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CLINICAL TRIAL

Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer

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Abstract Long-term bisphosphonate therapy is associated with increased risk of osteonecrosis of the jaw (ONJ). In a retrospective analysis, a 16% ONJ incidence was reported in patients receiving bisphosphonates with anti-angiogenic therapy (bevacizumab or sunitinib) for bone metastases from breast, colon, or renal cell cancers. To assess ONJ incidence with bevacizumab, we analysed data from 3,560 patients receiving bevacizumab-containing therapy for locally recurrent or metastatic breast cancer (LR/MBC) in two double-blind, randomised trials (AVADO and RIBBON-1) and a large, non-randomised safety study (ATHENA). The overall incidence of ONJ with bevacizumab was 0.3% in the blinded phase of the two randomised trials and 0.4% in the single-arm study. There was a trend towards increased ONJ incidence in patients who received bisphosphonate therapy versus those with no bisphosphonate exposure (0.9 vs. 0.2%, respectively, in the pooled analysis of the randomised trials; 2.4 vs. 0%, respectively, in ATHENA). In conclusion, this is the largest analysis of ONJ in patients receiving bevacizumab for LR/MBC. The 0.3–0.4% incidence is considerably lower than previously suggested with anti-angiogenic therapy in a small retrospective analysis. The risk of ONJ appeared to be increased in patients exposed to bisphosphonates, a pattern consistent with observations before the introduction of anti-angiogenic therapy to breast cancer management. The 0.9–2.4% incidence seen in bisphosphonate-exposed patients receiving bevacizumab is within the 1–6% range reported for bisphosphonates alone. Good oral hygiene, dental examination, and avoidance of invasive dental procedures remain important in patients receiving bisphosphonates, irrespective of bevacizumab administration.

Keywords Osteonecrosis of the jaw · Bisphosphonate · Angiogenesis · Bevacizumab · Metastatic breast cancer

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Abbreviations

5-FU	5-Fluorouracil
LR/MBC	Locally recurrent or metastatic breast cancer
MSKCC	Memorial Sloan-Kettering Cancer Center
ONJ	Osteonecrosis of the jaw
VEGF	Vascular endothelial growth factor

Introduction

The anti-angiogenic agent bevacizumab is an established component of breast cancer therapy. Three large, randomised, phase III trials (E2100, AVADO and RIBBON-1) have demonstrated significantly improved progression-free survival and response rate when bevacizumab is combined with taxane therapy, anthracycline-based therapy or capecitabine [1–3] as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer (LR/MBC). In all three of these trials, two of which were placebo controlled, the addition of bevacizumab to chemotherapy had a limited impact on the safety profile of chemotherapy.

With growing experience of treating patients with bevacizumab-containing regimens, it has become apparent that there is some variation in the safety profile of bevacizumab according to disease setting and tumour type. For example, patients with late-stage, heavily pretreated ovarian cancer, gastrointestinal cancer, or renal cell cancer are at higher risk of gastrointestinal perforation than those with breast cancer [4, 5]. Of particular relevance to the breast cancer setting, a possible link between osteonecrosis of the jaw (ONJ) and bevacizumab, particularly when combined with bisphosphonates, has recently been suggested, based initially on isolated cases reported in the literature.

ONJ, first reported in the dental literature in the early 2000s, is a serious complication affecting the maxillofacial region. ONJ is defined by the presence of exposed bone in the jaw that fails to heal after appropriate intervention over a period of 6 or 8 weeks [6]. The mandible is more commonly involved than the maxilla [7–10]. ONJ is typically associated with intravenous bisphosphonate use. Among patients receiving bisphosphonates (without anti-angiogenic therapy), the reported incidence of ONJ ranges from 1 to 6% [7, 8, 10–15]. An additional trigger factor, such as previous tooth extraction, surgical dental procedures or *Actinomyces* infection, is often reported in patients developing ONJ [7, 12, 16]. It has been suggested that bisphosphonate-related ONJ might be attributable to the anti-angiogenic effect of more potent bisphosphonates. Bisphosphonates block angiogenesis via inhibition of cell proliferation and vessel sprouting and are associated with a durable reduction in circulating vascular endothelial growth factor (VEGF) concentrations [17]. A decrease in VEGF concentrations has been described in patients treated with zoledronate [18]. The possible role of angiogenesis in ONJ is supported by the higher incidence of ONJ in patients with multiple myeloma, who are frequently treated with the anti-angiogenic agent, thalidomide. However, in the M.D. Anderson Cancer Center analysis [7], thalidomide use was not a significant predictor of ONJ in patients receiving bisphosphonates.

