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Medication-Related Osteonecrosis of the Jaw in Women with Breast Cancer: A Narrative Review

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ABSTRACT

Breast cancer remains a leading cause of premature death in women globally, spurring the adoption of comprehensive treatment approaches. Despite therapeutic progress, significant challenges persist for patients, especially those with advanced breast cancer prone to bone metastases. Bisphosphonates and Denosumab are key bone-modifying agents used to target bone metabolism, reduce metastatic risk, and enhance adjuvant therapy efficacy in early-stage breast cancer. However, using these agents carries risks, including adverse events such as osteonecrosis of the jaw. Due to the impact of these drugs on the jaw bone, this condition is now known as Medication-related osteonecrosis of the jaw (MRONJ). The aim is to provide a comprehensive investigation into MRONJ in the context of breast cancer treatment, with a specific focus on the effects of antiresorptive drugs such as Bisphosphonates and Denosumab. The objective of this article is to review clinical and radiographic manifestations, evaluate the pathophysiology, determine risk factors and incidence and provide guidelines to healthcare professionals for the management and treatment of MRONJ.

Medication-related osteonecrosis of the jaw is a condition that occurs in breast cancer patients due to various risk factors. The treatment of MRONJ depends on the different stages of the condition. Recent research suggests that optimal management of patients prone to MRONJ necessitates a multidisciplinary approach, and the dentist is one of the team members who play a crucial role in patient care by assessing modifiable risk factors, establishing follow-up protocols, and maintaining open communication with oncologists. Preventive measures should be implemented before and during treatment with antiresorptive drugs. However, despite increased awareness, many doctors and dentists still have a limited understanding of MRONJ. Therefore, this research provides practical guidelines for preventing, managing, and treating MRONJ in breast cancer patients based on currently available literature. Dentists should follow specific protocols for patients undergoing antiresorptive therapy. The primary goals are to prevent MRONJ and maintain patients' quality of life. Therefore, dental students and specialists must stay updated and consider this side effect.

Introduction

Breast cancer is the primary cause of premature death among women in many countries worldwide. Multimodality treatment strategies have been advocated for the comprehensive management of breast cancer, aiming to address the disease from various angles. However, despite advancements in treatment options, many breast cancer patients continue to face significant challenges that pose threats to their lives [1]. Advanced breast cancer often affects bones, resulting in bone metastases. The bone microenvironment plays a vital role in harbouring disseminated tumor cells and serves as a potential source of late relapse in breast cancer patients. Therefore, agents that affect bone metabolism might significantly reduce the risk of metastasis and adjuvant therapy in the early stage of the disease. Both bisphosphonates (BPs) and Denosumab (DNB) are bone-modifying agents (BMAs) because they directly affect bone structure and bone metabolism. Bone metabolism is a continuous process throughout one's life. It involves the removal of mature bone tissue from the skeleton (bone resorption) and forming new bone tissue (ossification or new bone formation). Bisphosphonates and Denosumab are categorized as antiresorptive drugs (ARDs) because they primarily inhibit bone resorption, prevent bone loss, and reduce the risk of fractures. Despite different mechanisms of action and administration routes, both BPs and DNBs play crucial roles in the management of bone health in breast cancer patients and other conditions associated with bone loss [2–4]

Although agents such as BPs and other ARDs have been shown to complement cancer-specific treatments by improving bone structure and quality, thereby reducing the risk of skeletal morbidity, they have also been associated with an increased risk of adverse events such as atypical femur fracture, vertebral body compression fracture, and osteonecrosis of the jaw (ONJ) [5,6]. Among these adverse events, ONJ is the most harmful one that can seriously affect patients' quality of life. It was first reported in association with BPs in 2003 and has been called bisphosphonate-related osteonecrosis of the jaws (BRONJ). This definition has undergone several alterations, and after marketing new ARDs such as DNB, this complication changed its name from BRONJ to medications-related osteonecrosis of the jaws (MRONJ). Oncological patients are much more at risk of developing MRONJ, and it tends to be observed more frequently in jaw bones because of their higher rate of remodelling capacity, as well as infectious agents in the oral cavity that can quickly spread to the jaw bone [7,8].

Since 2003, works of literature have been warning about the increased number of MRONJ cases, and there is currently an increasing interest in MRONJ. It is widely discussed in the scientific community, and dentists from different specialities and postgraduate and undergraduate dental students must improve and update their knowledge about patients who are at risk of developing MRONJ, such as breast cancer patients. However, despite this attention, doctors and dentists still need a better understanding of the subject or do not follow the appropriate guidelines for patients, and little progress has been made toward knowledge diffusion, education, and improvement of dental practices. Geographical regions or economic conditions are not significant factors influencing professional awareness, indicating the necessity for universal educational initiatives [9,10]. Addressing the existing gaps in our understanding of MRONJ is imperative for optimizing the care and outcomes of breast cancer patients. By enhancing our knowledge of the risk factors, pathophysiology, clinical manifestations, incidence, and management strategies and treatment of MRONJ, healthcare professionals, particularly dentists, can better anticipate, prevent, and mitigate this debilitating complication. Moreover, bridging the divide between research findings and clinical practice is essential for ensuring timely and effective interventions, improving patient outcomes and enhancing the overall quality of breast cancer care.

1 Breast Cancer

Breast cancer primarily affects women and occurs when cells in the breast start growing abnormally, often beginning in the milk ducts or lobules [1]. Various factors can increase the risk of breast cancer, such as late age for marriage and childbirth, as well as late menopause, leading to prolonged exposure to estrogen [11,12]. Breast cancer can be classified based on histological types, with the most common being infiltrating duct carcinoma non-specific type (IDC-NST)[13] and molecular characteristics based on hormonal receptors [14], which are essential for determining treatment options[15,16]. Breast cancer is categorized into four stages based on tumor size, lymph node involvement, metastasis, and biological markers [17]. Diagnostic methods based on imaging and molecular biotechnology have been developed for quick and accurate breast cancer screening [18]. Breast cancer treatment aims to reduce symptoms, prolong life, and maintain quality of life. Treatment approaches, such as endocrine therapy, chemotherapy, and immunotherapy, are tailored to the specific cancer subtype. Surgical interventions or radiation may be recommended after systemic therapy to alleviate the impact of tumor burden on the patient's quality of life. Additionally, antiresorptive therapy, such as DNB or BPs, is used as an additional treatment method [14,17].

