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REVIEW ARTICLE

A systematic review of bisphosphonate osteonecrosis (BON) in cancer

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Abstract
Purpose This systematic review aims to examine the prevalence of bisphosphonate osteonecrosis (BON) in the cancer population, prevention and treatment protocols, and quality of life issues.
Methods A search of MEDLINE/PubMed and EMBASE form October 2003 to December 31, 2008 was conducted with the objective of identifying publications that contained original data regarding BON.
Results A total of 28 publications fulfilled inclusion criteria, but only 22 were used for prevalence analysis. No randomized controlled clinical trials, meta-analysis, or quality of life papers were found that contained information regarding either prevalence or treatment protocols for the management of BON. The overall weighted prevalence of BON included a sample of 39,124 patients with a mean weighted prevalence of 6.1%. The weighted prevalence was 13.3% for studies with documented follow-up with a

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sample size of 927 individuals. The weighted prevalence in studies with undocumented follow-up was 0.7% in a sample of 8,829 chart reviews. Epidemiological studies evaluated a total of 29,368 individual records, and the weighted BON prevalence was 1.2%.
Conclusions High-quality studies are needed to accurately characterize the prevalence of BON, and to determine effective treatment protocols.

Keywords Cancer therapy · Bisphosphonate osteonecrosis · Bisphosphonate therapy · Management strategies

Introduction

This manuscript is the result of a systematic review that searched and evaluated the literature published since October 2003, when the first cases of bisphosphonate osteonecrosis (BON) were reported [28, 32, 43], to December 2008. BON is defined as the presence of necrotic bone anywhere in the oral cavity of an individual on bisphosphonate therapy with no history of radiation of the head and neck [36, 41]. Recently, a stage 0 category has been proposed for patients who do not present with obvious exposed bone, but have clinical symptoms (such as persistent sinus tracts) and radiographic findings suggesting that BON has developed [31, 41].

The pathobiologic process involved in the formation of BON is not completely understood, but it seems that the profound suppression of osteoclasts plays an important role, together with the toxic effect of bisphosphonate on soft tissues, including anti-angiogenesis [35, 36, 40, 44]. Recently, it was reported that patients on antiangiogenic agents such as bevacizumab and sunitinib may develop osteonecrosis that appears to be clinically similar to BON [3, 12, 17, 21, 34]. The role of infection may also be an important factor that needs further investigation [44, 45].

In 1989, when the NIH Development Consensus Conference on the Oral Complications of Cancer Therapies was held in Bethesda, MD, USA [1], BON was unknown. Since 2003, many cases of BON and numerous treatment protocols have been published, mostly based on expert opinion and case series studies. Thus, it is timely to evaluate this new oral complication that affects cancer patients disproportionately.

An important aspect regarding BON is the accurate determination of the prevalence of this oral complication. The generally accepted definition of BON was only recently developed, and most of the information available in the literature regarding prevalence comes from retrospective reviews of various cancer populations. In addition, there may be under-reporting of BON cases [16]. It is largely accepted that the prevalence of BON in cancer patients using intravenous infusion of pamidronate or zoledronic acid is between 3% and 12% [23, 41, 48, 51]. However, recent prospective studies of cancer populations have found prevalence as high as 28% in patients with breast cancer and multiple myeloma [8] or 18.6% in prostate cancer patients [47] and 5.3% in breast cancer patients [46]. It is important to consider that some of the centers conducting prevalence studies included in their evaluations not only patients diagnosed at their centers but also patients with BON referred by outside practitioners. Study designs vary from retrospective chart reviews, to epidemiological surveys that rely on disease codes that could identify potential cases of BON, to prospective studies. Therefore, several factors can influence the quality of the studies and the determination of accurate prevalence rates for BON.