The potential association between bevacizumab and ONJ in patients with breast cancer is based on three recent publications: two describing case studies and one describing a retrospective analysis. The first report of ONJ in a patient receiving bevacizumab was described by Estilo et al. [19]. A 51-year-old patient with MBC developed ONJ during therapy with bevacizumab 15 mg/kg every 3 weeks in combination with capecitabine (starting dose of 1,000 mg/m^2 twice daily). She had previously received doxorubicin, cyclophosphamide, and then letrozole in the adjuvant setting and albumin-bound nanoparticle paclitaxel in the metastatic setting, but had no history of bisphosphonate exposure. Six weeks after the eighth dose of bevacizumab, the patient presented with a small area of bone exposure, which appeared necrotic. This resolved within a few weeks following treatment with chlorhexidine oral rinse and discontinuation of both bevacizumab and capecitabine, but another area of necrotic bone with bacterial infection was observed a few weeks later. Greuter et al. [20] described another breast cancer patient who developed ONJ after treatment with bevacizumab. The patient experienced maxillary pain 1 month after starting treatment with bevacizumab in combination with liposomal doxorubicin for locally advanced breast cancer. She had no history of bisphosphonate exposure. Two infected teeth were extracted and 1 month later ONJ was diagnosed.

In addition to the two cases described above, a retrospective analysis of patients receiving bisphosphonates for bone metastases from breast, colon, or renal cell cancers was reported recently by Greek investigators [21]. Of the 116 bisphosphonate-treated patients included in the analysis, 25 had received concurrent treatment with anti-angiogenic agents (bevacizumab in 22 patients, sunitinib in two patients and sorafenib in one patient). In this subgroup of patients receiving anti-angiogenic therapy, four (16%; three receiving bevacizumab, one receiving sunitinib) developed ONJ.

Outside the breast cancer setting, Estilo et al. [19] described a patient with glioblastoma multiforme who presented with exposed necrotic bone 13 weeks after beginning treatment with bevacizumab 10 mg/kg every 2 weeks. An analysis of ONJ among patients receiving bevacizumab, docetaxel, thalidomide, and prednisone for metastatic endocrine-resistant prostate cancer suggested an 18% incidence of ONJ [9]. Individual cases of ONJ have been reported in the literature among zoledronate-exposed patients treated with sunitinib for renal cell carcinoma [22, 23].

Mechanistically, a relationship between ONJ and agents that target VEGF is plausible. VEGF is essential for bone formation through upregulation of osteoclastic function and promotion of osteoclast differentiation and survival [24–26]. Thus, inhibition of VEGF might hinder repair of physical trauma [19]. ONJ may also result from compromised microvessel integrity in the jaw. In addition, inhibition of capillary angiogenesis and altered angiogenesis during wound healing (for example after dental extraction) potentially play a role in the development of ONJ [16, 19, 27]. It has been suggested that the combined anti-angiogenic activities of agents such as bevacizumab with zoledronate may lead to enhanced avascularisation [9].

To understand better whether administration of bevacizumab increases the risk of ONJ, we analysed data from two large, randomised, placebo-controlled trials (AVADO and RIBBON-1), and a large safety study (MO19391, ATHENA) evaluating bevacizumab-containing therapy as first-line treatment for HER2-negative LR/MBC.

