboprophylaxis may also have a contributory role in the healing process as it blocks several reactions in the coagulation cascade. Furthermore, this analysis is retrospective and it is difficult to delineate risk attributable to ZA versus those due to the study agents (thalidomide or bevacizumab or prednisone or docetaxel) or to their combinational effects. Nevertheless, our analyses set the groundwork for possible future prospective studies utilizing these agents to identify possible biomarkers, including bone turnover markers, in the development of ONJ.

Despite the lack of true evidence implicating anti-angiogenesis and/or chemotherapy as the underlying mechanism of ONJ, the observation of increased ONJ incidence in this trial and other epidemiologic associations would help in better understanding the risks and work towards refining treatment strategies for patients who develop this complication. Given the view of perceived and true benefits of bisphosphonates and new emerging anti-angiogenic therapies, strategic ways of combining them and avoiding the complication of ONJ is of paramount importance. In our phase II trial, we have increased efforts to give ZA only after dental clearance and have continued vigilance regarding patients' dental care and symptoms. Also, since the skeletal half-life of bisphosphonates have been shown to be in excess of 10 years (33), it is possible to consider administering ZA less frequently, though future studies are needed to determine utility of this approach. Although standard practice has not been uniformly developed for the management of ONJ (5), most practitioners would also discontinue bisphosphonate use at the first suspicion of ONJ development. Future prospective cohort studies should also attempt rigorous documentation of risk factors to better define patients at greater risk for developing this complication.

Acknowledgements

This project has been supported by the Intramural Research Program of the National Cancer Institute, Center for Cancer Research, National Institutes of Health. The content of this publication does not reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

References

1. Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. Crit Rev Oncol Hematol 2007;62(2):148–152. [PubMed: 17336086]
2. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61(9):1115–1117. [PubMed: 12966493]
3. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62(5):527–534. [PubMed: 15122554]
4. Bagan J, Blade J, Cozar JM, Constela M, Garcia Sanz R, Gomez Veiga F, et al. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates. Med Oral Patol Oral Cir Bucal 2007;12(4):E336–340. [PubMed: 17664922]
5. Burr DB. Summary of ASBMR Task Force on ONJ. J Musculoskelet Neuronal Interact 2007;7(4): 354–355. [PubMed: 18094510]
6. Schwartz HC. Osteonecrosis of the jaws: a complication of cancer chemotherapy. Head Neck Surg 1982;4(3):251–253. [PubMed: 6896046]
7. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/ osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63(11):1567–1575. [PubMed: 16243172]
8. Woo S-B, Hellstein JW, Kalmar JR. Systematic Review: Bisphosphonates and Osteonecrosis of the Jaws. Ann Intern Med 2006;144(10):753–761. [PubMed: 16702591]
9. Woo SB, Hande K, Richardson PG. Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 2005;353(1):99–102. [PubMed: 16003837]discussion 199-102

