

ORIGINAL ARTICLE

Bisphosphonate induced osteonecrosis of jaw in breast cancer patients: A systematic review

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ABSTRACT

Background: Bisphosphonate therapy is widely used for the treatment of bone metastasis in breast cancer patients. **Aim:** The aim of this study is to estimate the overall prevalence of bisphosphonate induced osteonecrosis of jaw (BONJ) in breast cancer patients with bone metastasis. **Materials and Methods:** A literature review was conducted to search and evaluate all the articles that contained original data on the prevalence of BONJ in breast cancer patients from the year 2003-2009. Pubmed search terms used were bisphosphonate, osteonecrosis, breast cancer and jaw. Eleven publications that fulfilled the inclusion criteria were chosen for the study. Case reports and reviews were excluded from the analysis based on assessing the title and abstract. **Results:** Of the 2490 breast cancer patients, 69 developed BONJ with the overall prevalence rate of 2.8%. All the patients with BONJ had received zoledronate or pamidronate, either alone or in combinations. **Conclusion:** BONJ is a significant complication occurring in 2.8% of the breast cancer patients receiving bisphosphonates for metastatic bone disease. It is very important to identify the trigger factors associated with BONJ and also to establish guidelines for the prevention and effective treatment of this condition.

Key words: Bisphosphonate, breast, cancer, osteonecrosis

INTRODUCTION

Bisphosphonates are analogues of inorganic pyrophosphates, which are commonly used in the treatment of osteoporosis, metastatic osteolytic bone disease and primary resorptive malignancies of bone like multiple myeloma.^[1] Breast and lung cancers usually metastasize to the bone and produce osteolytic lesions. The indications of bisphosphonate therapy in patients with metastatic breast cancer are to reduce the resorption of bone and to correct hypercalcemia of malignancy.^[2] These drugs improve the quality of life of the breast cancer patients by decreasing the pain and skeletal-related events (pathologic fracture, spinal cord compression and the need for surgery or radiation therapy) by 30-40%.^[3,4]

Bisphosphonate-induced osteonecrosis of jaw (BONJ) is a potential complication associated with long term use of

bisphosphonates, especially pamidronate and zoledronate and was first described by Marx in 2003.^[5] BONJ is a condition characterized by hypocellularity, tissue dehiscence, chronic bone necrosis and osteolytic radiographic features.^[6] The prevalence of BONJ has not been well established and the underlying pathogenesis still remains to be fully elucidated. Knowledge about the prevalence and pathogenesis of BONJ will help in patient education and development of appropriate management guidelines. The aim of the present study is to estimate the overall prevalence of BONJ in breast cancer patients with bone metastasis. The paper also highlights the proposed guidelines for diagnosis, staging and management of BONJ.

MATERIALS AND METHODS

A systematic literature search was conducted in Pubmed database for articles published between 2003 and 2009. The Pubmed search terms used were bisphosphonate, osteonecrosis, jaws and breast cancer. All the articles containing original data on the prevalence of BONJ in breast cancer patients were identified. Articles involving randomized controlled clinical trials, case-control studies and retrospective studies were included. Articles with anecdotal information, case reports and literature reviews were not included. Specific information collected also included the type of bisphosphonate and study design along with the prevalence of BONJ.

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RESULTS

A total of 126 potentially relevant articles containing information on BONJ in breast cancer patients were identified from Pubmed database, of which 115 articles were excluded after assessing the title and abstract. Eleven articles which fulfilled the inclusion criteria were retrieved in full text. Of the 2490 breast cancer patients, 69 developed BONJ with the overall prevalence rate of 2.8%. Majority of the patients with BONJ had received a combination of zoledronate and pamidronate (63.6%), while 27.2% and 9.2% of them had only zoledronate or pamidronate respectively. Table 1 lists the published studies on the prevalence of BONJ in breast cancer patients from 2003 to 2009.^[7-17]