Methods

The objectives of the analysis were: to determine the incidence of ONJ in a large population of patients with LR/MBC treated with bevacizumab in prospective clinical trials; and to assess whether administration of bevacizumab (with or without bisphosphonate exposure) increases the risk of ONJ. Data from three trials (AVADO, RIBBON-1 and ATHENA) in patients with HER2-negative LR/MBC were reviewed. In all three trials, patients were treated for LR/MBC in the first-line setting. Both AVADO and RIBBON-1 were randomised, placebo controlled, phase III trials with the primary objective of evaluating the efficacy of combining bevacizumab with chemotherapy versus chemotherapy alone in terms of progression-free survival. In AVADO, patients were randomised to 3-weekly docetaxel in combination with placebo or bevacizumab (either 7.5 or 15 mg/kg every 3 weeks). The RIBBON-1 trial consisted of two independently powered cohorts, with chemotherapy selected by the investigator before randomisation to either placebo or bevacizumab (15 mg/kg every 3 weeks). In one cohort, patients received capecitabine with either placebo or bevacizumab. In the second cohort, patients received a taxane (3-weekly docetaxel or nab-paclitaxel) or an anthracycline-based combination regimen (epirubicin plus cyclophosphamide or doxorubicin plus cyclophosphamide, with or without 5-fluorouracil [5-FU]) with either placebo or bevacizumab. The ATHENA study was a large, single-arm study with the primary objective of assessing the safety of bevacizumab in combination with standard (non-anthracycline) first-line chemotherapy in the general oncology practice setting. In all trials, adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

In order to determine the incidence of ONJ, each of the trial databases was searched for the terms "osteonecrosis" and "osteonecrosis of the jaw". For the ATHENA trial, the additional search terms "jaw", "mandibular", "mandible", "maxilla," and "maxillary" were used. All identified cases of ONJ were reviewed by medically qualified personnel; patients with necrosis at sites other than the jaw area were excluded. The incidence of ONJ was determined and the chi-squared test was used to compare the incidence of ONJ in patients receiving bevacizumab versus placebo and in patients with versus without bisphosphonate exposure.

Results

The present analysis includes 3,560 patients treated with first-line bevacizumab-containing therapy for LR/MBC (1,309 patients treated in randomised trials, 2,251 treated in the non-randomised, open-label safety study). Median follow-up was 10.2 months in AVADO, 15.6 months in the capecitabine cohort of RIBBON-1, 19.2 months in the taxane/anthracycline cohort of RIBBON-1, and 12.7 months in the non-randomised ATHENA study. The time of data cut-off for the randomised trials represents the primary efficacy analysis. In AVADO this was triggered after occurrence of a prespecified number of progression-free survival events. In RIBBON-1, the cut-off date for the primary analysis was prespecified based on the anticipated event rate. For ATHENA, the time of data cut-off represents the first analysis of the entire study population. The baseline characteristics of the patients have been described previously [2, 3, 28].

The overall incidence of ONJ among patients receiving bevacizumab-containing therapy in the two randomised trials was 0.3%. Table 1 shows incidences by trial, by treatment arm and according to prior bisphosphonate exposure. None of the patients in the pooled placebo arm experienced ONJ. However, there was no significant difference in the incidence of ONJ in the bevacizumab versus the placebo arms for the overall population (0.3 vs. 0%, respectively) or the individual trials ($P > 0.15$). Similarly, there was no difference in the incidence of ONJ in patients who had received bisphosphonate therapy versus those with no bisphosphonate exposure (0.9 vs. 0.2%; $P > 0.15$).