10. Wang J, Goodger NM, Pogrel MA. Osteonecrosis of the jaws associated with cancer chemotherapy. J Oral Maxillofac Surg 2003;61(9):1104–1107. [PubMed: 12966490]
11. Marymont JV, Kaufman EE. Osteonecrosis of bone associated with combination chemotherapy without corticosteroids. Clin Orthop Relat Res 1986;(204):150–153. [PubMed: 3006960]
12. Obrist R, Hartmann D, Obrecht JP. Osteonecrosis after chemotherapy. Lancet 1978;1(8077):1316. [PubMed: 78083]
13. Estilo CL, Van Poznak CH, Williams T, Evtimovska E, Tkach L, Halpern JL, et al. Osteonecrosis of the maxilla and mandible in patients treated with bisphosphonates: A retrospective study. J Clin Oncol (Meeting Abstracts) 2004;22(14suppl):8088.
14. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005;23(34):8580–8587. [PubMed: 16314620]
15. Ning, YM.; Gulley, J.; Arlen, P.; Latham, L.; Srinavasan, R.; Wright, J. A phase II trial of thalidomide, bevacizumab, and docetaxel in patients (pts) with metastatic castration-refractory prostate cancer (CRPC). ASCO Genitourinary Cancers Symposium; San Francisco, CA. 2008. Abstract # 164
16. Cavanna L, Berte R, Arcari A, Mordenti P, Pagani R, Vallisa D. Osteonecrosis of the jaw. A newly emerging site-specific osseous pathology in patients with cancer treated with bisphosphonates. Report of five cases and review of the literature. Eur J Intern Med 2007;18(5):417–422. [PubMed: 17693231]
17. Mashiba T, Mori S, Burr DB, Komatsubara S, Cao Y, Manabe T, et al. The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib. J Bone Miner Metab 2005;23(Suppl):36–42. [PubMed: 15984412]
18. Scavelli C, Di Pietro G, Cirulli T, Coluccia M, Boccarelli A, Giannini T, et al. Zoledronic acid affects over-angiogenic phenotype of endothelial cells in patients with multiple myeloma. Mol Cancer Ther 2007;6(12):3256–3262. [PubMed: 18089719]
19. Santini D, Caraglia M, Vincenzi B, Holen I, Scarpa S, Budillon A, et al. Mechanisms of disease: Preclinical reports of antineoplastic synergistic action of bisphosphonates. Nat Clin Pract Oncol 2006;3(6):325–338. [PubMed: 16757970]
20. Ferretti G, Fabi A, Carlini P, Papaldo P, Felici A, Tomao S, et al. Zoledronic acid and angiogenesis. Clin Cancer Res 2007;13(22 Pt 1):6850. [PubMed: 18006788]author reply 6850–6851
21. Wood J, Bonjean K, Ruetz S, Bellahcene A, Devy L, Foidart JM, et al. Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J Pharmacol Exp Ther 2002;302(3):1055–1061. [PubMed: 12183663]
22. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M, et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002;62(22):6538–6544. [PubMed: 12438248]
23. Garcia Saenz JA, Lopez Tarruella S, Garcia Paredes B, Rodriguez Lajusticia L, Villalobos L, Diaz Rubio E. Osteonecrosis of the jaw as an adverse bisphosphonate event: three cases of bone metastatic prostate cancer patients treated with zoledronic acid. Med Oral Patol Oral Cir Bucal 2007;12 (5):E351–356. [PubMed: 17767097]
24. Wang EP, Kaban LB, Strewler GJ, Raje N, Troulis MJ. Incidence of osteonecrosis of the jaw in patients with multiple myeloma and breast or prostate cancer on intravenous bisphosphonate therapy. J Oral Maxillofac Surg 2007;65(7):1328–1331. [PubMed: 17577497]
25. Ortega C, Faggiuolo R, Vormola R, Montemurro F, Nanni D, Goia F, et al. Jaw complications in breast and prostate cancer patients treated with zoledronic acid. Acta Oncol 2006;45(2):216–217. [PubMed: 16546871]
26. Ortega C, Montemurro F, Faggiuolo R, Vormola R, Nanni D, Goia F, et al. Osteonecrosis of the jaw in prostate cancer patients with bone metastases treated with zoledronate: a retrospective analysis. Acta Oncol 2007;46(5):664–668. [PubMed: 17562443]
27. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94(19):1458–1468. [PubMed: 12359855]

28. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008;19(3):420–432. [PubMed: 17906299]

29. Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006;134(6):620–623. [PubMed: 16889620]

30. Durie BGM, Katz M, Crowley J, Woo S-B, Hande K, Richardson PG, et al. Osteonecrosis of the Jaw and Bisphosphonates. N Engl J Med 2005;353(1):99–102. [PubMed: 16000365]

31. Zanglis A, Andreopoulos D, Dima M, Baltas G, Baziotis N. Jaw uptake of technetium-99 methylene diphosphonate in patients on biphosphonates: A word of caution. Hell J Nucl Med 2007;10(3):177–180. [PubMed: 18084661]

32. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. Dentomaxillofac Radiol 2006;35(4):236–243. [PubMed: 16798918]

33. Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res 1997;12(10):1700–1707. [PubMed: 9333131]

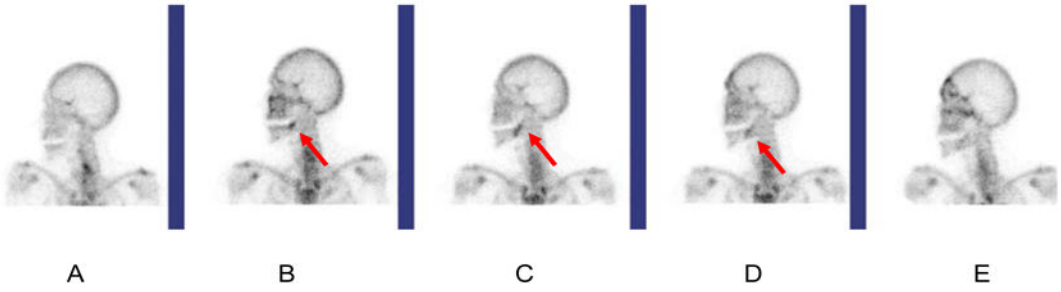

Figure 1.
Patient number 6 showing a negative bone scan upon study enrollment (A); Positive uptake over the left mandibular area appeared approximately 6 weeks prior to ONJ diagnosis (B); Increasing (worsening) uptake over the left mandibular area noted 4 months later (C); Improvement in the intensity noted after 4 months (D); Resolution and return to baseline 6 months later.