TREATMENT IN EARLY-STAGE

The presence of disseminated tumour cells in the bone marrow of around 25% of patients with early-stage breast cancer is associated with an increased risk of recurrence [5]. Recent studies suggest using selective bone-modifying agents (BMAs) as adjuvant therapy for postmenopausal women with early-stage breast cancer [19]. Additionally, non-metastasis breast cancer patients undergoing hormonal therapy are often prescribed low doses of BMAs for the prevention and treatment of cancer treatment-induced bone loss (CTIBL) [8]. Despite these recommendations, the findings across studies have not been consistent, and there is no unanimous endorsement for universal adjuvant therapy with BMAs [20]. joint guidelines from Cancer Care Ontario (CCO) and the American Society of Clinical Oncology (ASCO) recommend zoledronic acid every six months for 3–to 5 years in postmenopausal women on adjuvant BP therapy. A study conducted by Michael Gnant shows a 50% reduction in fractures with DNB 60 mg every six months for three years in early-stage breast cancer patients on

aromatase inhibitors [21]. Another study by Robert Coleman's research highlights DNB's impact on breast cancer outcomes rather than bone health [22].

In contrast, another study by Mauceri suggests that low-dose BMAs for CTIBL prevention pose a similar MRONJ risk as osteoporosis. Clinicians, especially dentists, may not fully understand the increasing risk of MRONJ in these patients in the early stage. It can lead to overestimating or underestimating the risks and necessary preventive measures. Therefore, early-stage breast cancer patients on BMAs should undergo regular monitoring for MRONJ prevention, as they may transition to higher BMA doses in the future, increasing their risk [8].

TREATMENT IN METASTASIS STAGE

Metastatic breast cancer can lead to skeletal-related events (SREs) in up to 80% of patients, primarily due to increased RANKL expression, which stimulates osteoclast activity and causes bone resorption. This results in complications like fractures, hypercalcemia, spinal cord compression, and pain, so bone-targeted treatments are essential[23]. Adding BPs to standard care can reduce SRE risk by 15%, delay their occurrence, and improve bone pain[24,25]. Intravenous Zoledronic acid (4mg every 3-4 weeks) is particularly effective and safe for rapid administration [5]. Subcutaneous DNB, administered at 120 mg every four weeks, inhibits osteoclast activity and delays SRE onset compared to Zoledronic acid. The American Society of Clinical Oncology (ASCO) recommends continuing these treatments until significant declines in patient performance status. At the same time, the European Society for Medical Oncology suggests indefinite treatment under normal conditions[23,26]. Current international guidelines do not favour DNB over BPs[27].

2 Antiresorptive Drugs

Antiresorptive drugs are crucial in preventing SERs and complications in breast cancer patients. The most commonly used ARDs are BPs and DNB. While more potent agents like zoledronic acid and DNB are effective, they carry a heightened risk of MRONJ [28,29].BPs can be taken orally or via injection to reduce cancer-related bone loss. The American Society of Clinical Oncology recommends zoledronic acid at 4 mg every 3-4 weeks for bone metastases and every six months for early-stage disease [5,21,28,30]. DNB is an antiresorptive agent that exists as a fully humanized antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits osteoclast function and associated bone resorption [30]. While BPs have been used for many years, in November 2010, the Food and Drug Administration (FDA) approved DNB (XGEVA) as a subcutaneous injection for patients with bone metastases from solid tumors. The recommended dose is 120mg every four months. Additionally, DNB (Prolia) is approved in doses of 60mg every six months for patients at high risk of fracture receiving adjuvant aromatase inhibitors or hormonal therapy for breast cancer [31,32]. It has also shown direct or indirect anti-tumour effects in preclinical models and clinical applications [33].

DRUG EFFECTS

Bisphosphonates can help to increase bone mineral density (BMD) over time. This effect usually levels off after about 3-4 years of treatment, but it can help to prevent bone loss and reduce the risk of fractures [34]. Out of all the BPs, zoledronic acid is especially effective in reducing the risk of adverse skeletal events, including bone loss, in women with breast cancer. In addition to these benefits, BPs can also help to relieve bone pain. This effect can benefit people with rare bone diseases like fibrous dysplasia, bone cancer, and bone metastasis [6]. BMD responses to DNB follow a pattern similar to the BPs, although the increases are more significant and continue through 10 years [34]. BP treatment is generally well tolerated, with benefits outweighing side effects, though issues like hypocalcemia, renal toxicity, gastrointestinal symptoms, atypical bone fractures, and ONJ can occur [2,5].

Osteonecrosis of the jaw was initially noticed in patients with disseminated malignancy undergoing monthly BP infusions to prevent skeletal-related events (SREs) [34] and is more familiar with higher doses, prolonged treatment, or shorter intervals in metastatic disease [5]. With newer antiresorptive drugs like DNB, distinct from BPs, this complication has shifted from BRONJ to MRONJ, indicating bone exposure in the maxillofacial and intraoral areas with delayed healing [7]. However, it has been observed that patients with cancer who receive monthly DNB have a similar frequency as BPs [34]. ONJ is more common in the jaw due to high bone turnover, frequent dental trauma, and vulnerability to infections [35], with the mandible showing a higher incidence (73%) compared to the maxilla (22.5%). Its thinner mucosa and single blood supply for the mandible increase susceptibility to necrosis and infections [36].

3 Medication-Related Osteonecrosis of the Jaw (MRONJ):

DIAGNOSIS and STAGES

Medication-related osteonecrosis of the jaw is defined as a harmful drug reaction characterized by the gradual decay and demise of bone tissues in the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease in the absence of previous radiation treatment [8].The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established specific criteria to diagnose MRONJ, which healthcare professionals commonly use and one of those criteria is bone exposure or an intraoral or extraoral fistula in the maxillofacial region through which the bone can be probed and is present for more than eight weeks [30] however, during the European task force on MRONJ workshop held in 2019, it was proposed that an eight-week observation period should not be a requirement to establish the diagnosis of MRONJ [37]. So, in general, the diagnosis is based on clinical examination and radiographic findings, which help to determine the extent of necrosis and the presence of a sequestrum [38]. A summary of clinical and radiograph manifestations can be found in **Table 1** [30,32,39–42].