In AVADO, there were three reported cases of ONJ in the pooled bevacizumab–docetaxel arms. The first patient reported a right mandibular abscess 9 days after starting study therapy. The abscess resolved temporarily after treatment with amoxicillin and clavulanic acid, nystatin and general mouth wash. At reappearance 12 days later,

Table 1 Summary of incidence of osteonecrosis of the jaw (ONJ) in randomised, placebo-controlled trials of bevacizumab-containing therapy according to bisphosphonate exposure

Patients with ONJ/total patients	AVADO[a]		RIBBON-1[b]		Total	
	Bevacizumab ($n = 492$)	Placebo[c] ($n = 238$)	Bevacizumab ($n = 817$)	Placebo ($n = 412$)	Bevacizumab ($n = 1,309$)	Placebo ($n = 650$)
Overall population	3/492 (0.6%)	0/238 (0%)	1/817 (0.1%)	0/412 (0%)	4/1,309 (0.3%)	0/650 (0%)
Bisphosphonate	1/77 (1.3%)	0/33 (0%)	1/156 (0.6%)	0/66 (0%)	2/233 (0.9%)	0/99 (0%)
No bisphosphonate	2/415 (0.5%)	0/205 (0%)	0/661 (0%)	0/346 (0%)	2/1,076 (0.2%)	0/551 (0%)

[a] Bevacizumab 7.5 and 15 mg/kg arms pooled

[b] Taxane/anthracycline and capecitabine cohorts pooled

[c] One case of osteonecrosis was reported in the placebo arm; the investigator described the event as "avascular necrosis (right shoulder)," and therefore, this event was not considered relevant for the analysis

the patient received further clavulanic acid and the tooth was extracted shortly after she had received zoledronate. Grade 1 ONJ was diagnosed 6 months after starting study therapy (4 months after tooth extraction). The patient discontinued study therapy 3 months later because of disease progression. The two remaining patients who experienced ONJ while receiving bevacizumab–docetaxel had no reported history of bisphosphonate exposure. In the first patient, grade 3 ONJ (defined as a serious adverse event) was observed 7 months after starting study therapy and resolved 3 months later. The patient subsequently underwent decortication of the lower jaw and tooth extraction. Wound dehiscence and osteomyelitis were reported and resolved without sequelae 6 months later (9 months after the first diagnosis of ONJ) after appropriate medication and temporary interruption of bevacizumab. In the second patient, grade 3 ONJ was reported 2 months after starting study therapy. Surgery was planned after discontinuation of bevacizumab, which was still ongoing at the time of data cut-off.

During the blinded phase of RIBBON-1, one patient (treated with bevacizumab in combination with capecitabine) experienced grade 2 ONJ 3 months after enrolment. The 68-year-old patient started treatment with zoledronate 2 weeks before ONJ was diagnosed. No dental-related medical history was reported. ONJ was described by the investigator as resolved 12 months later. During the open-label phase of RIBBON-1, after disease progression, one additional patient treated with bevacizumab combined with capecitabine developed grade 3 ONJ. She had started bisphosphonate therapy before enrolment to the trial and had no dental-related medical history. Bevacizumab was discontinued following diagnosis of ONJ. At the last follow-up, ONJ was persisting.

Analysis of data from the ATHENA safety study revealed similar results. The overall incidence of ONJ in patients receiving bevacizumab-containing regimens was 0.4%. All 10 reported cases were in patients treated with bisphosphonates (Table 2). Thus, the incidence of ONJ was 2.4% in the 425 patients with bisphosphonate exposure versus 0% in the 1,826 patients with no prior bisphosphonate exposure. The case report forms of the 10 patients with reported ONJ showed that six had received zoledronate, two had received clodronate, one had received pamidronate, and one had received ibandronate. Bevacizumab was given in combination with docetaxel in five patients, paclitaxel in four patients, and vinorelbine in one patient. Additional risk factors for development of ONJ included recent dental extraction in two of the 10 patients and maxillary surgery after a fall in one patient. ONJ in the patient who underwent maxillary surgery was considered to be related to her previous history of trauma and fracture.