DISCUSSION

Bisphosphonates are analogs of pyrophosphate in which carbon replaces the oxygen molecule thereby forming a phosphate-carbon-phosphate (P-C-P) structural backbone. Different bisphosphonates were designed by changing the two side chains on the carbon atom in P-C-P structure. The binding affinity of bisphosphonates to mineralized structure and their effectiveness is due to the phosphate ends of P-C-P structure, while the two side chains determine the anti resorptive potential of individual bisphosphonates.^[18] Bisphosphonates have increased affinity for hydroxyapatite crystals and they remain unmetabolized for prolonged duration of time. This property of bisphosphonates is because of the attachment of phosphate ends to calcium ions, forming both insoluble and soluble complexes.^[19]

Bisphosphonates act directly on the osteoclasts, reducing recruitment and proliferation of osteoclast precursors and

also inducing osteoclast apoptosis. They inhibit “receptor activator of nuclear factor κ B ligand (RANKL) expression and increase osteoprotegerin production by bone marrow stromal cells and osteoblasts so that RANK-RANKL interaction is disrupted. These synergistic actions result in the suppression of osteoclast recruitment and decrease the bone resorption.^[20] Bisphosphonates also exhibit anti-angiogenic activity by inhibiting vascular endothelial growth factor and formation of new blood vessels.^[21]

Currently, seven bisphosphonates have been approved for clinical use in the USA by FDA: alendronate, pamidronate, risedronate, zoledronate, ibandronate, etidronate and tiludronate. Five of them have been approved for oral administration while pamidronate and zoledronate are for intravenous use.^[6] The intravenous bisphosphonates are approved for patients with multiple myeloma, metastatic breast cancer and for bone metastases from any solid tumor. The intravenous bisphosphonates are pamidronate (Aredia) that is administered at a dose 90 mg every 3-4 weeks and zoledronate (zometa) administered at a dose of 4 mg every 3-4 weeks.^[1] When compared to pamidronate, zoledronate is more potent and effective in reducing the skeletal complication and hypercalcemia of malignancy.^[22] The oral bisphosphonates such as alendronate and risedronate are commonly used for the treatment of postmenopausal and glucocorticoid induced osteoporosis. The treatment protocol is alendronate 70 mg given once weekly and risedronate 35 mg once weekly. Ibandronate is the most recent bisphosphonate to receive FDA approval in March 2005 for the treatment of osteoporosis and is given as monthly regimen.^[1] Etidronate and tiludronate are approved by the FDA to treat Paget’s disease.^[6]

Table 1: Studies that met the inclusion criteria on the prevalence of BONJ in breast cancer patients from 2003-2009.^[7-17]

Studies	Study design	Number of patients on bisphosphonates (n=2490)	Patients with BONJ (n=69)	Rate of occurrence of BONJ (%)	Drugs used
Bamias <i>et al</i> (2005) ^[7]	Prospective	70	2	2.9	Zoledronate + Pamidronate
Durie <i>et al</i> (2005) ^[8]	Retrospective	299	13	4.3	Zoledronate + Pamidronate
Guarneri <i>et al</i> (2005) ^[9]	Retrospective	48	3	6.2	Pamidronate
Sanna <i>et al</i> (2006) ^[10]	Prospective	81	5	6.2	Zoledronate + Pamidronate
Bujanda <i>et al</i> (2007) ^[11]	Retrospective	35	4	11.4	Zoledronate
Wang <i>et al</i> (2007) ^[12]	Retrospective	81	2	2.5	Zoledronate + Pamidronate
Ibrahim <i>et al</i> (2008) ^[13]	Retrospective	220	5	2.3	Zoledronate + Pamidronate
Hoff <i>et al</i> (2008) ^[14]	Retrospective	1338	16	1.2	Zoledronate + Pamidronate
Boonyapakorn <i>et al</i> (2008) ^[15]	Prospective	10	5	50	Zoledronate + Pamidronate
Walter <i>et al</i> (2009) ^[16]	Retrospective	75	4	5.3	Zoledronate
Fehm <i>et al</i> (2009) ^[17]	Prospective	233	10	4.3	Zoledronate