Table 1: Summary of Clinical and Radiographic Manifestations of MRONJ

Clinical and Radiograph Manifestations	
Clinical manifestations	**Radiograph manifestations**
Exposure of bone	Sclerosis
Signs of inflammation	Increase lamina dura and narrow PDL
Increase soft tissue volume	Mottled osteosclerotic in jaw bone
Swelling with or without suppuration	Bone resorption
Fistula	Persistence alveolar socket after extraction
Halitosis	Bone necrosis or sequestrum
loosening of teeth	
Non-healing socket	
Hypoesthesia or paraesthesia in lip or chin	
Pain	
Oroantral and oronasal communication	
Pathological fracture of jaw	

Stages:
The AAOMS has proposed a classification system for MRONJ with four stages based on clinical features. The initial stage includes a group "at risk," encompassing those who have received antiresorptive medication. Management involves close multidisciplinary observation and good oral hygiene [9].

Stage 0: Patients in this stage may not show any signs of necrotic bone but may experience non-specific symptoms such as dull pain in the mandible, sinus pain, unexplained tooth mobility, odontalgia without any visible cause, and gingival swelling. Other symptoms may include unexplained resorption of alveolar bone and changes in bone pattern [30,39,40,43].

Stage 1: Patients in this stage are asymptomatic, with exposed necrotic bone but no signs of infection [43] .

Stage 2: Patients in this stage exhibit the presence of symptomatic necrotic bone and may experience pain, erythema, infection with or without purulent drainage [39,41,43].

Stage 3: This stage is quite severe and is characterized by severe necrosis, including symptoms like pathologic fracture, extra-oral fistula, osteolysis that extends beyond the region of alveolar bone, for example, inferior border and ramus in the mandible, and sinus floor or zygoma in the maxilla. In addition to these symptoms, this stage may include oroantral or oronasal communication, which can further complicate the condition [30,43].

PATHOPHYSIOLOGY
The exact cause of MRONJ is not fully understood and is believed to involve multiple factors [44]. One theory proposes that the condition may arise from the inhibition of bone remodelling or alteration of bone turnover within the jaw, which could delay and impair bone healing [45]. Specifically, DNB has been found to reduce bone turnover more than zoledronic acid [3]. Another hypothesis suggests that the inhibition of angiogenesis may contribute to MRONJ. It is supported by studies indicating that MRONJ is typically characterised by avascular or aseptic necrosis. BPs such as zoledronic acid can directly inhibit angiogenesis both in vitro and in vivo [46], and they may also indirectly block blood vessel formation by targeting macrophages, which produce matrix metalloproteinase (MMP9) [47]. Additionally, BPs and DMB decrease the arterial and venous areas and the overall vascularity of periodontal tissues during MRONJ [48]. Inflammation and infection are crucial in the onset of osteonecrosis. Dental procedures like tooth extractions and implant placements can introduce bacteria into the bloodstream, leading to systemic inflammation. Periodontal disease can also contribute by causing temporary bacteraemia and subsequent inflammation. Bacterial lipopolysaccharides increase cytokine production and regulate RANKL, altering bone matrix through increased osteoclast activity. It disrupts regular bone maintenance, acidifying the bone environment and affecting turnover [47]. Additionally, low pH levels from infections can release BPs from bone, inhibiting osteoclast activity and affecting nearby cells like osteoblasts and lymphocytes, contributing to MRONJ[49].Studies on mice with rheumatoid arthritis showed a link between systemic inflammation and more severe MRONJ[50]. Patients with immune dysfunctions like rheumatoid arthritis, diabetes, or cancer are at higher MRONJ risk, even without antiresorptive agents. this can be confirmed by animal studies that have shown that certain medications, such as chemotherapy, steroids, disease-modifying antirheumatic drugs (DMARDs), and antiangiogenic medications when combined with antiresorptive agents, can increase the severity or prevalence of MRONJ [45].Several reports have identified single-nucleotide polymorphisms (SNPs) linked to genes involved in collagen formation, bone turnover, and metabolic bone diseases that may be associated with MRONJ. Sirtuin-1(SIRT1), which promotes bone formation and reduces inflammation, could offer protection against MRONJ. Other implicated genes which increase the risk of MRONJ include those related to angiogenesis and immune responses like PPAR gamma, CYP2C8 and others. Despite these findings, current research shows a weak connection between genetic factors and MRONJ risk, highlighting the need for larger, diverse studies to understand genetic predisposition better [30].

RISK FACTORS AND INCIDENCE
Medication-related osteonecrosis of the jaw is associated with several risk factors in breast cancer patients. Understanding these factors is crucial for both prevention and early intervention. Here are key MRONJ risk factors.

DRUG-RELATED RISK FACTORS

The primary drug-related risk for MRONJ is exposure to DNB or BPs, with increased risk from other cancer therapies like angiogenesis inhibitors, chemotherapy, hormonal therapy, cyclophosphamide, and corticosteroids. These drugs can cause immunosuppression, increasing local inflammation and MRONJ risk. The likelihood of MRONJ rises with higher doses, longer durations, and intravenous or subcutaneous administration routes, especially in metastatic cases. And at the end, breast cancer as an underlying disease also elevates MRONJ risk [10,39,44,51].

SYSTEMIC RISK FACTORS

Systemic risk factors affect bone and drug metabolism, oral health, and systemic diseases. Khan et al. found that some systemic risk factors for MRONJ for cancer patients include diabetes, erythropoietin usage, smoking, hyperthyroidism, and renal disease. These factors require special attention due to their influence on bone and mucosal microcirculation [52]. It should be considered that genetics and age can also affect the risk of MRONJ [39,40]. Specific biomarkers may indicate MRONJ risk. The American Society of Bone Mineral Research suggests a threshold of carboxy-terminal cross-linking telopeptide of type I collagen (CTX) levels (> 0.150 ng/mL) for safer invasive dental procedures in patients on BPs. However, low CTX levels (< 0.150 ng/mL) could pose risks. A study by Ana Laura Soares found higher (procollagen type 1 amino-terminal propeptide) P1NP levels in patients with bone metastasis, indicating P1NP might be a better marker for metastatic bone disease and MRONJ [10,31,52]. However, the potential use of these markers for invasive dental procedure selection in breast cancer patients remains to be determined, and more research needs to be done.