Discussion

This is the largest population of patients receiving bevacizumab for LR/MBC to be analysed to assess ONJ incidence. The 0.3–0.4% incidence of ONJ with bevacizumab among 3,560 patients treated in prospective trials is considerably lower than the apparent incidence of 16% suggested by a small, retrospective analysis of patients receiving anti-angiogenic therapy with bisphosphonates for a variety of tumour types [21]. Studies reported before the introduction of anti-angiogenic agents for breast cancer indicated a higher incidence of ONJ in patients with a history of bisphosphonate exposure than in those who had not received bisphosphonates. The same pattern was seen among patients receiving anti-angiogenic therapy in the current analysis: the incidence of ONJ was 0.9–2.4% in bevacizumab-treated patients who had been exposed to bisphosphonates (Table 1) compared with 0.0–0.2% in patients who had not received bisphosphonates. The 0.9–2.4% incidence in patients exposed to bisphosphonates is within the 1–6% range reported for bisphosphonates alone in large studies [7, 8, 10–15].

Table 2 Cases of osteonecrosis of the jaw (ONJ) in the non-randomised ATHENA study

Patient	Age, years	Chemotherapy partner	Bisphosphonate	Other relevant medical history	Interval from start of bevacizumab to onset of ONJ (months)	Grade of ONJ	Outcome of ONJ
Non-serious adverse events							
A	61	Paclitaxel	Ibandronate		5	Unknown	Ongoing at study end
B	61	Paclitaxel	Clodronate		7	2	Resolved 6 months later
C	47	Docetaxel	Pamidronate		5	1	Ongoing at time of death
D	45	Paclitaxel	Zoledronate	Loose tooth	9	1	Ongoing at study end
Serious adverse event							
E	40	Docetaxel	Zoledronate	Dental extractions	13	3	Surgically resected; ONJ ongoing; bevacizumab restarted
F	56	Docetaxel	Clodronate	Dental extraction	12	2	
G	54	Docetaxel	Zoledronate		10	Unknown	Ongoing at time of progression 1 month after ONJ onset
H	56	Vinorelbine	Zoledronate		9	Unknown	Resolved after 2 days; bevacizumab restarted
I	73	Paclitaxel	Zoledronate		15	Unknown	Ongoing at last follow-up
J	73	Docetaxel/5-FU	Zoledronate	Fractured maxillary, malar, and orbital bones after fall	5	Unknown	Surgery, resolved after 4 months; bevacizumab restarted

5-FU 5-fluorouracil

There was no consistent pattern in the timing of onset of ONJ. There was considerable variation, with ONJ occurring at any time between 2 and 15 months after initiation of bevacizumab. Confounding factors, such as dental extraction and fracture, further complicate interpretation of the time of onset.

The findings of this analysis are consistent with results of an analysis from Memorial Sloan-Kettering Cancer Center (MSKCC) of patients developing ONJ after intravenous bisphosphonate and/or bevacizumab therapy [29]. The MSKCC investigators found that among 1,711 patients receiving bevacizumab without intravenous bisphosphonates, only two patients (0.1%) developed ONJ. The incidence was 0.0–0.2% in the corresponding population from our analysis. In the MSKCC analysis, the incidence of ONJ was 2% among patients receiving bevacizumab with bisphosphonate therapy compared with 0.9% in the randomised trials in our analysis and 2.4% in the non-randomised safety study.

The precise mechanism of ONJ associated with bisphosphonate use remains unknown, but as well as the anti-angiogenic effects described above, suppression of bone remodelling appears likely [16]. Considerable and ongoing microtrauma in the jaws leads to rapid bone turnover. The jaws have a rich vascular supply, resulting in accumulation of bisphosphonate in the jaw [30]. Consequently, bone resorption is prevented by osteoclast inhibition and this potentially leads to necrosis [9].

Several risk factors for ONJ have been identified [7, 8, 11, 15, 16, 30–33]. One of the most commonly associated risk factors in cancer patients is the use of intravenous bisphosphonate therapy. Variation between different types of bisphosphonates has been reported: the nitrogen-containing bisphosphonates zoledronate and, to a lesser extent, pamidronate appear to be associated with the highest risk of ONJ [7]. The duration and dose of bisphosphonate therapy also influence the likelihood of patients developing ONJ [7, 8, 15, 34]. For example, in the analysis reported by Bamias et al. [8], the median number of bisphosphonate infusions was 35 (range 13–68) in patients who developed ONJ compared with 15 (range 6–74) in patients without ONJ ($P < 0.001$). Median duration of bisphosphonate exposure was 39 versus 19 months, respectively ($P = 0.001$).