The management of BON can be difficult. Mild cases are usually asymptomatic and often present with only small areas of exposed bone, with little to no soft tissue inflammation or active infection such as suppuration or sinus tracts. However, larger areas of exposed necrotic bone are usually infected and surrounded by inflamed oral mucosa, resulting in severe pain, nerve tissue involvement, and discomfort [33]. Conventional techniques to treat osteomyelitis and necrotic bone in the oral cavity have been only partially successful. Therefore, management of BON requires further investigation. Furthermore, the impact of this oral complication on quality of life and cost of care are unknown.

Aims of this review

The aim of this systematic review was to evaluate current literature regarding the following:

1. Prevalence of BON
2. Impact on quality of life
3. Economic impact
4. Prevention and management strategies for BON

Methods

Search strategy and criteria for selecting articles

This paper is part of an effort by a group of researchers from the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO). The group aimed to systematically review the current literature addressing a group of oral complications of cancer therapies. The methodology used in the literature search was common for all oral complications

evaluated and will be presented in a separate methodology manuscript that will accompany this paper [37].

Briefly, a specific systematic literature search for BON was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between October 1, 2003 and December 31, 2008. The primary objective was to identify all articles containing original data on prevalence of BON as well as the economic burden, impact on oral health-related quality of life, or management strategies in patients with cancer metastatic to bones and multiple myeloma. We focused on randomized controlled clinical trials, meta-analyses, and controlled studies that would provide data on BON. Other types of articles involving case–control studies and retrospective reviews were also included. Articles with anecdotal information, case reports, and literature reviews were not included. We aimed to select studies based on the availability of documented baseline and patient follow-up data. For example, we assumed a prospective evaluation of patients on bisphosphonate therapy with oral examination conducted by dental professionals or studies where patients had complete dental records would have more complete and accurate data compared with retrospective chart reviews where information may be incomplete, missing, or based on assumptions. We also considered epidemiological data collection separately.

Reviewers with knowledge in BON diagnosis and management evaluated selected articles. Each article was reviewed by two independent reviewers using data extraction tools especially designed for the study. Specific information collected included types of cancer populations, study design, cancer therapies, bisphosphonate use, discontinuation of bisphosphonate therapy when BON was diagnosed, management strategies, and quality of life issues, amongst many other aspects. Data from each study were entered in the data extraction tool and further evaluated by the principal reviewer (CAM) and the study leader (MB) for data quality control and for summarizing the information collected. The quality of selected articles was assessed and scored with respect to sources of bias, representativeness, scale validity, and sample size. These parameters were utilized to determine the weighted prevalence of BON. Further details of this methodology and the statistical analyses used in the determination of prevalence rates can be reviewed in the methodology paper [37].

Results

Articles reviewed

Although the literature search of BON studies identified hundreds of publications, only 28 articles fulfilled the criteria for the present review. There were no randomized clinical trials available, no meta-analysis studies, and no studies that specifically evaluated quality of life issues, although a few studies presented limited information about pain and pain control. There were no studies that specifically evaluated outcomes of BON therapy when bisphosphonate use was discontinued. Only 22 of the studies dealt with representative cancer populations. These articles were used for the prevalence analysis [2, 5, 6, 8, 10, 11, 13, 15, 18, 19, 22, 24, 27, 29, 30, 35, 38, 43, 49, 50, 52, 53]. Amongst these 22 studies, three different groups based on design and patient follow-up schedule were used in the evaluations (Table 1).

Prevalence

The prevalence results observed were different depending on the type of study design, patient follow-up (documented, undocumented, or epidemiological), and the type of bisphosphonate used.