LOCAL RISK FACTORS

It is essential to consider any condition that can cause inflammation or infection in the dental supporting structures as a local risk factor. Specialists must promptly recognise and treat these factors to ensure the safe initiation of medical therapy [53]. Some factors include anatomic features such as bone exostoses and mandibular and palatal torus [54]. Dentists should also pay attention to subclinical trauma [40]. The elevated risk of MRONJ can associated with periodontal disease and apical periodontitis, underscoring the role of inflammation in its pathogenesis [8,51]. Denture-associated sore spots may cause permanent mucosal inflammation and make micro lesions, which facilitate the penetration of bacteria into the bone and increase susceptibility to infection and MRONJ [51]. Dentoalveolar operations such as tooth extraction are a common predisposing factor for MRONJ. Studies show tooth extraction is cited as a predisposing event in 62% to 82% of MRONJ cases [30]. Also, studies estimate the risk of MRONJ after tooth extraction in cancer patients exposed to IV BPs is estimated to be between 1.6% and 14.8%. Some studies suggest that tooth extraction is a significant risk factor for developing MRONJ in cancer patients receiving antiresorptive drugs. For example, in a longitudinal cohort study, Vahtsevanos et al. found that 60 out of 1621 (4.9%) patients with breast cancer, prostate cancer, or multiple myeloma treated with BPs developed MRONJ. Furthermore, tooth extraction was linked to a 33-fold increased risk of MRONJ, consistent with similar studies identifying it as a risk factor [55].

In contrast, others indicate that tooth extraction does not significantly influence the risk of MRONJ, instead highlighting inflammation and dental infections as the primary concerns. A non-randomised retrospective cohort study by Avishai found that tooth extraction contributes to the development of MRONJ in nearly 20% of cases. Still, inflammation or infection is the primary cause in 95% of MONJ cases [56]. Also, a retrospective observational study by Soutome et al. revealed that tooth extraction itself is not a risk factor for MRONJ in cancer patients on high-dose drugs; however, preserving infected teeth that require extraction increases the risk. Therefore, if local inflammation/infection is treated before extraction, MRONJ may be avoided [55,56]. Studies suggest dental implants may increase the risk of MRONJ in patients treated with BPs or DNB for two reasons. First, peri-implantitis (inflammation around implants placed before antiresorptive therapy) can lead to MRONJ. Second, MRONJ is related to the insertion of implants in patients during or after taking antiresorptive medication.

Moreover, the duration between implant insertion and MRONJ onset was significantly shorter in patients with cancer compared to those with osteoporosis. It is still unclear which of these two factors is more associated with the risk of MRONJ [51,57]. In general, based on the works of literature, three main groups of patients are at risk of developing MRONJ: first, breast cancer patients with bone metastases receiving high doses of BMAs; second, early-stage breast cancer patients at risk of non-metastatic bone fractures due to CTIBL; and third, patients with osteoporosis or other non-malignant diseases on low-dose BMAs regimens [8,30].

MEDICATION-RELATED OSTEONECROSIS OF THE JAW INCIDENCE IN BREAST CANCER

There have been several studies on the incidence of MRONJ in oncology, which refers to the number of new cases per sample or population per unit of time [30]. However, there are limitations in studies focused on the incidence of MRONJ in breast cancer patients. Fredrik Hallmer's study found that the incidence rate of MRONJ in metastasis breast cancer patients in the total population is 6.6%, while the incidence rate of MRONJ with zoledronic acid is 4.1% [3]. It is to the report by Bamias et al., who found an incidence rate of 2.9% of MRONJ in patients with breast cancer treated with BPs. The incidence rate in the total population is higher than in the BP population because the risk of MRONJ from constipation DNB is three times higher than that of zoledronic acid. Recent randomised controlled trials on breast cancer patients without bone metastasis under a low dose of BMAs for CTIBL prevention reported MRONJ rates between 0% and 0.5%. Further investigation is needed to clarify the risk in these cases.

PREVENTION STRATEGY

It is essential to evaluate a patient's MRONJ risk group, along with any additional risk factors that may be present, and then create an individualised treatment plan [40]. A recent study involving 129 dental practitioners in the

UK revealed a notable gap in knowledge, with over 90% exhibiting poor awareness of medications associated with MRONJ. Furthermore, only 40% expressed comfort in treating patients with antiresorptive-related MRONJ. Therefore, educating healthcare professionals and patients about the risk of MRONJ following certain medications is crucial for prevention [9]. Furthermore, recent research suggests optimal management of patients prone to MRONJ necessitates a multidisciplinary approach. In light of these findings, a collaborative effort involving dentists, OMFSs, primary care physicians (family doctors), and oncologists, alongside active patient participation and oncology nurses, is essential to achieve optimal outcomes for individuals affected by MRONJ (**Figure 1**) [40–42,52,58,59].

Additionally, developing and implementing educational programs become imperative to enhance interdisciplinary collaboration and deepen healthcare professionals' understanding of bone-modifying agents' benefits and potential side effects across dental and medical specialities [30,40,41,59,60]. Due to limited studies on MRONJ in women with breast cancer, all healthcare professionals must pay special attention to those who are using or planning to use antiresorptive drugs. Mitigating potential risks and ensuring comprehensive care is necessary.