Table 1

Patient characteristics

Characteristic	Osteonecrosis	
	Yes	No
	Number of patients	Number of patients
Total number of patients	11*	48
Age, years		
Median (Range)	64 (49 – 79)	65.5 (44 – 79)
Race		
Caucasian	9	38
Black	1	8
Hispanic	1	2
Site of metastasis		
Bone only	7	17
Bone and soft tissue	4	27
Soft tissue only	0	4
Alkaline phosphatase levels		
Mean	145	172
ZA duration		
Number of patients who received ZA	11	42
Mean, months	18	13
Median, months	19	11
Range	3 – 36	1 – 39
Cycles of ATTP		
Mean (Median)	12.5 (13)	16 (14.5)
Range	4 – 23	3 – 51
Location		
Mandibular only	9	
Maxilla only	1	
Mandibular and maxilla	1	

Legend: *-one additional patient already had ONJ prior to going on-study and is not included in the total number

Table 2

oped ONJ during clinical trial

ene	Full ATTP dose?	Dose adjustments	S/p cycle of ATTP at ONJ	Location	Symptoms	Biopsy done?	Treatment	Clinical and Functional Outcome
6 mos Dx	No	Doc held C11 & 12	15	Maxilla and Mandible	Mouth soreness, gum swelling, pain on chewing	No	Maintenance of good oral hygiene	Eating well at the last follow- up visit, gum swelling resolved
fection	No	Thal dec to 50% after C4, Doc dec 25% after C3, Resumed full dose after C7	10	Mandible	Jaw pain worsening;developed fracture of mandible	Yes	Peridex; sequestrectomy; Surgery for mandibular fracture and antibiotics	Completely healed ONJ
illa (on	No	Thal held after C2, then 50% decrease	8	Mandible	Ulcer	Yes	Maintenance of good oral hygiene	Healed ulcer, eating well and asymptomatic
	Yes	None	4	Mandible	Jaw pain	Yes	Peridex/Sequestrectomy and antibiotics	Still had pain in another tooth but ONJ remained stable
titis	No	Doc dec to 75% s/p C12;Thal dec by 50% s/p C12;Pred dec by 50%	15	Maxilla	Gum swelling, pain	No	Peridex	Healing well, asymptomatic
iene	No	Thal dec to 75% s/p C7; Doc held C9 &10	13	Mandible	Tooth pain	No	Peridex	Completely healed ONJ
tal tooth ental	No	Thal held d/t depression, Doc held s/p C17 d/t pleural effusions	20	Mandible	Tooth pain	Yes	Peridex; sequestrectomy	Still had pain at ONJ site with slight increase in exposed bony area at last follow-up
iene	No	Thal dec to50% after C12 d/t memory prob, Doc held C10 as per pt request	17	Mandible	Pain	No	Peridex; Sequestrectomy	Completely healed ONJ; mild tooth sensitivity to cold
iene	Yes	None	6	Mandible	Pain	No	Peridex; Sequestrectomy	Completely healed ONJ
ower ooth rwise iene	Yes	None	7	Mandible	Mild discomfort over previous tooth extraction socket	No	Peridex	Occasional ache over ONJ area; no interference with chewing
noted; e with aques	No	Doc held C12 – 22 and C23 –27 d/t pleural effusions	23	Mandible	Spontaneous tooth loss followed by failure to heal	No	Peridex; Sequestrectomy advised	Asymptomatic but with persistence of exposed bone

* Legends: Patient previously on oral alendronate for 3 years prior to switch to intravenous zoledronic acid (ZA); ONJ – osteonecrosis of the jaw; RP – radical prostatectomy; ADT – Androgen deprivation therapy; RT – Radiation therapy; Keto – ketoconazole; Doc – Docetaxel; Thal – thalidomide; Pred – prednisone; prob – problem; C – cycle; pt – patient; d/t – due to; dec – decrease; HTN – hypertension; s/p – status post; Dx – diagnosis; s/p – status post;

Table 3

Summary of bone scan results of 11 patients who developed ONJ

Patient number	Baseline(+ or −)	Before ONJ symptoms	After ONJ symptoms	Resolution seen?
Patient number 1	−	+	+	No
Patient number 2	−	−	+	Yes
Patient number 3	−	−	+	Yes
Patient number 4	−	−	+	No
Patient number 5	−	−	+	Yes
Patient number 6	−	+	+	Yes
Patient number 7	+	+	+	No
Patient number 8	−	−	+	Yes
Patient number 9	−	−	+	No
Patient number 10	−	−	+	No
Patient number 11	−	−	–*	N/A

* Legend: -patient went off-study after diagnosis of ONJ, no follow-up available; N/A – not applicable