In the first analysis, we included 11 studies [5, 6, 8, 10, 13, 15, 18, 22, 50, 52, 53], which were selected based on several quality factors like sources of bias, representativeness, scale validity, and sample size (Table 1). The sample size for this calculation was 39,124 patients, and the mean weighted prevalence of BON was 6.1%. The weighted prevalence was different when studies with different designs were evaluated separately (Table 1). After separating the three study groups, the following results were obtained: studies with documented follow-up included a total of 927 individuals with a weighted BON prevalence of 13.3%; studies with undocumented follow-up included a cohort of 8,829 chart reviews with a weighted BON prevalence of 0.7%. Epidemiological studies evaluated a total of 29,368 individual records, and the weighted BON prevalence was 1.2%. The importance of using weighted prevalence rates can be seen when comparing it with the following raw prevalence results for the same studies: cancer cohort with documented follow-up (104/927=11.2%), cancer cohort with undocumented follow-up (64/8,829=0.72%), and epidemiological studies (152/29,368=0.05%).

Next, we evaluated BON prevalence in studies that reported bisphosphonate use. The overall prevalence for patients using zoledronic acid only was 8.6%, for pamidronate 7.3%, and 21% for patients who used both.

The second analysis included 11 studies that assessed actual cases of BON and looked retrospectively for risk factors. This analysis included a total of 614 cases (Table 2) of patients exposed to both intravenous and oral infusion of bisphosphonates. Cases of BON were identified first and then retrospectively examined for potential risk factors. There were a total of 547 (89%) cancer patients and 67 (11%) cases in non-cancer patients. Patients with multiple myeloma were the most affected cancer group with 245 cases (45%). The distribution of BON cases in other cancer

Table 1 Weighted prevalence of BON by study design and bisphosphonate type

	Study reference	Sample population	Mean weighted prevalence (%)	Standard error	Confidence interval (%)
All studies (11)	[5, 6, 8, 10, 13, 15, 18, 22, 49, 50, 52, 53]	39,124	6.1	0.03	0.3–11.9
Cancer cohort- documented follow-up (5)	[5, 6, 8, 13, 53]	927	13.3	0.04	1.6–25.1
Cancer cohort-undocumented follow-up (2)	[18, 22]	8,829	0.7	0.00001	0.71–0.74
Epidemiologic study (4)	[10, 15, 50, 52]	29,368	1.2	0.01	0–5.1
Zoledronic acid only					
All studies (8)	[5, 6, 8, 13, 15, 18, 22, 53]	10,380	8.6	0.02	3.4–13.9
Cancer cohort- documented follow-up (5)	[5, 6, 8, 13, 53]	927	9.0	0.03	0.4–17.4
Cancer cohort-undocumented follow-up (2)	[18, 22]	8,829	7.4	0.06	0–84.7
Epidemiologic study (1)	[15]	624	10.0	NA	NA
Pamidronate only					
All studies (8)	[5, 6, 8, 13, 15, 18, 22, 53]	10,380	7.3	0.05	0–19.2
Cancer cohort- documented follow-up (5)	[5, 6, 8, 13, 53]	927	10.5	0.08	0–32.6
Cancer cohort-undocumented follow-up (2)	[18, 22]	8,829	1.4	0.01	0–14.4
Epidemiologic study (1)	[15]	624	4.1	NA	NA
Zoledronic acid+pamidronate					
All studies (7)	[5, 6, 8, 13, 18, 22, 53]	9,756	21.0	0.06	5.7–36.3
Cancer cohort- documented follow-up (5)	[5, 6, 8, 13, 53]	927	24.5	0.08	2.2–46.7
Cancer cohort-undocumented follow-up (2)	[18, 22]	8,829	13.1	0.10	0–100
Epidemiologic study	None				

populations is presented in Table 2. The analysis of studies that reported bisphosphonate use confirmed that intravenous infusion of zoledronic acid and pamidronate alone or in combination were the most used bisphosphonate in cancer populations with metastatic bone disease (Table 3).

In order to determine BON prevalence by type of cancer, follow-up documentation was again used as the defining parameter. As it can be seen in Table 4, multiple myeloma is the predominant cancer diagnosis followed by metastatic breast and prostate cancer independent of study design.