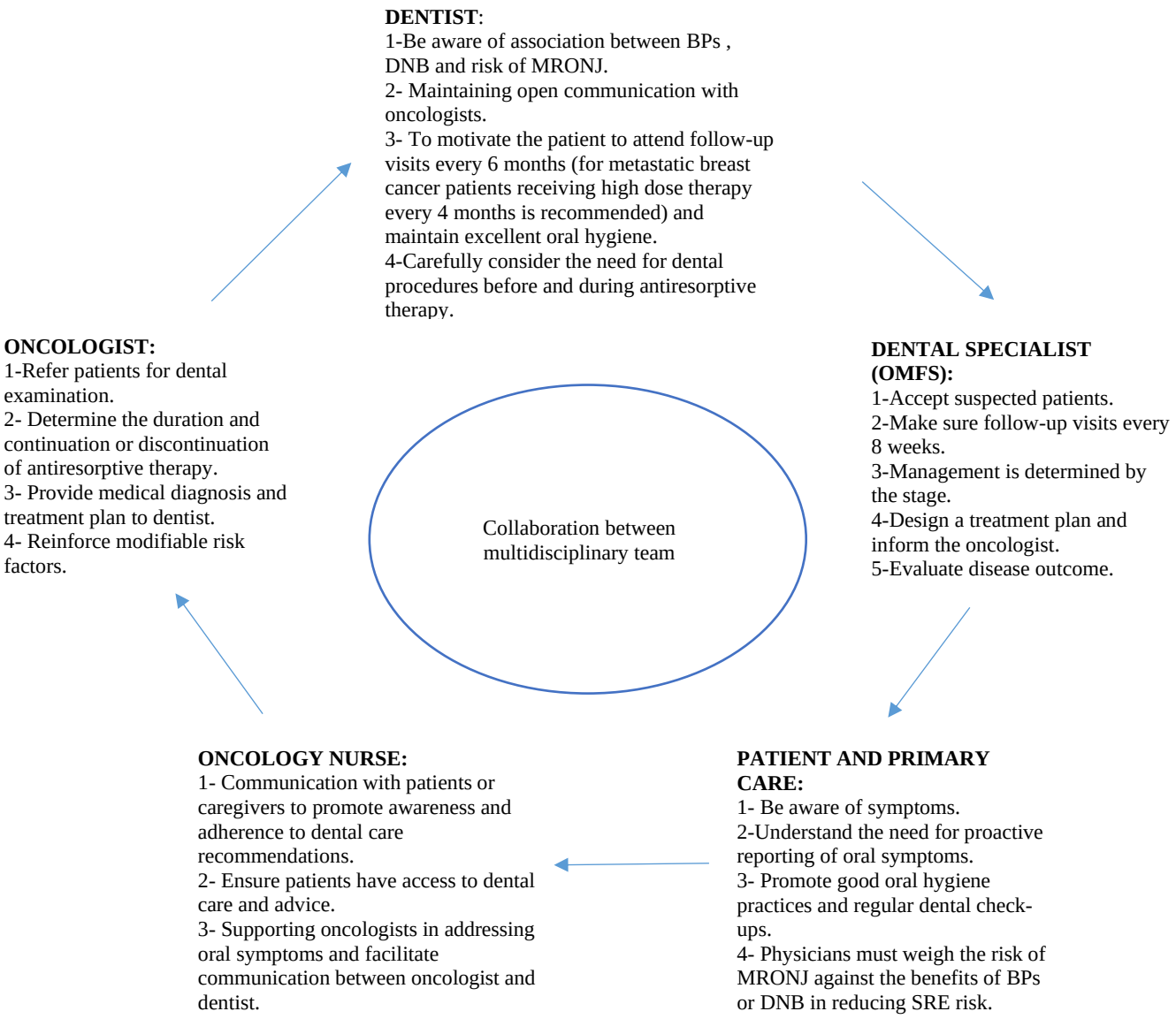

Figure 1. Multidisciplinary approach to managing the risk of MRONJ.

CLINICAL PRACTICE GUIDELINES FOR DENTAL TREATMENT ACCORDING TO TIMING. PREVENTIVE MEASURES

In the context of MRONJ prevention, it is essential to note that there was no standard and comprehensive protocol. The literature presents various protocols, from antibiotic regimens to autologous platelet concentrates and innovative approaches such as laser therapy [61]. However, due to the need for a complete protocol, this study aimed to create a comprehensive guide for healthcare professionals, especially dentists. The guide addresses dental care for women with breast cancer or those starting anti-resorptive medications. The protocol also aims to instruct on what and how dental treatments should be performed when breast cancer patients are under these medications. The goal of the prevention of MRONJ is to eliminate dental risk factors and maintain a healthy oral environment [62]. Patients are divided into two groups based on their history with ARDs. The first group, the pretreatment phase, includes patients who have never taken ARDs and are scheduled to start antiresorptive treatment. Their oral health must be assessed precisely through clinical and radiographic examinations, particularly for cancer patients. The second group, the in-treatment phase, consists of patients already exposed to ARDs. These patients will participate in an oral health assessment program to minimise local risk factors for MRONJ [63]. To gain a better understanding of this topic, all recommendations are listed in (**Table 2,3,4,5**).

CANCER PATIENTS IN THE PRE-TREATMENT PHASE

Preventing MRONJ requires a multidisciplinary approach and active patient involvement. Healthcare professionals should educate cancer patients treated with DNB or BP about MRONJ risks [40]. Patients must maintain good oral hygiene with fluoride products, avoid smoking and alcohol, and attend regular dental checkups. They should also be aware of MRONJ symptoms like exposed bone, jaw pain, loose teeth, pus, and non-healing sores for early detection and management [41,59,64].

DENTAL TREATMENTS IN THE PRE-TREATMENT PHASE

In the pretreatment phase, non-restorable teeth and those with poor prognosis should be extracted, along with any necessary elective dentoalveolar surgery. Antibiotics and antimicrobial rinses are recommended pre- and post-operatively [30]. In cancer patients with hopeless teeth or any other dental infection, if systemic conditions permit, initial antiresorptive therapy should be delayed for 45-60 days after dental surgeries to allow soft tissue healing before starting the medications. [30,63]. In another study, Singh concluded that when a pretreatment extraction is completed, the tooth should be removed traumatically, and osseous healing should be complete, usually requiring 4 to 6 weeks before antiresorptive medication is started. This study emphasises the importance of avoiding tooth extractions in patients undergoing high-dose drug therapy for cancer [59]. Invasive procedures like implants or bone surgery are contraindicated due to their potential risk of MRONJ. However, non-invasive dental procedures such as restorative dentistry and endodontic treatment can proceed without delaying antiresorptive therapy [30,63].

Medical oncologists play a crucial role in educating patients about the importance of dental health and preventive measures to reduce the risk of MRONJ. They should check for exposed bone during chemotherapy while assessing oral mucositis. Dentists must perform oral examinations, radiographic assessments, and review dental histories for local infections before starting antiresorptive therapy [30,40]. Necessary treatments like endodontics, dental cleanings, and restorative and non-surgical periodontal procedures should be done to remove infection sources [41,59]. Poorly performed root canals can increase MRONJ risk, so evaluating the tooth and clinician's skill is vital [62]. Other considerations, such as denture wearers, should also be checked for irritation or trauma, particularly from ill-fitting dentures, as these can lead to mucosal injury and infection [40]. These assessments should be integrated into the treatment plan to minimise MRONJ risks (**Table 3**).