Other important risk factors include dental extraction, dental trauma or use of dentures [7, 11, 31, 34, 35]. Recent guidelines recommend that invasive dental procedures are completed before initiation of high-dose bisphosphonate therapy [36, 37]. Non-urgent procedures should be delayed for 3–6 months following interruption of bisphosphonate therapy. In the analysis by Christodoulou et al. [21], two of the three patients receiving bevacizumab with bisphosphonates had undergone dental extraction. In our analysis,

two of the patients in the ATHENA study and one in AVADO had undergone dental extraction before diagnosis of ONJ.

Chemotherapy may be implicated in ONJ and has a negative impact on bone mineral density [12]. However, because the majority of patients with bone disease receive chemotherapy with bisphosphonates, it is difficult to determine the contribution of chemotherapy agents to ONJ risk [9]. Docetaxel may be associated with increased risk of ONJ in patients with prostate cancer [34], possibly attributable at least in part to the anti-angiogenic properties of docetaxel [38]. No such finding has been reported in breast cancer, but all patients in AVADO received bevacizumab combined with docetaxel and five of the 10 patients in ATHENA who developed ONJ received docetaxel in combination with bevacizumab.

A limitation of this analysis is that information on the exact duration of bisphosphonate exposure was not collected consistently in all trials, as this effect was not anticipated at the time the trials were designed. Second, although no dental risk factors were identified in three of the patients developing ONJ during bevacizumab-containing therapy in the randomised trials, prospective dental evaluation was not performed. In addition, all patients received chemotherapy, many with docetaxel, which may represent a confounding factor. Thorough review of case report forms enables relatively detailed but not comprehensive assessment of medical history and relevant risk factors. Thus, other risk factors may have been present but not reported in the case report or serious adverse event forms.

Conclusion

The incidence of ONJ is not significantly increased in patients receiving bevacizumab combined with chemotherapy for LR/MBC compared with patients receiving chemotherapy alone, either with or without concurrent bisphosphonate therapy ($P > 0.15$). The suggested 16% incidence of ONJ reported in a small retrospective analysis of patients receiving bisphosphonates with concomitant anti-angiogenic therapy is not supported by our analysis of 3,560 patients treated with bevacizumab in large, prospective, international clinical trials. It is possible that other factors contributed to the appearance of ONJ in the case studies and the retrospective analysis reported by Christodoulou et al. [21]. For example, three of the six published cases of ONJ with bevacizumab were in patients who had undergone recent dental extraction, a known risk factor for ONJ [7, 8, 30, 31, 35].

In order to minimise the risk of ONJ developing in patients receiving bisphosphonates, irrespective of bevacizumab therapy, it is important that patients observe good oral hygiene and undergo regular dental examination. The avoidance of invasive dental procedures remains important and patients and the healthcare team must be aware of possible dental side effects of therapy. Recent data suggest that dental preventative measures can further reduce the risk of ONJ in patients with solid tumours and bone metastases [39]. Dental examinations (with or without orthopantomography of the jaw) to detect potential dental conditions, and subsequent dental care if required, together with identification of patients at risk of ONJ, can improve outcomes and reduce risk of ONJ.

Finally, further investigation of the pathophysiology and risk factors for ONJ is important. Recognition, awareness, and reporting of ONJ were rapid after the first suggestion that this effect may be associated with bisphosphonate use [40]. A similar increase in reporting has been seen with bevacizumab and ONJ. However, as noted by Christodoulou et al., small retrospective analyses warrant further evaluation in larger, prospectively studied cohorts. In the present report, we have aimed to address this need, and our findings indicate that the incidence of ONJ is not significantly increased among patients receiving bevacizumab, with or without bisphosphonates. Such analyses are important to enhance our understanding of other potential risk factors. Continued pharmacovigilance with new agents is essential, as are hypothesis-driven studies to elucidate the pathophysiology of ONJ.

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