Table 2 Analysis of 11 studies that evaluated 614 cases of BON [2, 11, 19, 24, 27, 29, 30, 35, 38, 43, 49]

Diagnosis	BON cases	Percentage of total
BON—non-cancer patients	67	11
BON—cancer patients	547	89
Multiple myeloma	245	45
Breast cancer	166	30
Prostate	30	5
Lung	9	2
Other cancer	97	18
Total		100

Impact on quality of life

There were no studies that systematically evaluated quality of life measure in patients with BON. Four studies did

Table 3 Frequency of bisphosphonate use [2, 11, 19, 24, 27, 29, 30, 35, 38, 43, 49]

Type of bisphosphonate	Total of patients treated (percentage)
Zoledronic acid	196 (31.9%)
Zoledronic acid+pamidronate	190 (30.9%)
Pamidronate	117 (19.1%)
Alendronate	60 (9.8%)
Residronate	5 (0.8%)
Clodronate	3 (0.5%)
Zoledronic acid+ibandronate	2 (0.3%)
Ibandronate	1 (0.2%)
Not reported	40 (6.5%)
Total	614 (100%)

Table 4 BON prevalence by type of cancer [2, 11, 19, 24, 27, 29, 30, 35, 38, 43, 49]

Type of study	Cancer type	BON cases (percentage)
Cohorts with documented follow-up	Multiple myeloma	86/764 (11.3%)
	Breast	7/80 (8.8%)
	Prostate	4/49 (8.2%)
	Lung	1/1 (100%)
Epidemiological studies	Multiple myeloma	69/2,479 (2.8%)
	Breast	23/3,213 (0.7%)
	Prostate	1/754 (0.1%)
	Lung	5/1,491 (0.3%)
Cohorts with undocumented follow-up	Multiple myeloma	19/693 (2.7%)
	Breast	34/1,472 (2.3%)
	Prostate	4/216 (1.9%)
	Lung	0/380 (0%)

evaluate pain experienced by 172 patients with BON. The overall prevalence of pain in these studies was 47%, but one study reported a low prevalence of 10% (9/91) [29], while the other three demonstrated a high prevalence of 90% (72/81) [38, 39, 53].

Economic impact

There were no studies evaluating the economic impact of BON.

Treatment strategies

The management of BON was evaluated in 13 studies (Table 5). A total of 658 BON cases were treated. Treatment techniques included conservative procedures such as minor local debridement with elimination of sharp bone edges, local hygiene of the area of exposed bone, the use of topical antibacterial agents, and systemic antibiotics for infection and pain control. Additional techniques included extensive surgical debridement (such as surgical resection) in combination with topical and systemic antibacterial therapy. Antibiotics were prescribed in about two thirds of the cases, and bone sequestrectomy was used in 23.4% of the cases. The poor reporting of outcomes of treatment did not allow us to determine success or failure rates with accuracy or preferred type of antibiotic therapy. Bisphosphonate use was discontinued in only 16.1% of the cases.

Discussion

This manuscript is part of a series of systematic review papers published in the journal that had the aim of evaluating the prevalence of oral complications of cancer therapy and management strategies [37]. We focused the current review on BON in cancer patients, a new and serious oral complication. Although the number of publications addressing BON continues to grow, we did not find any large, prospective multi-center studies that confirmed the true prevalence of BON. Several of the prevalence studies were based on retrospective chart examinations and did not have clear documentation of patient follow-up. The importance of well-documented follow-up information became evident when studies for prevalence analysis were divided in three groups: those with documented follow-up information [5, 6, 8, 13, 53], those with undocumented follow-up information [18, 22], and epidemiological studies [10, 15, 50, 52]. Each of the studies was assigned study specific quality points such as sources of bias, representativeness, scale validity, and sample size. A higher prevalence of BON was observed in the group with documented follow-up (mean weighted