BONJ: Bisphosphonate-induced osteonecrosis of jaw

The most common side effects of bisphosphonates include gastrointestinal intolerance, flu like symptoms, nausea, vomiting, dizziness and headaches.^[6] BONJ is a recently described complication, which was first reported by Marx in 2003. He had reported painful exposure of maxilla, mandible or both in 36 patients receiving bisphosphonates for malignancy.^[5] In the same year, Migliorati reported 5 cases of mandibular osteonecrosis, while Wang *et al* described osteonecrosis in 3 patients receiving intravenous bisphosphonates for metastatic breast cancer.^[23, 24]

Long-term use of pamidronate and zoledronic acid have been associated with up to 600 cases of BONJ.^[1] Woo *et al*, after reviewing 368 cases of bisphosphonate associated osteonecrosis, have reported that 97% of the cases were treated with pamidronate or zoledronate or both, which similar to our study where 63.6% of the patients had pamidronate and zoledronate.^[25] The strong association of these two drugs to BONJ may be due to higher bioavailability of intravenous bisphosphonates as compared with oral formulations. Approximately 50% intravenous bisphosphonates are available for incorporation into the bone matrix compared to an average of 1% of oral bisphosphonates absorbed by the gastrointestinal tract.^[26] About 170 cases of alendronate, 12 cases of risedronate and only one case of ibandronate-induced osteonecrosis have been reported world wide.^[27] There are currently no reported cases of etidronate and tiludronate related osteonecrosis.

Jaw susceptibility

It has been proposed that the jaw bones are highly susceptible to osteonecrosis based on certain anatomical and physiological factors. Bisphosphonates are highly concentrated in the jaw rather than other skeleton because of high vascularity and bone turnover of the jaws. The forces of mastication and periodontal ligament around numerous teeth ensure rapid bone turnover around the periodontium and can induce microfractures in bisphosphonate-induced acellular and avascular bone. The thin oral mucosa can be easily traumatized during surgical procedures, allowing oral microbes to enter into the necrotic bone.^[28]

Risk factors

It has been suggested that BONJ could be caused by a combination of environmental and genetic risk factors. Various retrospective studies have identified the potential risk factors which include use of oral vs. intravenous bisphosphonates, duration of bisphosphonate therapy, concomitant use of chemotherapy or glucocorticoids, pre existing dental or periodontal diseases, advanced age of the patient and presence of co-morbid conditions such as obesity, tobacco and alcohol abuse.^[1]

Of all these environmental factors, dental trauma is considered to be the most common precipitating factor for the development

of BONJ.^[29] In a review of 368 cases by Woo *et al*, 60% of the cases occurred after dental extraction.^[25] Of the 119 BONJ cases reported by Marx *et al*, 37.8% occurred following tooth removal, 28.6% had periodontitis, and 25.2% occurred spontaneously, 11.2% after periodontal surgery, 3.4% after dental implants and 0.8% following root canal surgery.^[28]

The more potent intravenous bisphosphonates such pamidronate and zoledronate have significantly higher risk of producing BONJ than the oral bisphosphonates.^[8] The duration of bisphosphonate therapy is also associated with the development of osteonecrosis with longer duration of treatment related to greater risk of developing the disease. The incidence of BONJ increased from 1.5% treated for 4-12 months to 7.7% when treated for 37-48 months.^[7] The synergistic effect of the combination of bisphosphonate-induced stress of bone marrow stromal cells, chemotherapy, cancer-related co-morbid factor, reduced vascularity, bone microfractures and tracking or oral microbes through the periodontium may act together to produce “band wagon” effect which increases the disease burden and decreases the susceptibility threshold in favor of BONJ. The median time of treatment with bisphosphonates in patients with metastatic breast cancer before developing BONJ was 72 months for pamidronate and 18 months for zoledronate.^[6]