CANCER PATIENTS IN THE TREATMENT PHASE

Cancer patients treated with drugs related to MRONJ are considered at high risk of developing MRONJ due to the presence of multiple known risk factors [63]. Teeth extractions or procedures that impact the bone are considered risk factors for developing MRONJ in patients. Literature reports that following a tooth extraction, there is a 2.9% incidence of MRONJ in cancer patients and 0.15% in osteoporosis patients [41]. However, surgical procedures are considered necessary to eliminate infective outbreaks of MRONJ in cancer patients during the treatment when dental diseases cannot be resolved through other means [63]. Spontaneous development of MRONJ without any invasive dental treatment has also been reported (**Table 4**) [41].

DENTAL TREATMENTS IN THE TREATMENT PHASE

Atraumatic surgical procedures (extraction): The Italian Society of Oral and Maxillofacial Surgery and the Italian Society of Oral Pathology and Medicine advocates a protocol for dental extractions in at-risk cancer patients. This protocol includes a combination of medical prophylaxis and specific surgical procedures; a standardized example of this protocol entails the following steps:

Pre and post-procedure Medical Prophylaxis: Patients are instructed to use a 0.12% chlorhexidine (CHX) antiseptic mouthwash at home thrice daily, starting seven days before the dental procedure [64]. Postoperatively, they should continue using CHX mouthwash thrice daily for 15 days. Patients are also advised to apply a hyaluronic acid gel thrice daily for 15 days [65,66].

Antibiotic Therapy Administration: Concurrently, antibiotic therapy (e.g., Ampicillin/ Sulbactam intramuscular and Metronidazole orally) is administered, starting the day before the intervention and continuing for at least six days post-procedure [65].

Surgical Procedure Guidelines: During the surgical extraction, specific recommendations include the use of local anaesthesia without adrenaline, performing a full-thickness flap, gently extracting the tooth with less bone manipulation, conducting alveoloplasty of the post-extraction site, if necessary, and applying a tension-free soft tissue closure. These measures aim to facilitate healing through first intention [65]. It is also advisable to proceed with one tooth extraction at a time, especially

when multiple extractions are necessary. Sutures should be removed between the seventh and tenth day after surgery and during the first year of follow-up; it is essential to have periodic clinical checkups scheduled accurately at 3, 6, and 12 months [63]. If the extraction socket has not healed after eight weeks, MRONJ should be suspected [41]. Recent advancements in surgical techniques have introduced autologous platelet concentrates (APCs) and lasers for MRONJ presentation. In clinical studies, both Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) have demonstrated effectiveness in reducing the onset of MRONJ and expediting epithelisation, particularly in patients undergoing BPs therapy [67]. PRP, rich in growth factors, and PRF, a second-generation autologous product, play pivotal roles in modulating inflammation and enhancing immune responses mediated by chemotactic molecules [67]. The evidence suggests that PRF may intervene with bisphosphonate-induced effects on osteoclasts and mucosal cells. Also, the high level of leukocyte content serves to combat emerging infections in sites with challenging healing processes. It appears to be a favourable material in oral surgery; Plasma Rich in Growth Factor (PRGF) is another APC that contains various growth factors and shows the potential to induce mitosis of target cells, leading to favourable outcomes [61]. Clinical observations reveal that adjunctive therapy with leukocyte–PRF (L-PRF) during tooth extraction in oncologic patients reduces MRONJ incidence [68]. For those reasons, it should be considered a dentist-friendly material in oral surgery where patients show a high risk of developing complications that can lead to infections. In patients with a BP history, laser use after dentoalveolar surgery showed no signs of MRONJ after six months post-surgery [61]. The combination of L-PRF and laser in patients cured with BPs showed physiological wound healing after one month, and none experienced MRONJ [68].

The clinician must adhere to consistent guidelines when dealing with inflammatory-infective issues that can be resolved through endodontic or periodontal surgical procedures. It includes applying the same protocols relevant to dental extractions. The guidelines should cover critical aspects such as medical prophylaxis and surgical procedure guidelines [66].

Non-Invasive Dental Treatments: To prevent the spread of infectious processes, it is highly recommended that non-invasive dental treatments like restoration and root canal treatment be undertaken [66,69]. During those treatments, the dentist should always work with rubber dam isolation and avoid trauma to oral mucosa due to wrong-position clamps. It is recommended not to use Vasoconstriction anaesthetics and to provide antiseptic mouthwash to reduce the bacterial load in the oral cavity during endodontic treatments, as well as to avoid exceeding the limits of the root canal with endodontic instruments and root canal filling material [69].

Non-surgical Periodontal Therapy: Recent studies suggest that cancer patients who are at risk of MRONJ should receive professional oral hygiene and is indicated. Non-surgical periodontal therapy that is non-invasive should be carried out cautiously to ensure regular plaque removal. It is also important to periodically screen patients undergoing treatment to monitor their oral and eriodontal health [70]. As a result, it is essential to schedule a follow-up period of 3-4 months for patients undergoing high doses of treatment with ARDs and every six months for those who have early-stage breast cancer for CTIBL prevention [8,70]. For the management, it is recommended to use chlorhexidine rinses with concentrations between 0.12% and 0.2% and administered 2 to 4 times a day, depending on the severity. Educating individuals on proper home oral hygiene practices is also essential, as it should cover both the oral cavity and dentures. These measures can help reduce the risk of periodontal infection [70].

Dental implants: It is a contraindication and is not recommended for in-treatment cancer patients to get dental implants due to the extensive bone manipulation that is required for placing the implant fixtures. Additionally, cancer patients' systemic health conditions can increase the risk of developing peri-implantitis, which is also a significant risk factor for MRONJ [30,63].

Dental prostheses: Cancer patients with removable dental prostheses should have checkups every four months. These checkups aim to assess denture fit, prevent pressure ulcers, and enhance stability [71]. Patients should avoid wearing dentures for about 8–12 hours daily, especially at night. For fixed prostheses like crowns and bridges, it is crucial to consider the biological width and avoid infringing on the junctional epithelium. Supragingival prosthetic margins should be established to minimise trauma to the surrounding soft tissues and support periodontal health [63].

Considerations for Orthodontics: Orthodontic treatment is viewed as an elective option. While concerns exist about potential drug accumulation in the jawbone, cancer patients undergoing ONJ-related drug treatment seldom request orthodontic procedures [63].

Table2: The instructions for Breast Cancer Women before cancer therapy.