Table 5 Management protocols for BON and treatment outcomes reported in 13 studies [2, 5, 6, 8, 13, 19, 27, 29, 30, 35, 38, 43, 53] for a total of 658 cases

Type of procedure (procedures could have been used in combination)
Antibiotics=393 (59.7%)
Simple bone sequestrectomy=154 (23.4%)
Bisphosphonate stopped=106 (16.1%)
Conservative therapy=100 (15.2%)
Extensive surgical debridement=84 (12.8%)
Unspecified surgery with antibiotics=45 (6.8%)
IV antibiotics with hospitalization=4 (0.6%)
Response to therapy (most frequent to least frequent)
Not clearly specified=309 (47%)
Stable BON=215 (32.7%)
BON resolved completely=79 (12%)
Progressing BON=43 (6.5%)
Died of cancer=12 (1.8%)

Most frequent to least frequent, excluding stopping of bisphosphonates

prevalence 13.3%). A noticeable difference in prevalence rates was also observed when the cases of BON were estimated according to the type of bisphosphonate used. There was a high overall prevalence of BON in patients treated with pamidronate and zoledronic acid (21%) when all seven studies that reported bisphosphonate use and frequency were evaluated together. The prevalence of BON cases was 24.5% when only studies with documented follow-up were analyzed. Cancer patients with metastatic bone disease were initially treated with pamidronate until zoledronic acid received approval by FDA in the early 2000s. Because of the short administration time of zoledronic acid (15–20 min) compared with pamidronate (60–90 min) and the higher potency of zoledronic acid, many patients were switched to zoledronic acid [13], extending their time on intravenous infusion of bisphosphonate therapy. Additional factors that may have influenced prevalence include referral bias, geographic differences between populations, and possible genetic predisposition that may exist for different ethnic backgrounds. Another factor that can influence prevalence rates would be underreporting [16], but this was not evaluated in the present review.

This review included articles published before December 31, 2008. Only one study published in 2009 was included in the review, but the results were not used in the prevalence estimation, because the publication only became available after the data analysis had been completed [46]. Therefore, we recognize that the inclusion of more recent studies will increase the number of BON cases for future prevalence analyses.

The management of BON has proven to be difficult since the first cases of this complication were reported in the literature [29, 33, 43]. The initial management of BON was based on protocols used to treat osteomyelitis and osteoradionecrosis, including local debridement, curettage and topical and systemic antibiotic therapy, as well as hyperbaric oxygen therapy [33, 42]. The absence of response to therapy became the initial hallmark of BON leading clinicians to search for other more effective therapies [29, 41]. The studies reviewed in the present manuscript suggested a large number of treatment protocols, but the outcomes of these protocols did not favor a particular modality of therapy. It is still uncertain whether one should use a conservative approach with antibiotics and anti-microbial rinses and oral hygiene maintenance or use a surgical intervention to achieve a positive outcome, namely reduction of symptoms and complete healing with re-epithelialization of the wound [4]. A consistent therapeutic approach used in studies was topical and systemic antibiotics and oral hygiene maintenance. This indicates that controlling local infection has an important role in the treatment of BON [45].

It has been proposed that prior to starting bisphosphonate therapy, patients should have a complete clinical and radiographic oral evaluation with the objective of diagnosing and treating oral disease [9]. Although there is evidence that a preventative approach with oral evaluation, oral hygiene maintenance, and periodic follow-up under the supervision of dental professionals may decrease the number of cases of BON [14, 25], the effectiveness of this evaluation in the prevention of BON needs to be demonstrated in well-designed trials.