As only few patients using bisphosphonates develop osteonecrosis, it is possible that individual genetic variations in the drug metabolism or bone homeostasis may confer susceptibility or resistance in the development of BONJ. Polymorphic variations in CYP2C8 gene are associated with increased risk of BONJ in patients with multiple myeloma; specifically single nucleotide polymorphism in intron 8 of CYP2C8 was significantly associated with BONJ when the T allele was present.^[30]

Clinical features

BONJ may be asymptomatic for weeks, months or years and become symptomatic when the surrounding tissues are inflamed or infected. Prior to the development of clinically detectable osteonecrosis, patient may complain of pain, erythema, ulceration, tooth mobility and altered sensation of the affected area. In patients with maxillary involvement, chronic maxillary sinusitis with or without oral-antral fistula can be present secondary to osteonecrosis. In cases of extensive bone involvement, mottled bone similar to diffuse osteomyelitis and widening of periodontal ligament space are noted radiographically.^[1]

Staging

Ruggiero *et al*^[1] have implemented a staging system to stratify the patients with BONJ.

Stage 1: The disease is characterized by exposed necrotic bone which is asymptomatic without any evidence of soft tissue inflammation or infection.

Stage 2: The disease is characterized by exposed necrotic bone associated with pain and soft tissue inflammation or infection

Stage 3: The disease is characterized by exposed necrotic bone associated with pain, soft tissue inflammation or infection, pathologic fracture, extra oral fistula formation or osteolysis extending to the inferior border.

Management protocol

Patients about to start bisphosphonate therapy

Majority of the patients receiving bisphosphonates are affected with BONJ following extraction, dental implant placement or apical surgery. Hence, optimizing the dental health should be the primary goal in patients receiving bisphosphonates. The teeth which cannot be restored and those with poor prognosis should be extracted. The bisphosphonate therapy should be delayed by at least 4-6 weeks after extraction to ensure complete healing. The patients should be educated about the importance of maintaining good oral hygiene and regular dental evaluations.

Patients receiving bisphosphonates without any evidence of osteonecrosis

Maintaining good oral hygiene is of paramount importance to prevent dental disease and thereby to avoid dento alveolar surgery. Placement of dental implants should be avoided in patients receiving potent intravenous bisphosphonates. If the tooth is non restorable, the crown portion can be removed and the endodontically treated roots can be left behind.

Patients with established BONJ

A thorough history and clinical examination along with radiographs helps in establishing the diagnosis of BONJ. The associated oral infectious agents can be identified and the appropriate antibiotics can be selected using microbial cultures. Stage 1 dictates daily use of oral antimicrobial rinses with 0.12% chlorhexidine and regular clinical follow-up. Stage 2 necessitates the use of antimicrobial therapy along with analgesics and daily oral antimicrobial rinses. Stage 3 disease represents the most difficult group to treat as they are refractory to antibiotic therapy. These patients require surgical debridement in addition to analgesics and oral antimicrobial rinses.

CONCLUSION

BONJ is a significant complication occurring in 2.8% of the breast cancer patients receiving bisphosphonates for metastatic bone disease. The prevalence of BONJ can vary depending on the type and duration of bisphosphonate therapy, with the combination of pamidronate and zoledronate yielding the highest prevalence. BONJ can be distressing to patients, causing severe pain and discomfort lasting for several months, requiring frequent visits to the dental office, surgical interventions and antibiotic use. Patients treated with these drugs should be aware of the potential complications in the

jaws and importance of maintaining good oral hygiene should be emphasized in these patients to prevent osteonecrosis. As the patient's medical history and thorough oral examination is the most effective method to detect BONJ, dentists are in a unique position to identify the disease process early and manage the patients appropriately.

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