Different phase of treatment	
Breast Cancer Women before cancer therapy	**1.Clinical examination** 1.1. Assessment of the extra-oral structures for any sources of pain and infection 1.2. Systemic assessment of the oral mucosal tissue for soft tissue pathologies 1.3. Examination Intraoral: Teeth for caries Quality of existing restorations Evaluation teeth for pulpal and periapical pathologies (pulp sensitivity tests) Oral Prosthesis should be check Periodontal index evaluation **2.Radiograph Examinations**

	3. Treatment protocol Treatment planning is guided by the dental issue's urgency, available time for treatment	
	Full dental clearance protocol	**Partial dental clearance protocol**
	3.1. Caries prevention: Consider regular use of high fluoride toothpaste 3.2. Dental Caries: Restore all carious teeth Extract non-restorable teeth, poor prognosis, retained roots Replace all defective restoration 3.3. Pulpal and periapical pathology: Root canal treatment should ideally start at least 1 week before cancer therapy for non-vital teeth, if not possible, extraction should be considered. Retreatment for apical periodontitis 3.4. Periodontal disease: Professional oral hygiene Extract teeth with advanced periodontal disease (probing depth ≥ 6mm, furcation I, II, III, tooth mobility II-III) 3.5. Prosthesis: Check dentures for irregularities or sharp edges and adjust accordingly Modify, disassemble, or replace fixed prosthesis if suspected of recurrent caries, marginal leakage, or functional problems 3.6. Extraction: Extraction should be performed typically 2 weeks before chemotherapy For immunosuppressed patients, pre-treatment blood tests are important. If neutrophil counts drop below 1×109/L (<1000/mm3) or platelet counts below 60×109/L (<60,000/mm3), adjustments to antibiotics and platelet transfusions may be needed, but recommendations can differ.	3.1. Caries prevention: Consider regular use of high fluoride toothpaste 3.2. Dental Caries: Treat only large or symptomatic carious teeth Treat only defective restorations that are symptomatic 3.3. Pulpal and periapical pathology: Treat only symptomatic teeth with apical periodontitis and/or periapical lesion ≥ 5 mm 3.4. Periodontal disease: Professional oral hygiene Extract only teeth with severe periodontal disease (probing depth ≥ 8mm, mobility III) 3.5. Prosthesis: Check dentures for irregularities or sharp edges and adjust accordingly Modify, disassemble, or replace fixed prosthesis with large or symptomatic caries 3.6. Extraction: Extraction at least 1 week before chemotherapy Prescription antibiotics

Table3: The instructions for Breast Cancer Women in Pre-treatment Phase.

Breast Cancer Women in Pre-treatment Phase	**1.Oral Examination and Patient Education** 1.1. Perform a thorough oral examination, radiographic assessment, and gather a brief dental history from patients. 1.2. Educate patients: Promoting good oral hygiene with fluoride toothpaste and mouthwash Avoiding smoking and alcohol. Getting regular dental checkups every 6 month Educate patients about the signs of MRONJ **2.Dental Treatment** 2.1. Extraction is indicated for hopeless teeth or any other dental infection (4 to 6 weeks before start using ARDs) 2.2. Implant surgery, preimplant bone surgery are contraindication 2.3. Other non-invasive dental procedures such as Restorative dentistry, Endodontic treatment (pay attention to avoid over or under filled canals), non-surgical Periodontal treatments are indicated and does not need make delay in suing ARDs. 2.4. Prosthesis and Orthodontic procedures are possible and pay attention to Individuals with full or partial dentures any signs of irritation 2.5. If non-invasive procedures are insufficient to treat infectious processes, studies indicate that periodontal and endodontic surgery may be warranted

Table4: The instructions for Breast Cancer Women in-treatment Phase.

Breast Cancer Women in-treatment Phase	**1.Oral Examination and patient Education** 1.1. Perform a thorough oral examination, radiographic assessment, and gather a brief dental history from patients. 1.2. Educate patients: Promoting good oral hygiene with fluoride toothpaste and mouthwash Avoiding smoking and alcohol. Getting regular dental checkups every 6 months (some studies recommend every 4 months in metastasis case) Educate patients about the signs of MRONJ **2.Dental Treatment** **2.1. Extraction:** 2.1. Use 0.12% chlorhexidine (CHX) seven days before the procedure and three times per day for 15 days after extraction. 2.2. Apply gel containing hyaluronic acid three times per day for 15 days after extraction. 2.3. Administer antibiotic therapy with Ampicillin/Sulbactam IM and Metronidazole orally, starting the day before the intervention and continuing for at least six days' post-procedure. 2.4. Follow specific guidelines for extraction procedures: Use local anaesthesia without adrenaline. Perform a full-thickness flap. Gently extract the tooth with minimal bone manipulation. Conduct alveoloplasty of the post-extraction site if necessary. Apply tension-free soft tissue closure. Remove sutures between the seventh and tenth day after surgery. 2.5. Schedule periodic clinical check-ups accurately at 3, 6, and 12 months' post-extraction **2.2. Non-Invasive Dental Treatments:** **2.2.1 Restoration and Endodontics:** Use rubber dam and pay attention to position clamps. Avoid Vasoconstriction anaesthetics. Use antiseptic mouthwash during endodontic treatments. Ensure not to overextend root canal instrumentation or filling materials. **2.2.2 Non-Surgical Periodontal Therapy:** Regularly remove plaque. Schedule follow-up appointments, every 3-4 months for breast cancer with bone metastasis and every 6 months for who in early stage of cancer Rinse with CHX mouthwash 0,12% or 0.2% for two or four time per day **2.2.3 Surgical periodontal Therapy:** If non-surgical procedures are insufficient to treat infection, periodontal surgery indicated **2.2.4. Dental Prostheses:** Removable Prosthesis: Schedule check-ups every 4 months. Recommend not wearing dentures for 8-12 hours per day, especially during the night. Fixed Prosthesis: Avoid invading the junctional epithelium. Establish a supragingival prosthetic margin **2.2.4 Orthodontic Procedures:** Seldom request orthodontic procedures. **2.2.5 Implants:** Not recommended for cancer patients

Table5: The instructions for Breast Cancer Women with MRONJ.