Another controversial issue in the management of patients who develop BON is whether or not bisphosphonate therapy has to be discontinued. This issue was not addressed in any of the studies reviewed. The presence of bisphosphonate incorporated in bone matrix has been demonstrated several years after discontinuation of use [7]. It appears that after several months of bisphosphonate discontinuation, there is a better possibility for the necrotic bone to sequester and be eliminated, facilitating local

Fig. 1 Suggestions to investigators of standardized information that should be included in future studies of BON

1. State clearly the total number of individuals in the study (denominator number) and whether patients were drawn from a single pool or were referred from outside of the center.
2. Obtain a progressive pain score on all patients (Visual Analogue Scale – VAS or similar)
3. State the duration, the total dose, and range of bisphosphonate therapy.
4. Include information on all other possible aggravating factors such as: smoking, diabetes, use of antiangiogenic agents, use of thalidomide or lenolidomide, use of cholesterol lowering medications, and use of glucocorticosteroids.
5. Stage the BON lesions according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) staging system or other comparable system.
6. Specifically and clearly define end-points and outcomes. For example: healing of the lesion means complete clinical mucosal coverage. If this includes complete return of radiographic findings to normal, this should be stated.

wound healing [4]. There is partial in vitro evidence that keratinocyte proliferation may be hampered by bisphosphonates although in vivo data are lacking [26]. However, discontinuation of bisphosphonate therapy can place patients at risk for fractures and/or hypercalcemia. The decision about discontinuation of bisphosphonate therapy should be made by the patient's oncologist [20].

Conclusion

The overall weighted prevalence of BON based on the findings of the present study is 6.1%. However, prevalence can be as high as 13.3% when its estimation comes from studies with documented patient follow-up. The prevalence of BON can also vary depending on the type of bisphosphonate, with the combination of pamidronate and zoledronic acid yielding the highest prevalence (24.5%). The ideal BON management protocol has yet to be determined. BON can be distressing to patients, causing severe pain and discomfort lasting for several months or years, requiring frequent visits to the dental office, surgical interventions, and antibiotic use. Nevertheless, quality of life studies and studies on the economic impact of BON are lacking and must be the focus of future studies.

Due to flaws in design, a large number of articles did not meet criteria to be included in the present study. A list of suggestions for investigators to use in future BON studies can be seen in Fig. 1. We believe that such information will make osteonecrosis studies more accurate and of higher scientific content.

Conflict of interest statement None to declare.

References

1. (1990) National Institutes of Health Consensus Development Conference on Oral Complications of Cancer Therapies: diagnosis, prevention, and treatment, Bethesda, Maryland, April 17–19, 1989 NCI Monogr: 1–184
2. Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, Russo PA, Kreusch T (2008) "Bis-phossy jaws"—high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. J Craniomaxillofac Surg 36:95–103
3. Aragon-Ching JB, Ning YM, Chen CC, Latham L, Guadagnini JP, Gulley JL, Arlen PM, Wright JJ, Parnes H, Figg WD, Dahut WL (2009) Higher incidence of Osteonecrosis of the Jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. Cancer Invest 27:221–226
4. Badros A, Terpos E, Katodritou E, Goloubeva O, Kastritis E, Verrou E, Zervas K, Baer MR, Meiller T, Dimopoulos MA (2008) Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 26:5904–5909
5. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, Fenton R, Gahres N, Sausville E, Ord R, Meiller T (2006) Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 24:945–952
6. Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA (2005) Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 23:8580–8587
7. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296:2927–2938
8. Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G (2008) Bisphosphonate-induced osteonecrosis of the jaws: prospective study of 80 patients with multiple myeloma and other malignancies. Oral Oncol 44:857–869
9. Campisi G, Di Fede O, Musciotto A, Lo Casto A, Lo Muzio L, Fulfaro F, Badalamenti G, Russo A, Gebbia N (2007) Bisphosphonate-related osteonecrosis of the jaw (BRONJ): run dental management designs and issues in diagnosis. Ann Oncol 18(Suppl 6):vi168–172
10. Cartsos VM, Zhu S, Zavras AI (2008) Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714, 217 people. J Am Dent Assoc 139:23–30
11. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova MA, Di Lenarda R (2006) Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. Dentomaxillofac Radiol 35:236–243
12. Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, Visvikis A, Nikolakopoulou A, Acholos V, Karapanagiotidis G, Batziou E, Skarlos DV (2009) Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 76:209–211
13. Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA, Bamia C, Terpos E, Tsionos K, Bamias A (2006) Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. Haematologica 91:968–971
14. Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, Migkou M, Eleftherakis-Papaiakovou E, Christoulas D, Terpos E, Bamias A (2009) Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 20:117–120
15. Durie BG, Katz M, Crowley J (2005) Osteonecrosis of the jaw and bisphosphonates. N Engl J Med 353:99–102, discussion 199-102
16. Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, Marx R, Ruggiero S, Dimopoulos M, Raisch DW, Singhal S, Carson K, Obadina E, Trifilio S, West D, Mehta J, Bennett CL (2008) Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol 9:1166–1172
17. Estilo CL, Fornier M, Farooki A, Carlson D, Bohle G 3rd, Huryn JM (2008) Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol 26:4037–4038
18. Estilo CL, Van Poznak CH, Wiliams T, Bohle GC, Lwin PT, Zhou Q, Riedel ER, Carlson DL, Schoder H, Farooki A, Fornier M, Halpern JL, Tunick SJ, Huryn JM (2008) Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist 13:911–920
19. Farrugia MC, Summerlin DJ, Krowiak E, Huntley T, Freeman S, Borrowdale R, Tomich C (2006) Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscope 116:115–120

20. Gallego L, Junquera L (2009) Consequence of therapy discontinuation in bisphosphonate-associated osteonecrosis of the jaws. Br J Oral Maxillofac Surg 47:67–68
21. Greuter S, Schmid F, Ruhstaller T, Thuerlimann B (2008) Bevacizumab-associated osteonecrosis of the jaw. Ann Oncol 19:2091–2092
22. Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, Nooka A, Sayegh G, Guarneri V, Desrouleaux K, Cui J, Adamus A, Gagel RF, Hortobagyi GN (2008) Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 23:826–836
23. Jadu F, Lee L, Pharoah M, Reece D, Wang L (2007) A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol 18:2015–2019
24. Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, Elad S (2007) Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 92:1172–1175
25. La Verde N, Bareggi C, Garassino M, Borgonovo K, Sburlati P, Pedretti D, Bianchi C, Perrone S, Mihali D, Cobelli S, Mantica C, Rizzo A, Farina G (2008) Osteonecrosis of the jaw (ONJ) in cancer patients treated with Bisphosphonates: how the knowledge of a phenomenon can change its evolution. Support Care Cancer 16:1311–1315
26. Landesberg R, Cozin M, Cremers S, Woo V, Kousteni S, Sinha S, Garrett-Sinha L, Raghavan S (2008) Inhibition of oral mucosal cell wound healing by bisphosphonates. J Oral Maxillofac Surg 66:839–847
27. Magopoulos C, Karakinaris G, Telioudis Z, Vahtsevanos K, Dimitrakopoulos I, Antoniadis K, Delaroudis S (2007) Osteonecrosis of the jaws due to bisphosphonate use. A review of 60 cases and treatment proposals. Am J Otolaryngol 28:158–163
28. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61:1115–1117
29. Marx RE, Sawatari Y, Fortin M, Broumand V (2005) Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 63:1567–1575
30. Mavrokokki T, Cheng A, Stein B, Goss A (2007) Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 65:415–423
31. Mawardi H, Treister N, Richardson P, Anderson K, Munshi N, Faiella RA, Woo SB (2009) Sinus tracts—an early sign of bisphosphonate-associated osteonecrosis of the jaws? J Oral Maxillofac Surg 67:593–601
32. Migliorati CA (2003) Bisphosphanates and oral cavity avascular bone necrosis. J Clin Oncol 21:4253–4254
33. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB (2005) Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. J Am Dent Assoc 136:1658–1668
34. Migliorati CA, Covington JS 3rd (2009) New oncology drugs and osteonecrosis of the jaw (ONJ). J Tenn Dent Assoc 89:36–38, quiz 38-39
35. Migliorati CA, Schubert MM, Peterson DE, Seneda LM (2005) Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: an emerging oral complication of supportive cancer therapy. Cancer 104:83–93
36. Migliorati CA, Siegel MA, Elting LS (2006) Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol 7:508–514
37. Brennan MT, Elting LS, Spijkervet FK (2010) Systematic reviews of oral complications of cancer therapies. Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature. Support Care Cancer Mar 20 [Epub ahead of print] PMID 20306090