	Stage 0	Stage 1	Stage 2	Stage 3
Breast Cancer Women with MRONJ	**1.Conservative treatments:** 1.1. Multidisciplinary approach 1.2. symptomatic care such as analgesics and antimicrobial mouth rinses 1.3. Maintaining good oral hygiene 1.4. Periodic evaluation (every 8 weeks to OMFS)	**1.Conservative treatments:** 1.1. Multidisciplinary approach 1.2. symptomatic care such as analgesics and antimicrobial mouth rinses 1.3. Maintaining good oral hygiene 1.4. Periodic evaluation (every 8 weeks to OMFS) 1.5. Local wound care to exposed bone 1.6. Remove sequestrations bone **2.Surgical treatments:** 2.1. Marginal resection for mandible 2.2. Alveolectomy for maxilla	**1.Conservative treatments:** 1.1. Multidisciplinary approach 1.2. symptomatic care such as analgesics and antimicrobial mouth rinses and antibiotics therapy 1.3. Good oral hygiene 1.4. Periodic evaluation (every 8 weeks to OMFS) 1.5. Local wound care to exposed bone 1.6. Remove sequestrations bone **2.Surgical treatments:** 2.1. Segmental resection for mandible 2.2. Partial infrastructure maxillectomy	**1.Conservative treatments:** 1.1. Multidisciplinary approach 1.2. symptomatic care such as analgesics and antibiotics therapy 1.3. Good oral hygiene 1.4. Periodic evaluation (every 8 weeks to OMFS) 1.5. Local wound care to exposed bone 1.6. Remove sequestrations bone **2.Surgical treatments:** 2.1. Segmental resection for mandible 2.2. Partial infrastructure maxillectomy

Table 2,3,4,5: These instructions provide dentists a comprehensive guide on managing and treating breast cancer patients and also in both the pre-treatment and in-treatment phases to minimize the risk of developing MRONJ and ensure optimal oral health outcomes.

TREATMENT

The main goals of treating patients who are at risk of developing or have established MRONJ are to prevent MRONJ and preserve the quality of life, and this can be achieved through patient education and comforting, infections and pain control, as well as preventing the spread of the lesion and the development of new areas of necrosis. Additionally, for oncology patients, it is essential to prioritise and support continued oncologic treatment for those receiving antiresorptive therapy to control bone pain and reduce the incidence of SREs [30]. The therapy of MRONJ is based on disease stage and can be either conservative (non-operative) or surgical [9,39], and decisions regarding surgical versus non-operative treatment should be personalized to each patient and adapted to their unique requirements (**Table 5**). Evaluating the risk-to-benefit ratio is crucial in this process [72].

The effectiveness of conservative therapies in managing MRONJ is discussed in many kinds of literature. This treatment method is based on the use of drugs to control symptoms such as pain and infection. Infections are common complications of MRONJ and can contribute to its development. Therefore, non-operative treatment is mainly recommended, particularly in the early stage of MRONJ. However, according to the AAOMS classification update 2022, it can be helpful in all stages [30,73]. Conservative therapy includes systemic antibiotic therapy in combination with antimicrobial therapy and oral hygiene. Sometimes, the removal of movable bony sequestrum segments and the extraction of symptomatic teeth from the exposed necrotic bone are also part of the treatment. The main goal of these treatments is the stabilisation of lesions [53,73]. In the past, guidelines for managing MRONJ discouraged surgical intervention due to inconsistent evidence of favourable results in cancer patients. However, as experience has grown over the years, more evidence has emerged to support the use of surgery in treating MRONJ for patients who have not responded to conservative treatment or are not suitable for them. Surgery procedures can be used even in earlier stages of MRONJ [40].

Additionally, the necrotic bone removed during surgery should be sent for histopathological processing, as it may uncover metastases in the jaw specimen. However, this occurs in only a minority of cases [30,39]. Surgical procedures for MRONJ include debridement, sequestrectomy, segmental and marginal resection. However, Davide De Cicco's study states that debridement and sequestrectomy procedures should not be considered surgical interventions but rather conservative therapies. Surgical interventions are primarily categorised based on the extent of necrotic bone resection [53]. However, other studies categorise those procedures as surgical interventions [9,39,44,73,74]. Antibiotics are commonly prescribed before and after surgery, and perioperative antibiotic treatment should be administered to help prevent infection. There are also several additional possible treatments for MRONJ, including ozone therapy, laser therapy, growth factors combined with antibiotics, and vitamin D supplements for patients with vitamin D deficiency [39].

4 Enhancing Annotation Sheet Recommendations

In complete prescribing information about BPs and DNB, written in the annotation sheet by the FDA, it was mentioned that "cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry before treatment with BPs." Or "A dental examination with appropriate preventive dentistry should be considered before treatment with DNB in patients with risk factors for ONJ such as invasive dental procedures and diagnosis of cancer" [32]. Using words such as "should" in the annotation sheet of DNB and BPs related to the treatment of breast cancer are non-committal words. According to clinical guidelines in the pretreatment phase expressed by Sven Ottoa [40], they are inappropriate. Nita Singh [59] strongly recommends that physicians conduct oral examinations and take a brief dental history. It is most important to educate the patients about the risk of MRONJ and discuss the importance of oral hygiene and dental treatments. The word "essential "indicates that this particular action is fundamental and necessary and cannot be omitted without compromising the desired outcome or objective; however, using a word such as "should" conveys the sense to the reader that this is a recommendation or preferred under the circumstances and is not imply absolute necessity or obligation and there may be some flexibility or discretion in adhering to it. So, stronger terms like "must" are recommended to emphasise the critical role of dental care in preventing MRONJ and minimising the adverse effects of these medications.

Conclusion

Medication-related osteonecrosis of the jaw is a serious condition that can affect women with breast cancer, presenting through various stages that range from asymptomatic to severe bone exposure and pathological fractures. Its pathophysiology remains poorly understood but may involve factors such as inhibited bone remodelling, inflammation, immune dysfunction, and genetic predisposition. Additionally, systemic and local risk factors, including invasive dental procedures, anatomical issues, and periodontal disease, contribute to the disease's development and severity. The incidence of MRONJ varies with different antiresorptive medications, showing higher rates associated with Denosumab compared to Zoledronic acid. Therefore, it is crucial for both dental students and specialists to stay informed about MRONJ, especially regarding its implications for patients with early-stage and metastatic breast cancer. Adhering to established management guidelines is essential for providing appropriate care to those affected by this condition.

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