38. Pozzi S, Marcheselli R, Sacchi S, Baldini L, Angrilli F, Pennese E, Quarta G, Stelitano C, Caparotti G, Luminari S, Musto P, Natale D, Broglia C, Cuoghi A, Dini D, Di Tonno P, Leonardi G, Pianezze G, Pitini V, Polimeno G, Ponchio L, Masini L, Musso M, Spriano M, Pollastri G (2007) Bisphosphonate-associated osteonecrosis of the jaw: a review of 35 cases and an evaluation of its frequency in multiple myeloma patients. Leuk Lymphoma 48:56–64
39. Raje N, Woo SB, Hande K, Yap JT, Richardson PG, Vallet S, Treister N, Hideshima T, Sheehy N, Chhetri S, Connell B, Xie W, Tai YT, Szot-Barnes A, Tian M, Schlossman RL, Weller E, Munshi NC, Van Den Abbeele AD, Anderson KC (2008) Clinical, radiographic, and biochemical characterization of multiple myeloma patients with osteonecrosis of the jaw. Clin Cancer Res 14:2387–2395
40. Reid IR (2009) Osteonecrosis of the jaw: who gets it, and why? Bone 44:4–10
41. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B (2009) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg 67:2–12
42. Ruggiero SL, Fantasia J, Carlson E (2006) Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endo 102:433–441
43. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 62:527–534
44. Sedghizadeh PP, Kumar SK, Gorur A, Schaudinn C, Shuler CF, Costerton JW (2008) Identification of microbial biofilms in osteonecrosis of the jaws secondary to bisphosphonate therapy. J Oral Maxillofac Surg 66:767–775
45. Sedghizadeh PP, Kumar SK, Gorur A, Schaudinn C, Shuler CF, Costerton JW (2009) Microbial biofilms in osteomyelitis of the jaw and osteonecrosis of the jaw secondary to bisphosphonate therapy. J Am Dent Assoc 140:1259–1265
46. Walter C, Al-Nawas B, du Bois A, Buch L, Harter P, Grotz KA (2009) Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. Cancer 115:1631–1637
47. Walter C, Al-Nawas B, Grotz KA, Thomas C, Thuroff JW, Zinser V, Gamm H, Beck J, Wagner W (2008) Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. Eur Urol 54:1066–1072
48. Wang EP, Kaban LB, Strewler GJ, Raje N, Troulis MJ (2007) Incidence of osteonecrosis of the jaw in patients with multiple myeloma and breast or prostate cancer on intravenous bisphosphonate therapy. J Oral Maxillofac Surg 65:1328–1331
49. Wessel JH, Dodson TB, Zavras AI (2008) Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: a case–control study. J Oral Maxillofac Surg 66:625–631
50. Wilkinson GS, Kuo YF, Freeman JL, Goodwin JS (2007) Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. J Natl Cancer Inst 99:1016–1024
51. Woo SB, Hellstein JW, Kalmar JR (2006) Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 144:753–761
52. Zavras AI, Zhu S (2006) Bisphosphonates are associated with increased risk for jaw surgery in medical claims data: is it osteonecrosis? J Oral Maxillofac Surg 64:917–923
53. Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D, Krikelis D, Terpos E (2006) 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 134:620–623